

## Review Article

# Radionuclide generators: the prospect of availing PET radiotracers to meet current clinical needs and future research demands

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**Abstract:** Targeted molecular imaging with positron emission tomography (PET) constitutes a successful technique for detecting and diagnosing disease conditions promptly and accurately, and for effectively prognosticating outcomes and treating patients with a tailored and more individualized intervention. In order to expand the success of PET in nuclear medicine, it is important to assure access to radiotracers of desired quantities and qualities. In this context, the benefit of accessing PET radiotracers through a radionuclide generator (RNG) cannot be overstated, as generators offer the potential of enriching the PET radiotracer arsenal at the medical centers both with and without onsite cyclotrons. While RNG technology to avail PET tracers is in its infancy, their use is expected to revitalize current PET practices and seems poised to broaden the palette of PET in nuclear medicine in the foreseeable future. In this review, we discuss the principles of RNGs, assess major parent/daughter pairs of interest for PET, RNGs currently in use in clinical PET, and identify the potentially useful RNGs which have made substantial progress or are likely to be used in daily clinical practices in the near future. Availability of the parent radionuclides required for PET RNGs is an important criterion and hence their production will also be reviewed. This overview outlines a critical assessment of RNGs to avail PET tracers, the contemporary status of RNGs, and key challenges and apertures to the near future.

**Keywords:** Bifunctional chelator (BFC), coronary artery disease (CAD), parent/daughter radionuclide, positron emission tomography (PET), radionuclide generator (RNG), radiopharmaceuticals

## Introduction

The role of PET to enable *in vivo* visualization of physiological processes on the molecular level in real time and quantify them by measuring regional concentration of the radiotracer for diagnosing disease, monitoring disease progression, and tracking therapeutic response, hardly needs to be reiterated [1-12]. This momentous molecular imaging paradigm, straddling the disciplines of molecular biology and medical imaging technology, has not only brought a perpetual shift in healthcare practice but also heralds a significant leap forward in treatment outcomes [13-15]. Growth in the field of PET has been phenomenal and will continue in the foreseeable future. The expanding role of PET in nuclear medicine (NM) procedures has led to an exponential growth of the

research and development (R&D) efforts around the world. The driving force behind the success has been largely due to the rapid ascent of the positron emission tomography-computed tomography (PET/CT) system which offers anatomic (CT) as well as metabolic (PET) information, in addition to providing data for attenuation correction [16, 17]. While the utility of PET/CT lives at the interface between many scientific disciplines, cost effective availability of PET tracers of required quality and quantity is a key determinant that underpins survival, strength, and success of the modality. Currently,  $^{18}\text{F}$ ,  $^{15}\text{O}$ ,  $^{13}\text{N}$  and  $^{68}\text{Ga}$  are the most commonly used PET tracers, among which  $^{18}\text{F}$  has dominated significantly and has been regarded as the workhorse of PET in clinics [3, 6, 12, 18-22]. Reflecting on the last decade of development on PET, one can clearly see the impact of  $^{18}\text{F}$

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which was blended into a number of formulations to improve current imaging practices and overall performance. Although the use of these tracers in clinical PET constitutes successful advancement in the field and heralds a new era of molecular imaging, the requirement of an onsite cyclotron to produce these tracers, due to their short half-life, has emerged as the major impediment that continues to thwart efforts for their widespread use in daily NM routines. In this context, the prospect of accessing PET tracers through an RNG seems to be a promising proposition as it enables PET examinations at remote hospitals and at the same time offers the prospect of enriching the PET radiotracer arsenal at the medical centers both with and without onsite cyclotrons. The tremendous prospects associated with the use of RNGs, along with the challenge of providing PET tracers of requisite quality for a variety of NM diagnostic procedures, have led to a considerable amount of fascinating research and innovative strategies, the flow of which shows no sign of diminishing. With the aim of obtaining PET tracers in an acceptable chemical form amenable for the formulation of radiopharmaceuticals through the use of an RNG, essentially every conceivable strategy has been exploited.

Rapid and burgeoning research interests in the use of RNGs in PET have been the driving force to provide a detailed review on this subject, in an attempt to stimulate interest in this exciting field. In order to improve the utility of RNGs in PET, it is of utmost importance to nurture emerging RNG technologies in an appropriate manner to facilitate their transition from laboratory research to the clinical settings. The aim of this article is thus to provide an overview of RNGs to avail PET radiotracers which are currently in use in clinical practice, or which have made substantial progress or are likely to be materialized in the foreseeable future. In the following sections, we provide a detailed coverage on the different types of RNGs available to obtain PET tracers, their contemporary status, and their aperture to the near future. Given the multi-disciplinary field, speculative options reported mainly of academic interest are not included and the authors apologize for possible oversights of important contributions. This review is intended to serve as a resource for the researchers and to offer an impetus for further development, as well as to become famil-

iar with the expectations, capabilities, constraints, and gratification involved in the development of RNGs for today and tomorrow.

### Radionuclide generator

A RNG 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 the parent radionuclide [23-29]. The parent/daughter nuclear relationships offer the possibility of separating the daughter radionuclide at repeated time intervals [30]. The inherent determinant for the success of RNGs resides with the selection of parent/daughter pairs and appropriate radiochemical separation strategies, which are based on a number of considerations [31]. Overviews of the principle, criteria for selection of parent/daughter pairs, and growth and equilibrium of the daughter radionuclide with parent radionuclide have been elaborately discussed in detail in recent reviews [26, 30-32]. The striking diffusion and the exciting perspective of RNGs in NM are mainly attributed to the following causes:

RNGs ensure onsite availability of PET tracers on demand and without reliance on an onsite accelerator, thereby, representing a cost-effective proposition for the onsite formulation of radiopharmaceuticals.

Offer the prospect of availing PET tracers in no-carrier-added (NCA) form.

Provides the flexibility to perform multiple studies, due to ready availability of multiple doses of PET tracer on-demand.

Constitute the only on-site option of availing certain short-lived radionuclides ( $^{82}\text{Rb}$ ) which cannot be shipped as with commercial sources.

Several requirements need to be fulfilled for effective separation of the daughter radionuclide, and in general the process should be fast, reproducible and provide the daughter radionuclide of required radionuclidic, radiochemical and chemical purity with a high radiochemical yield [23-27, 29-32]. A wide range of separation procedures, each with different characteristics, are currently being used or can potentially be used for RNG technology. Overviews of

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**Table 1.** Key examples of RNGs to provide positron emitting radionuclides with potential for PET imaging

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

radiochemical separation processes with respect to RNGs are elaborated in recent reviews [26, 27, 31, 32]. In-growth of the daughter radionuclide is continuous and depends on its half-life as well as the frequency of separation. For practical considerations, RNGs are eluted at periodic intervals, depending on the daughter activity requirements.

**Table 1** presents examples of RNG systems capable of providing positron-emitting daughter nuclides relevant for quantitative PET. Generator produced, short half-life PET radionuclides (on the order of minutes) do not allow for radiochemical synthesis and are mainly used for characterizing the faster kinetics of smaller tracer molecules. The longer-lived PET radionuclides are better suited to studying the slower kinetics of labeled peptides, antibodies and cells.

### Potentially useful PET RNGs for biomedical applications

The interest in RNGs will vary according to the scenarios considered. The following section provides an overview of the potential RNGs that could be used to avail PET tracers for clinical and research needs.

#### $^{68}\text{Ge}/^{68}\text{Ga}$ generator

In recent years, the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator has evoked excitement among radiopharmaceutical researchers and captured the imagination of NM physicians, thanks to recent progress in

PET instrumentation, hybrid imaging modalities, and advances in molecular and cellular biology [33-40]. The parent  $^{68}\text{Ge}$  ( $t_{1/2} = 270$  d) radionuclide decays by EC to  $^{68}\text{Ga}$  ( $t_{1/2} = 68$  min) which subsequently decays to stable  $^{68}\text{Zn}$  via positron emission and electron capture (branching ratios:  $\beta^+ = 89\%$ , EC = 11%). The nuclear transitions are also accompanied by low intensity gamma emission [ $E_{\gamma} = 1077$  keV (3%)]. Decay characteristics of the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator are depicted in **Figure 1**.

The use of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators in PET is very attractive for the following reasons:

The 270-day half-life of  $^{68}\text{Ge}$  ensures the ability to use the generator for extended periods, potentially up to 1 year or longer.

The decay characteristics of the short-lived daughter  $^{68}\text{Ga}$  ( $t_{1/2} = 68$  min, 89%  $\beta^+$  and 11% EC,  $E_{\beta^+, \text{max}} = 1.92$  MeV) are convenient for PET imaging.

With a physical half-life of 68 min,  $^{68}\text{Ga}$  also matches the biological half-life of many peptides used for imaging, due to their rapid diffusion, localization at the target and fast blood clearance.

The ability of  $^{68}\text{Ga}^{3+}$  to form stable complexes with many ligands containing oxygen and nitrogen as donor atoms offers the prospect for complexation with a wide variety of chelators, as well as some macromolecules having significant clinical potential.

Commercial  $^{68}\text{Ge}/^{68}\text{Ga}$  generators have a longer history than many people would believe. Although  $^{68}\text{Ge}/^{68}\text{Ga}$  generators have been investigated since 1960s, the chemical forms of generator derived  $^{68}\text{Ga}$  and the unacceptable level of  $^{68}\text{Ge}$  breakthrough emerged as the major obstacles that continued to thwart efforts for the development of gallium radiochemistry and the practical application. The first  $^{68}\text{Ge}/^{68}\text{Ga}$  RNG based on liquid-liquid extraction technology, using acetyl-acetone in

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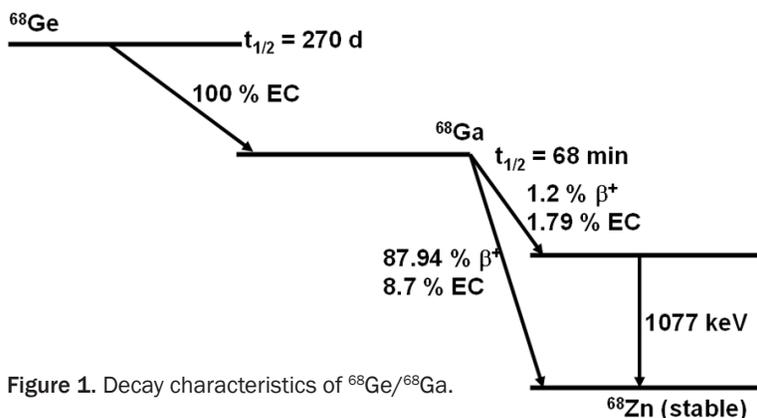


Figure 1. Decay characteristics of  $^{68}\text{Ge}/^{68}\text{Ga}$ .

cyclohexane, was described in 1960 [41]. Due to the inherent limitations of liquid-liquid extraction, and the requirement of three to four separation steps in order to obtain the requisite purity amenable for the preparation of  $^{68}\text{Ga}$  compounds for radiopharmaceutical applications, subsequent developmental efforts were directed toward the use of column chromatography techniques. The first  $^{68}\text{Ge}/^{68}\text{Ga}$  generator based on a column chromatography technique [42] consisted of an  $\text{Al}_2\text{O}_3$  matrix from which  $^{68}\text{Ga}$  was eluted as a strong  $^{68}\text{Ga}$ -EDTA complex using a 5-mM EDTA solution at pH 7.0. While the use of alumina based  $^{68}\text{Ge}/^{68}\text{Ga}$  generators is prolific in providing  $^{68}\text{Ga}$ -EDTA complex to measure the increased blood flow of brain tumors, it requires decomposition of the EDTA for the preparation of other  $^{68}\text{Ga}$ -radiopharmaceuticals because of the high stability of the complex ( $\log K = 21.7$ ). This extra step is not only cumbersome but also results in the loss of useful  $^{68}\text{Ga}$  radioactivity. In an attempt to mitigate this shortcoming, Kopecky et al. [43] eluted the column with 0.2 M HCl with a 48% elution yield. Malyshev et al. [44] used  $\text{ZrO}_2$ ,  $\text{SnO}_2$ , and  $\text{TiO}_2$  matrices and eluted  $^{68}\text{Ga}$  with either HCl,  $\text{HNO}_3$ , or  $\text{CH}_3\text{COOH}$  as eluents. Of the three-column matrices used,  $\text{ZrO}_2$  was found to be the best, in which  $^{68}\text{Ga}$  was eluted with 0.1 M HCl with 35% elution yield. Subsequently Arino et al. [45] used a polyantimonic acid column matrix and eluted  $^{68}\text{Ga}$  with 2% sodium oxalate. The poor elution yield of  $^{68}\text{Ga}$ , the toxicity of the eluent, and the presence of oxalic acid emerged as the major impediments that prevented clinical use without further chemical manipulation. A generator based on the tin dioxide/HCl couple has also been tried by Loc'h et al. [46]. In all these metal oxide

matrix-based systems, the release of column matrix due to limited solubility in the eluent constituted a major limitation which ruled out all possibility of clinical use. With the aim of circumventing this limitation, use of organic adsorbents and elution of  $^{68}\text{Ga}$  with dilute HCl or HF has also been tried, but met with limited success [47, 48]. McElvany et al., in 1984 [49], evaluated three  $^{68}\text{Ge}/^{68}\text{Ga}$  generators based on different metal oxide matrices

over a period of 1 year and compared their performances with respect to  $^{68}\text{Ga}$  elution profiles and yields, parent  $^{68}\text{Ge}$  breakthrough levels, amounts of column matrix contaminants present in the generator eluate, and the ease of  $^{68}\text{Ga}$ -radiopharmaceutical production. The ionic  $^{68}\text{Ge}/^{68}\text{Ga}$  generator utilizing a tin dioxide column eluted with 1 M HCl was found to be the most suitable for preparation of  $^{68}\text{Ga}$ -labeled compounds for use in conjunction with PET. In another embodiment,  $\alpha\text{-Fe}_2\text{O}_3$ , activated carbon, and graphite were tried [50], and it was found that  $\alpha\text{-Fe}_2\text{O}_3$ , having a  $^{68}\text{Ga}$  elution yield of 50-70% with a HCl solution of pH 2.0, was the most suitable. In spite of the great publicity received by  $^{68}\text{Ga}$  imaging, its impact in NM started to fade in the late 1970s due to the commercial non-availability of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators adaptable to the syntheses of a wide range of  $^{68}\text{Ga}$  radiopharmaceuticals, in comparison to the parallel and rapid developments of several new classes of radiopharmaceuticals based on  $^{99\text{m}}\text{Tc}$  and  $^{18}\text{F}$ . While the utility of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators for clinical  $^{68}\text{Ga}$  imaging would be in hibernation for decades, the foundation needed to build to the next level has been well established and separation procedures developed for the isolation of  $^{68}\text{Ga}$  from  $^{68}\text{Ge}$  with HCl solutions proved to be fertile ground for the realization of a generator for direct application in a clinical context.

The first commercial  $^{68}\text{Ge}/^{68}\text{Ga}$  generator based on a modified  $\text{TiO}_2$  solid phase support is the product of years of hard work by scientists of Cyclotron Ltd, Obninsk, Russian Federation [51]. Each generator contains  $^{68}\text{Ge}$  activities of up to 3.7 GBq from which "ionic"  $^{68}\text{Ga}^{3+}$  can be availed in 0.1 N HCl solution with ~80% initial

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**Table 2.** Types of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators

Years	Generator type	Remarks
1960-1970	liquid-liquid extraction	Tedious time consuming separation; not amenable for hospital radiopharmacy.
1970-2000	Column chromatography system based on $\text{Al}_2\text{O}_3$ and EDTA as eluent	This system served as a convenient and economical source of $^{68}\text{Ga}$ -EDTA; clinical use was limited to measure increased blood flow of brain tumors, in particular.
After 2000	Column chromatography system based on $\text{TiO}_2$ , $\text{ZrO}_2$ , $\text{CeO}_2$ , $\text{SnO}_2$ or an organic resin	$^{68}\text{Ga}$ is availed in an ionic form, with elution yields 70% to 80%; $^{68}\text{Ge}$ breakthrough still in the range, 0.01-0.001%.

**Table 3.** Commercial  $^{68}\text{Ge}/^{68}\text{Ga}$  generators

Manufactures	Type	Year	Column matrix	Eluent	Elution yield	$^{68}\text{Ge}$ breakthrough
Eckert & Ziegler AG, Berlin, Germany	Obninsk	1996	$\text{TiO}_2$	0.1 M HCl	60-75%	< 0.01%
	IGG100	2008	$\text{TiO}_2$	0.1 M HCl	70-75%	< 0.001%
iThemba, South Africa		2008	$\text{SnO}_2$	0.6 M HCl	80%	< 0.002%
ITG Garching, Germany		2010	Silica based organic matrix	0.05 M HCl	> 80%	< 0.005%



$\text{TiO}_2$   
column matrix  
Cyclotron Company,  
Russia, 1996



$\text{TiO}_2$   
column matrix  
Eckert and Ziegler,  
Germany, 2008



$\text{SnO}_2$   
column matrix  
iThemba Laboratory,  
South Africa, 2008



$\text{SiO}_2$ -based resin  
column matrix  
Isotope Technologies  
Garching,  
Germany, 2010

**Figure 2.** Commercially available  $^{68}\text{Ge}/^{68}\text{Ga}$  generators according to column matrix, manufacturers and the year of introduction to the market.

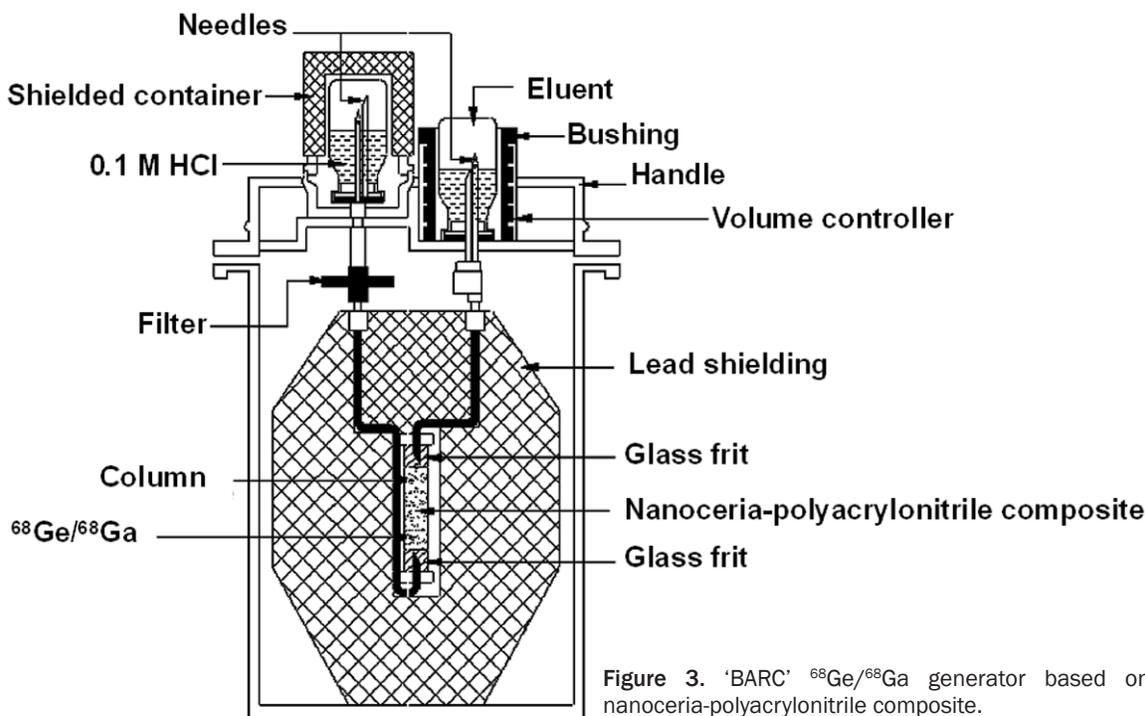
$^{68}\text{Ga}$  elution yields and with a  $^{68}\text{Ge}$  breakthrough of about  $1 \times 10^{-3}\%$ .

Commercial success of this generator, together with the advancement in imaging techniques, drew new players to enter the market.  $^{68}\text{Ge}/^{68}\text{Ga}$  generator development during the last few decades is briefly summarized in **Table 2**. Currently, four different  $^{68}\text{Ge}/^{68}\text{Ga}$  generators are commercially available and only a few of them (Eckert & Ziegler; iThemba Labs) hold license for good manufacturing practice (GMP)

production. It is pertinent to mention that a draft monograph, "Gallium ( $^{68}\text{Ga}$ ) chloride solution for radiolabeling", commensurate with the regulatory requirements for quality and patient safety, is available [52]. Characteristics of major commercial  $^{68}\text{Ge}/^{68}\text{Ga}$  generators available today for use in NM centers are tabulated in **Table 3** and shown in **Figure 2**.

Despite remarkable advancements, the low radioactive concentration, high  $[\text{H}^+]$  burden,  $^{68}\text{Ge}$  breakthrough, and the presence of poten-

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**Table 4.**  $^{68}\text{Ga}$  labeled radiopharmaceuticals substituting  $^{99\text{m}}\text{Tc}$

Diagnosics modality	Established $^{99\text{m}}\text{Tc}$ labeled agents	Potential $^{68}\text{Ga}$ labeled agents
Peptide receptors	$^{99\text{m}}\text{Tc}$ -HYNIC-peptide	$^{68}\text{Ga}$ -DOTA-peptide
Bone metastases	$^{99\text{m}}\text{Tc}$ -MDP	$^{68}\text{Ga}$ -phosphonates
Renal function	$^{99\text{m}}\text{Tc}$ -DTPA/MAG3/DMSA	$^{68}\text{Ga}$ -EDTA
Cardiac function	$^{99\text{m}}\text{Tc}$ -RBC/MIBI	$^{68}\text{Ga}$ -BAPEN
Lung function	$^{99\text{m}}\text{Tc}$ -MAA	$^{68}\text{Ga}$ -MAA
Hepatobiliary	$^{99\text{m}}\text{Tc}$ -IDA	$^{68}\text{Ga}$ -IDA
Infection	$^{99\text{m}}\text{Tc}$ -WBC	$^{68}\text{Ga}$ -citrate
Brain imaging (perfusion)	$^{99\text{m}}\text{Tc}$ -ECD	$^{68}\text{Ga}$ -ECD

tial metal ions such as Al, Fe, Cu, Zn, Ti or Sn from generator eluate have emerged as the major deterrents in the path of direct labeling of  $^{68}\text{Ga}$  to make radiotracers from generator availed  $^{68}\text{Ga}$ . Although the concentrations of these metallic impurities are low ( $\sim$  ppm level), their concentration can still be much higher than that of NCA  $^{68}\text{Ga}^{3+}$ , impeding efforts for the preparation of  $^{68}\text{Ga}$ -labeled radiopharmaceuticals. Most of the commercially available  $^{68}\text{Ge}/^{68}\text{Ga}$  generator systems demonstrate deteriorating performance in terms of increased  $^{68}\text{Ge}$  breakthrough and reduced  $^{68}\text{Ga}$  elution yields on repeated elutions over prolonged periods of time [53, 54]. In order to circumvent such limitations, a variety of post-elution purifi-

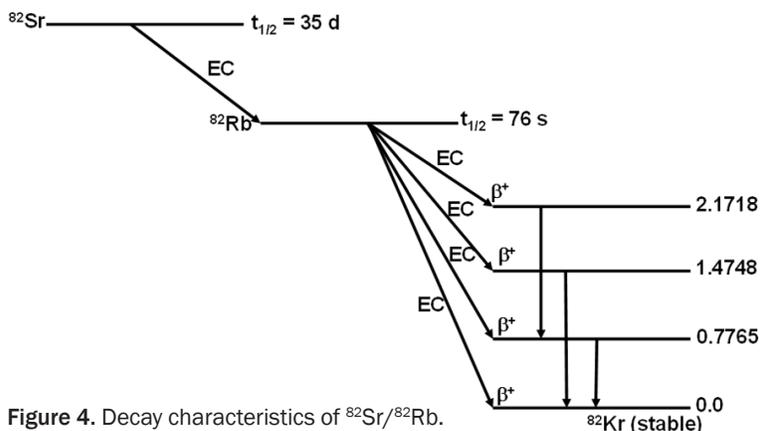
cation and/or concentration procedures based on (1) anion-exchange chromatography, (2) cation-exchange chromatography and (3) solvent extraction have been developed to obtain  $^{68}\text{Ga}$  of acceptable radionuclidic purity and radioactive concentration [53-59]. Among them, the chromatographic procedure reported by Zhernosekov et al. [54], based on selective tr-

apping of  $^{68}\text{Ga}$  eluate on a cation-exchanger, followed by elution in a small volume of acetone-HCl mixture, was a major step and has reached the stage of commercial exploitation. The trace level of acetone present in the final reaction mixture could be averted by making use of the column-based radiochemical procedure reported by Loktionova et al. [57]. Even though there is no technical impediment to adapt this efficient and robust procedure, the requirement of an automated module is viewed as a necessary one not only to minimize the decay loss of  $^{68}\text{Ga}$  but also to reduce the radiation exposure. Nevertheless, the scope of using this technique is restricted to  $\text{TiO}_2$  and organic-resin based generators due to the explicit need

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**Table 5.**  $^{68}\text{Ga}$  labeled radiopharmaceuticals substituting  $^{18}\text{F}$ ,  $^{11}\text{C}$  labeled compounds

Diagnostics modality	Established $^{11}\text{C}/^{18}\text{F}$ labeled agents	Potential $^{68}\text{Ga}$ labeled agents
Angiogenesis	$^{18}\text{F}$ -galacto-RGD	$^{68}\text{Ga}$ -DOTA-RGD, $^{68}\text{Ga}$ -VEGF
General cancer imaging	$^{18}\text{F}$ FDG	$^{68}\text{Ga}$ -CXCR4 biomarker, $^{68}\text{Ga}$ -uPAR biomarker, $^{68}\text{Ga}$ -SCN-NOTA-BZA
Hypoxia	$^{18}\text{F}$ -nitroimidazoles (FAZA, FMISO, FETNIM)	$^{68}\text{Ga}$ -DOTA-imidazoles
Proliferation	$^{18}\text{F}$ FLT	$^{68}\text{Ga}$ -DO3A-thymidine
Glioma	$^{18}\text{F}$ FET, $^{11}\text{C}$ -methionine	$^{68}\text{Ga}$ -glutamine, $^{68}\text{Ga}$ -DO3A-alanine, $^{68}\text{Ga}$ -DO2A-tyrosine
Prostate cancer	$^{18}\text{F}$ FDG, $^{11}\text{C}$ -acetate, $^{18}\text{F}$ -choline, $^{11}\text{C}$ -choline	$^{68}\text{Ga}$ -DOTA-PSMA



**Figure 4.** Decay characteristics of  $^{82}\text{Sr}/^{82}\text{Rb}$ .

[63]. A schematic diagram of the 'BARC'  $^{68}\text{Ge}/^{68}\text{Ga}$  generator is shown in **Figure 3**. Over the years, the 'BARC'  $^{68}\text{Ge}/^{68}\text{Ga}$  generator has been effectively developed and refined for use in the preparation of  $^{68}\text{Ga}$  tracers, both for research and limited clinical use. A comprehensive quality assurance system is necessary to ensure that the quality of  $^{68}\text{Ga}$  available from the generator meets the standards for clinical use.

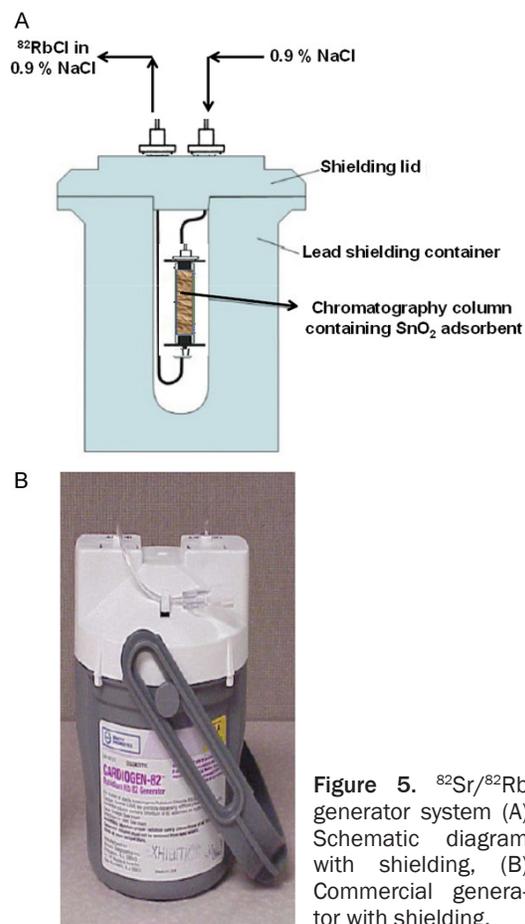
of primary  $^{68}\text{Ga}$  eluate in HCl concentration  $\leq 0.1$  N for effective sorption in the cation-exchange column. In the case of  $\text{SnO}_2$  based generators, where  $^{68}\text{Ga}$  is eluted in 0.6-1 N HCl, the aforementioned post-elution processing can be effectively adapted after appropriate dilution. Commercial availability of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators yielding the ionic form of  $^{68}\text{Ga}$ , along with a post-elution processing system, has led to the exploration of a broad spectrum of  $^{68}\text{Ga}$ -labeled products for use as radiopharmaceuticals for PET imaging of cancer [60].

The availability of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators providing  $^{68}\text{Ga}^{3+}$  of requisite quality amenable for direct radiolabeling is a much more desirable option. In this regard, the potential of the BARC-developed  $^{68}\text{Ge}/^{68}\text{Ga}$  generator, based on the nanoceria-polyacrylonitrile ( $\text{CeO}_2$ -PAN) composite [61, 62] sorbent, is capable of yielding  $^{68}\text{Ga}$  of requisite quality (free from metal ion impurities such as Al, Fe, Cu, Zn, Ti or Sn ions and very low  $^{68}\text{Ge}$  breakthrough) and without the need for any post-elution processing, and is poised to significantly expand the scope of  $^{68}\text{Ga}$  products formulation in radiopharmacy. Based on a similar strategy, a nano zirconia based  $^{68}\text{Ge}/^{68}\text{Ga}$  generator has also been developed, which demonstrates comparable performance

$^{68}\text{Ga}$  is exclusively in the oxidation state III in aqueous solution as well as at physiological pHs. In light of the perceived need to preclude the formation of insoluble  $\text{Ga}(\text{OH})_3$  and soluble  $\text{Ga}(\text{OH})_4^-$ , synthesis of  $^{68}\text{Ga}$ -labeled radiopharmaceuticals is carried out in the presence of weakly coordinating ligands such as citrate, acetate, or oxalate, which dramatically reduce the kinetics of complex formation [64]. Gallium (III) is classified as hard Lewis acidic, and therefore binds to hard Lewis base donor atoms such as nitrogen and oxygen, generally to form six coordinate bonds in close to octahedral geometry. Several promising  $^{68}\text{Ga}$  tracers comprising of small molecules, large biomolecules, and particles, targeting biological activities such as proliferation, angiogenesis, and apoptosis are currently under preclinical and clinical investigation [37, 60, 65-73]. Given the very broad field and long history of  $^{68}\text{Ga}$  tracers, agents that are being tested in preclinical and clinical trials, which promise an exciting future in clinical PET, are included in this review.

While  $^{68}\text{Ga}$  has made significant inroads into the field of clinical PET and undergone phenomenal expansion and growth, one of the most rapidly expanding areas is the development of  $^{68}\text{Ga}$  labeled peptide-based agents for targeted imaging, of tumors in particular [60]. The use of

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**Figure 5.**  $^{82}\text{Sr}/^{82}\text{Rb}$  generator system (A) Schematic diagram with shielding, (B) Commercial generator with shielding.

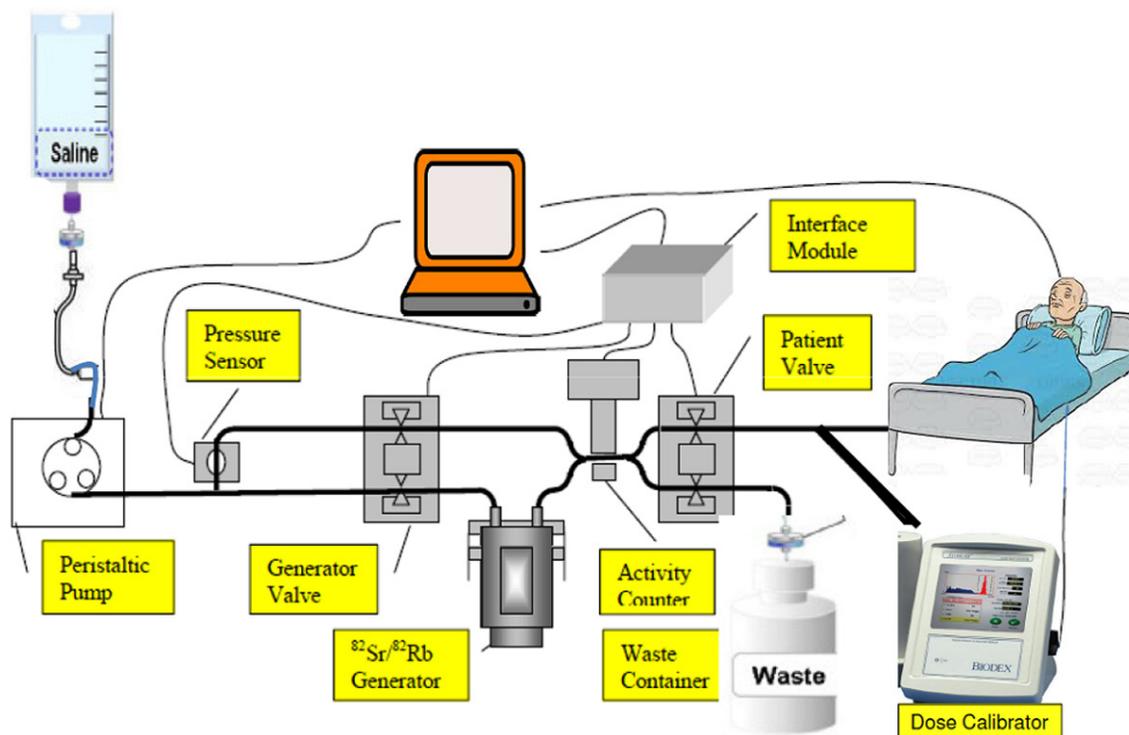
$^{68}\text{Ga}$  labeled small tumor-affine peptides targeting somatostatin receptors (SSTR) has not only changed the diagnostic approach to neuroendocrine tumors (NETs) such as pituitary adenoma, pancreatic islet cell tumor, carcinoid, pheochromocytoma, paraganglioma, medullary thyroid cancer, and small cell lung carcinoma, but also has unlocked the potential of these agents for molecular imaging applications [37, 38, 72, 74-78]. Among the SSTR agonists,  $^{68}\text{Ga}$ -labelled DOTA-conjugated somatostatin analogues have emerged as the breakthrough vector molecules owing to *in vivo* stability, favorable pharmacokinetics, and high and specific receptor-mediated tumor uptake [60]. They have proven to be increasingly useful due to several technical and biological advantages, such as fast clearance, rapid tissue penetration, and low antigenicity. The possibility of using  $^{68}\text{Ga}$ -labelled DOTA-conjugated somatostatin analogues for diagnosis is enticing, because the same compound labeled with  $^{90}\text{Y}$  or  $^{177}\text{Lu}$  can be used for therapy as a theranostic paradigm. This not only provides the prospect for

better planning of therapy but also offers the opportunity to evaluate the therapeutic outcome, as in personalized medicine. This will allow for dosimetry before therapy to ensure the optimum balance between risk and benefit by enabling prediction and avoidance of potential radiotoxicity. The Society of Nuclear Medicine and Molecular Imaging (SNMMI) announced on November 18, 2013 that,  $^{68}\text{Ga}$ -DOTATOC has been officially designated an orphan drug by the U.S. Food and Drug Administration for the management of neuroendocrine tumors (NET) [79]. This is considered as a potential step in right direction that will contribute not only to potentially faster regulatory approval but to streamlined clinical trials.

The currently available data for potential use of other  $^{68}\text{Ga}$ -labeled peptide analogs as PET tracers are mainly preclinical and limited human studies have been carried out. In this context,  $^{68}\text{Ga}$ -labeled DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH<sub>2</sub> peptide (BAY86-7548), having a high affinity for the bombesin receptor subtype II for the detection of primary and metastatic prostate carcinoma, merits attention [80, 81]. Integrin  $\alpha_v\beta_3$  is an important member of receptor family and expressed preferentially on regenerative vascular endothelial cells and some tumor cells. Preliminary clinical studies indicate that integrin is an effective target for detecting intra-prostatic prostate cancer [82].  $^{68}\text{Ga}$ -labeled  $\alpha_v\beta_3$  integrin-targeting  $^{68}\text{Ga}$ -c[Lys-(NOTA)-Arg-Gly-Asp-D-Phe] is one of the radiolabeled arginine-glycin-aspartic acid (RGD) peptides for which initial clinical data are available. A biodistribution and radiation dosimetry study containing 10 patients having lung cancer or lymphoma showed that the excretion route with the highest activity was found to be the renal pathway. A clinical trial on  $^{68}\text{Ga}$ -BNOTA-PRGD<sub>2</sub> [ $^{68}\text{Ga}$ -p-SCN-Bn-NOTA-PEG3-RGD<sub>2</sub>] through intravenous injection of a single dose of nearly 111 MBq ( $\leq 40 \mu\text{g}$  BNOTA-PRGD<sub>2</sub>), is in progress to investigate post-myocardial infarction and post-stroke repair. Preliminary clinical studies indicate that  $^{68}\text{Ga}$ -PRGD<sub>2</sub> uptake was found at or around the ischemic region in both MI and stroke patients, and significantly correlated with the disease phase and severity [83].

Urea-based low-molecular-weight peptidomimetic inhibitors of the prostate-specific membrane antigen (PSMA), a which is a cell surface

## Radionuclide generators for PET imaging



**Figure 6.** Schematic representation of  $^{82}\text{Rb}$  infusion system that can control concentration of  $^{82}\text{Rb}$  activity administered to the patient, perform quality assessment and flush the activity from the patient line at the end of the infusion.

protein and is expressed at higher levels in prostate cancer compared to other tissues, constitute a promising target for specific imaging due to the protein's transmembrane location and internalization after ligand binding [84-86].  $^{68}\text{Ga}$ -Glu-NH-CO-NH-Lys-(Ahx) [ $^{68}\text{Ga}$ -PSMA-11] has emerged as an attractive agent currently used in clinical studies for the detection of recurrent prostate cancer and metastatic spread [86].

The enormous success of  $^{68}\text{Ga}$ -labelled peptides served as a springboard to spur the development of other  $^{68}\text{Ga}$ -labelled radiopharmaceuticals, which is primarily based on two main trends. First is the technetium "shake and shoot" concept, which primarily relied on the substitution of  $^{68}\text{Ga}$  in lieu of  $^{99\text{m}}\text{Tc}$  in the preparation of radiopharmaceuticals. Some of the  $^{68}\text{Ga}$  labeled radiopharmaceuticals which can be substituted for  $^{99\text{m}}\text{Tc}$  are shown in **Table 4**. A few examples of this type include the use of commercially available phosphonate kits for bone scintigraphy of lesions, MAA (macroaggregated human serum albumin) particulate for perfusion studies,  $^{68}\text{Ga}$ -NOTA-MSA (mannosyl-

ated human serum albumin) for immune system imaging, and  $^{68}\text{Ga}$ -BAPEN myocardial uptake as substitute for MIBI [87]. The second trend is the development of  $^{68}\text{Ga}$  labeled radiopharmaceuticals in place of  $^{18}\text{F}$  and  $^{11}\text{C}$  labeled compounds with an aim to achieve on-line cyclotron independence. These are elaborated in **Table 5**.

Several innovative radiopharmaceuticals labeled with  $^{68}\text{Ga}$  are under active investigation and it is anticipated that quite a few novel agents labeled with this positron-emitting radionuclide will be available in the near future [88, 89]. With expanding areas of application and growing interest in the use of  $^{68}\text{Ga}$  labeled radiopharmaceuticals, it is simply a matter of time until imaging of bone, sentinel lymph node, and/or lung ventilation/perfusion will be carried out routinely by  $^{68}\text{Ga}$ /PET-CT. Conspicuous harnessing of the  $^{68}\text{Ga}$  tracers in conjunction with their convergence with theranostics seems poised to bridge the quantitative diagnosis with subsequent therapeutic management. This bridging will benefit from therapeutic strategies aimed at the same or closely related processes

## Radionuclide generators for PET imaging



**Figure 7.** Photograph of the CardioGen-82 Infusion System along with various part of the system.

and may be of great value for supporting and strengthening the concept of personalized medicine. It is time to bring this innovative paradigm changing concept out of the shadows and into the light.

### $^{82}\text{Sr}/^{82}\text{Rb}$ generator

There is a great deal of interest on the use of  $^{82}\text{Sr}/^{82}\text{Rb}$  generators to avail  $^{82}\text{Rb}$  for clinical myocardial perfusion PET investigations.  $^{82}\text{Rb}$  is the first of the generator-produced positron emitters that made its entry into clinical NM.  $^{82}\text{Rb}$ , with a half-life of 76 s, decays by positron emission into stable  $^{82}\text{Kr}$ , which is a noble element and is therefore non-reactive and safe for biological use. Decay characteristics of the  $^{82}\text{Sr}/^{82}\text{Rb}$  generator are depicted in **Figure 4**.

Being a cationic analogue of potassium with similar chemical and biological properties,  $^{82}\text{Rb}$  accumulates, as a function of blood flow, in cells of myocardium and other tissues in a manner similar to potassium. The myocardial uptake of  $^{82}\text{Rb}$  reflects blood flow through the myocardium. Compared with normal myocardi-

um, areas of ischemia or infarction exhibit low  $^{82}\text{Rb}$  uptake because of diminished blood flow and/or viability, and this is useful for qualitative infarct imaging and for the detection of coronary artery stenosis and characterization of the severity. Synthesis of  $^{82}\text{Rb}$  radiopharmaceuticals for diverse imaging applications is precluded not only by the relatively limited chemistry of the alkali metals, but also due to the short physical half-life of  $^{82}\text{Rb}$  [90]. The exciting perspective of  $^{82}\text{Sr}/^{82}\text{Rb}$  generators in clinical PET is attributed mainly due to the following:

The short half-life of  $^{82}\text{Rb}$  ( $t_{1/2} = 76$  s) enables rapid rest/stress paired studies within a very short time (30-45 min), allowing for rest and stress imaging under virtually identical conditions and decreasing the total time required to scan each patient. This is convenient for the patient and permits high-throughput imaging and efficient use of the technology.

The ultra-short half-life of  $^{82}\text{Rb}$  presents limited radiation exposure to the patients (whole body dose of 5.5 mSv for 2.22 GBq) during investiga-

## Radionuclide generators for PET imaging

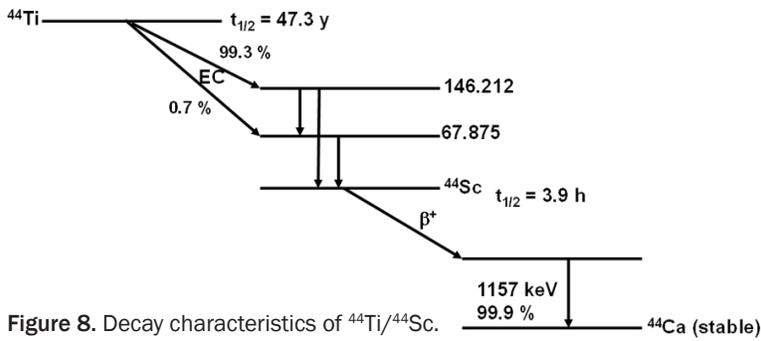


Figure 8. Decay characteristics of  $^{44}\text{Ti}/^{44}\text{Sc}$ .

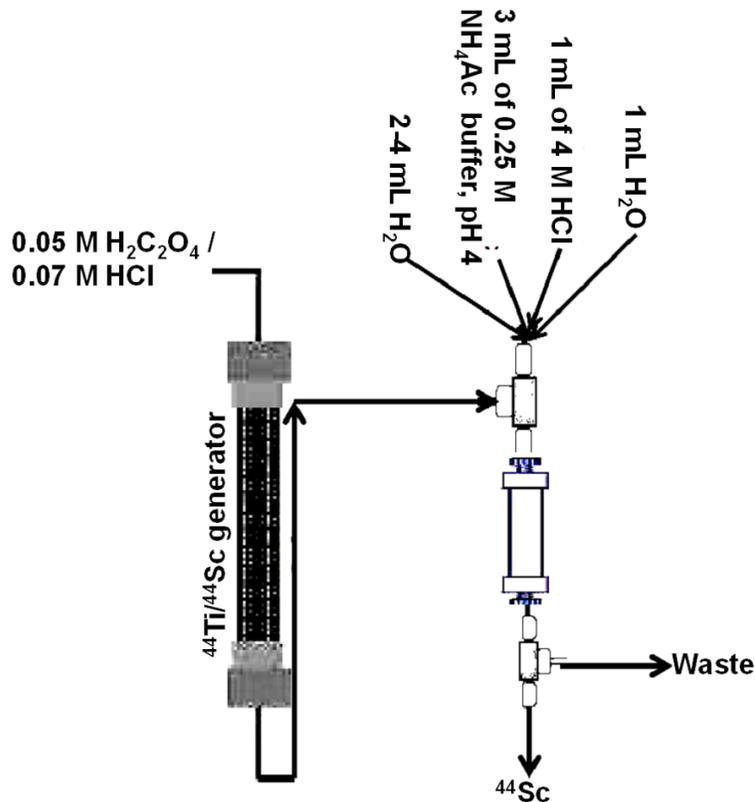


Figure 9. Post elution processing of  $^{44}\text{Sc}$  obtained from a  $^{44}\text{Ti}/^{44}\text{Sc}$  generator.

tion. The low-dose (10 MBq/kg) protocol allows simultaneous quantification of absolute flow, on 3D PET systems with adequate dynamic range to permit accurate measurement of the bolus first-pass activity, and measurement of ventricular function close to peak hyperemia with pharmacologic stress.

The suitably short physical half-life of  $^{82}\text{Rb}$  not only allows administration of high doses and short imaging times, but also offers the prospect of performing repeated and sequential perfusion studies within 20-minute intervals.

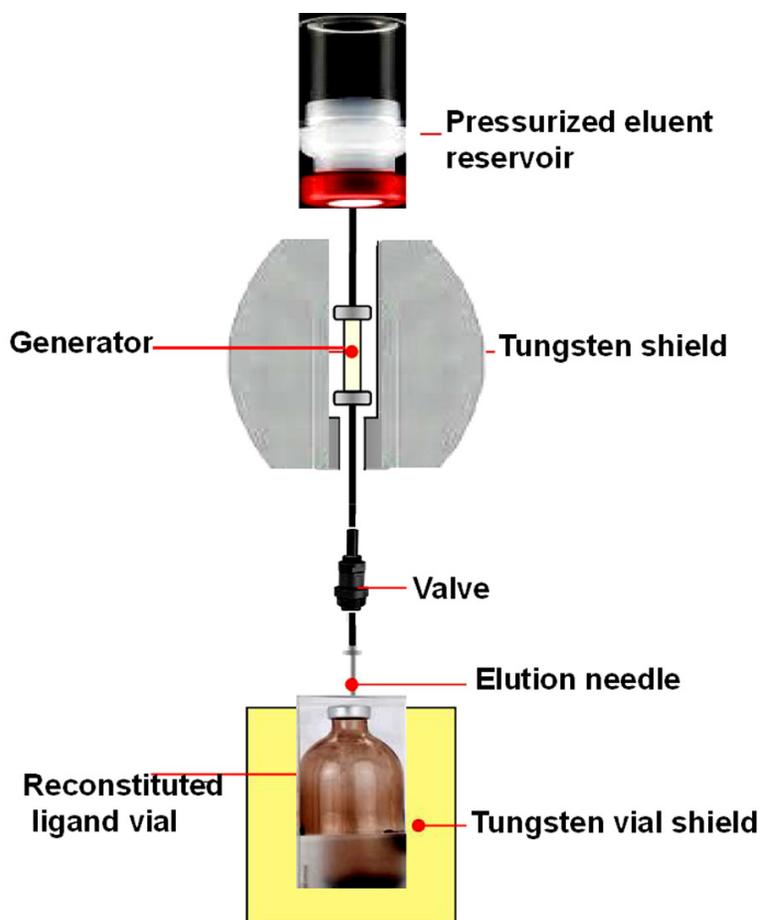
The 25.36 d half-life of parent radionuclide  $^{82}\text{Sr}$  is convenient for shipping and provides useful radioactivity in a generator for at least a month of frequent elutions.

Use of an RNG provides the scope to perform PET investigations in medical institutes without the necessity to maintain expensive cyclotron facilities.  $^{82}\text{Rb}$  has significant clinical potential and can be considered as a low-cost alternative to short-lived, cyclotron-produced PET isotopes.

$^{82}\text{Rb}$  is extracted from the plasma with high efficiency by myocardial cells via the  $\text{Na}^+/\text{K}^+$  ATPase pump [91]. While the myocardial extraction of  $^{82}\text{Rb}$  is similar to that of  $^{201}\text{Tl}$ , it is slightly less than  $^{13}\text{NH}_3$ . The uptake of  $^{82}\text{Rb}$  is a function of blood flow, metabolism, and myocardial cell integrity. Cardiac PET using  $^{82}\text{Sr}$  possesses several advantages over traditional SPECT, with direct patient centric benefits including the accurate, diagnosis of coronary artery disease in asymptomatic or symptomatic patients, assessment of coronary stenosis severity, myocardial infarct imaging, evaluation of myocardial viability, collateral function, and cardiomyopathy.

In 1989 the United States Food and Drug Administration (FDA) approved the use of  $^{82}\text{RbCl}$  available from a commercial  $^{82}\text{Sr}/^{82}\text{Rb}$  generator system trade name CardioGen-82, which has been available from Bracco Diagnostics Inc. for some years. This generator is composed of a small chromatography column [ $\sim 4$  cm (l)  $\times$  0.5 cm ( $\Phi$ )] containing hydrous  $\text{SnO}_2$  housed in a lead shielding container. A schematic diagram of the  $^{82}\text{Sr}/^{82}\text{Rb}$  generator system is depicted in Figure 5. When the column is flushed with a solution, such as 0.9% NaCl saline, the  $^{82}\text{Rb}^+$  is displaced by  $\text{Na}^+$  and is eluted. Quality control

## Radionuclide generators for PET imaging



**Figure 10.** Schematic diagram of  $^{62}\text{Zn}/^{62}\text{Cu}$  generator to avail  $^{62}\text{Cu}$  for radiopharmaceuticals formulation.

of the generator eluate includes  $^{82}\text{Sr}$  breakthrough measurements using a dose calibrator and pyrogen tests of the eluate.

As the  $^{82}\text{Rb}$  supply is 90% replenished within 5 to 10 minutes of the previous elution, serial studies can be performed in rapid succession, maximizing patient throughput. There appeared to be enticing interest in the use of an automated infusion system to administer the  $^{82}\text{Rb}$  eluted from the  $^{82}\text{Sr}/^{82}\text{Rb}$  generator directly to patients, in light of the short half-life of  $^{82}\text{Rb}$  and the decreasing amount of available  $^{82}\text{Rb}$  as the generator ages [92]. In the quest for an effective strategy to avail consistent levels of  $^{82}\text{Rb}$  activity from the  $^{82}\text{Sr}/^{82}\text{Rb}$  generator, Klein et al. have developed an automatic infusion system [93]. A schematic representation of such a conceptual  $^{82}\text{Rb}$  infusion system that can control the concentration of  $^{82}\text{Rb}$  activity administered to the patient, perform quality

assessment, and flush the activity from the patient line at the end of the infusion is shown in **Figure 6**.

Automated  $^{82}\text{Rb}$  infusion systems capable of accurate measurement and delivery of adequate doses of  $^{82}\text{RbCl}$  from a  $^{82}\text{Sr}/^{82}\text{Rb}$  generator have been developed by Bracco Diagnostics, NJ, USA (CardioGen-82 Infusion System) and Jubilant DraxImage Inc, Canada (Ruby-Fill™ Infusion System).  $^{82}\text{Rb}$  is eluted from the generator by a computer-regulated elution pump and infused directly into patients using commercially available IV infusion system. Use of these systems substantially reduces the radiation dose, ensures optimum performance of the  $^{82}\text{Sr}/^{82}\text{Rb}$  generator, and provides a log of the  $^{82}\text{Rb}$  activity infused into the patients. These developments are considered as successful steps forward in the promotion of widespread clinical use of  $^{82}\text{Rb}$ . A photograph of the CardioGen-82

Infusion System, along with various part of the system, is shown in **Figure 7**. Such  $^{82}\text{Rb}$  infusion systems clearly outperform conventional infusion systems or semi-automated systems, and their usefulness has been convincingly proven. Commercial availability of automated  $^{82}\text{Rb}$  infusion systems has a far-reaching effect on realizing the full promise and potential of  $^{82}\text{Rb}$  in the diagnosis of coronary artery disease (CAD) and is poised to bring functional imaging to the forefront in cardiac PET imaging.

$^{82}\text{Rb}$  permits clinical imaging with short protocols (20-30 min in total) and a high patient throughput, providing better image quality and overall sensitivity in the diagnosis of coronary artery disease (CAD) as compared to myocardial scintigraphy with  $^{201}\text{Tl}$  or  $^{99\text{m}}\text{Tc}$ -based radiotracers [94-96]. It also offers the potential for deriving absolute quantification of myocardial blood flow (MBF) [97]. New approaches to

## Radionuclide generators for PET imaging

**Table 6.** Components of H<sub>2</sub>PTSM, H<sub>2</sub>ETS and H<sub>2</sub>TASM kits

Component	H <sub>2</sub> PTSM kit	H <sub>2</sub> ETS kit	H <sub>2</sub> TASM kit
Sodium acetate	4.3 mg	4.3 mg	4.3 mg
Acetic acid	3.1 mg	3.1 mg	3.1 mg
Sodium chloride	30 mg	30 mg	30 mg
Excipient	20 mg	20 mg	20 mg
Free ligand	2 µg	2 µg	0.4 µg
<sup>62</sup> Cu labeled ligand (per 555 MBq (15 mCi) dose)	2.3 × 10 <sup>-7</sup> mg	2.2 × 10 <sup>-7</sup> mg	2.4 × 10 <sup>-7</sup> mg

**Table 7.** Possible routes for the production of <sup>82</sup>Sr

Reaction	Target material	Projectile energy (MeV)	Comment
<sup>89</sup> Y (p, spallation) <sup>82</sup> Sr	Yttrium oxide	60-240	Low radiopurity & yield
<sup>Nat</sup> Mo (p, spallation) <sup>82</sup> Sr	Molybdenum metal	500-700	Low radiopurity, high cost
<sup>Nat</sup> Rb (p, xn) <sup>82</sup> Sr	RbCl or Rb metal	40-90	Preferred
<sup>Nat</sup> Kr (α, pxn) <sup>82</sup> Sr	Kr gas	20-120	Low radiopurity, low yield, little availability
<sup>Nat</sup> Kr ( <sup>3</sup> He, xn)	Kr gas	20-90	Low radiopurity, low yield, very little availability

kinetic modeling and software tools for analysis of clinical <sup>82</sup>Rb studies are being developed and evaluated, which could enable quantification of absolute myocardial blood flow and flow reserve.

Use of generator availed <sup>82</sup>Rb in PET myocardial perfusion imaging has become far more accessible in daily practices, offers clinical feasibility of positron-based cardiac imaging without a cyclotron [98], and is poised to take a major leap forward to an exciting new stage. While the use of <sup>82</sup>Rb availed from <sup>82</sup>Sr/<sup>82</sup>Rb generators is a successful paradigm for the diagnosis of obstructive coronary artery disease (CAD) and has made considerable progress, the primary impediment for its widespread clinical use is the expense associated with <sup>82</sup>Sr production and the need for generator replacement at 3-5 week intervals. Conscientious utilization of the generator in high throughput will not only offset this cost but can foster sustainability. The improved accuracy of PET leads to total cost savings in CAD management in clinical practice by getting rid of unnecessary diagnostic and therapeutic procedures such as coronary arteriography and coronary artery bypass grafting (CABG). A number of studies have demonstrated the routine use of <sup>82</sup>Rb PET for myocardial perfusion imaging (MPI) at a cost similar to that for <sup>99m</sup>Tc SPECT [99]. With the advent of hybrid PET/CT driven by technological advances in medical imaging, there are a growing number of

centers using cardiac PET with <sup>82</sup>Rb [100] and this has greatly contributed to increasing acceptance of PET for clinical practice. This trend is expected to continue in the foreseeable future.

### <sup>44</sup>Ti/<sup>44</sup>Sc generator

The <sup>44</sup>Ti radionuclide (t<sub>1/2</sub> = 60.6 y) decays by electron capture (EC) to <sup>44</sup>Sc (t<sub>1/2</sub> = 3.97 h) which subsequently decays to stable <sup>44</sup>Ca. <sup>44</sup>Sc is also a positron emitter (β<sub>branch</sub><sup>+</sup> = 94.3 %) and is a valuable alternative to <sup>68</sup>Ga as a matched pair for radiotherapy. The use of <sup>44</sup>Sc with a half-life more than 3 times longer than that of <sup>68</sup>Ga (t<sub>1/2</sub> = 68 min) makes it a valuable alternative for diagnostic and dosimetry purposes. Decay characteristic of <sup>44</sup>Ti/<sup>44</sup>Sc system is shown in **Figure 8**.

The 3.97-hour half-life of <sup>44</sup>Sc is 3 times longer than that of <sup>68</sup>Ga and therefore it may be a useful alternative not only for diagnostic purposes but also for dosimetry studies and further therapy planning with the use peptides labeled with the β-emitting radionuclide such as <sup>177</sup>Lu or <sup>90</sup>Y as radiotherapeutic agents.

The 3.92-hour half-life of <sup>44</sup>Sc provides the ability to elute at 4 h interval with about a 50% elution yield. Hence, a 370 MBq (10 mCi) generator should be able to give 148-185 MBq (4-5 mCi) dose every four hours.

## Radionuclide generators for PET imaging

**Table 8.** Production details from the current suppliers of  $^{82}\text{Sr}$

Laboratory	Target	Irradiation conditions	Typical batch yield at EOB (GBq)
Brookhaven National Lab (BNL), NY, USA	RbCl pressed pellet in inconel	2 targets, 93-70 & 64-41 MeV	220-300 (5.9-8.1Ci)
Los Alamos National Lab (LANL), NM, USA	RbCl cast puck in inconel	2 targets, 97-71 & 65-45 MeV	300-450
Institute for Nuclear Research (INR), Troitsk Russia	Rb metal in stainless steel	100-40 MeV	120-220
iThemba Labs, Faure, S. Africa	Rb metal in stainless steel	66-44 MeV	100
Arronax, Nantes, France	RbCl pressed pellet in stainless steel	8 thin targets, 69-44 MeV	80-90
Nordion/TRIUMF, Vancouver Canada	Rb metal in stainless	60-48 MeV	60-100

**Table 9.** Possible ways for the production of  $^{72}\text{Se}$

Reaction	Energy Range (MeV)	Yield [ $\mu\text{Ci} (\mu\text{A}\cdot\text{h})^{-1}$ ]		
		$^{72}\text{Se}$	$^{73}\text{Se}$	$^{75}\text{Se}$
$^{75}\text{As} (\text{p}, 4\text{n})$	45-24	0.21	57	0.03
$^{75}\text{As} (\text{d}, 5\text{n})$	56-26	0.15	32	0.08
$^{\text{nat}}\text{Ge} (^3\text{He}, \text{xn})$	36	0.08	NR	NR
$^{70}\text{Ge} (^3\text{He}, \text{xn})$	36	0.22	NR	NR
$\text{Cu}_3^{\text{nat}}\text{Ge} (^4\text{He}, \text{xn})$	28-10	0.0005	0.09	0.0004
$\text{Cu}_3^{70}\text{Ge} (^4\text{He}, \text{xn})$	28-10	0.002	0.4	0.0003
$\text{K}^{\text{nat}}\text{Br} (\text{p}, \text{x})$	100-69	0.10	7.18	0.12
$\text{K}^{\text{nat}}\text{Br} (\text{p}, \text{x})$	62-42	0.05	2.36	0.03
$\text{Rb}^{\text{nat}}\text{Br} (\text{p}, \text{x})$	800	3.03	30.3	3.03

NR: Not reported.

The 60.6 years half-life of  $^{44}\text{Ti}$  offers long-term application without generator replacement.

Despite its high  $\beta^+$ -branching (94.3%),  $^{44}\text{Sc}$  shows an additional 99.9% photon emission of 1157 keV which is expected to be useful for nuclear medicine imaging using  $\beta$ - $\gamma$  coincidences.

The chemistry of  $^{44}\text{Sc}$  is similar to that of the lanthanides, and the “lanthanide like” elements. Hence chelators developed for the complexation of  $^{177}\text{Lu}$  and  $^{90}\text{Y}$  such as DOTA and DTPA analogs can also be used for the complexation of  $^{44}\text{Sc}$ .

While  $^{68}\text{Ga}$  labeled compounds have significant clinical potential and present a convenient, low-cost alternative to cyclotron-produced PET radiopharmaceuticals, the 68 min physical half-life of  $^{68}\text{Ga}$  limits the spectrum of clinical applications of  $^{68}\text{Ga}$ -labelled radiodiagnostics. In addition,  $^{68}\text{Ga}$ -labelled analogues of endoradiotherapeutics with longer biological half-lives, such as  $^{90}\text{Y}$ - or  $^{177}\text{Lu}$ -labeled peptides and proteins, cannot be used to determine individual radiation dosimetry directly. In this context, the notion of using generator-derived positron

emitters with longer physical half-lives, such as  $^{44}\text{Sc}$  ( $t_{1/2} = 3.97$  h), is deemed worthy of consideration.

While the outlook of  $^{44}\text{Ti}/^{44}\text{Sc}$  generator is promising, development of a generator amenable for clinical use will not be a trivial process and poses formidable scientific and technical challenges, such as effective separation strategies of availing optimum  $^{44}\text{Sc}$  elution yields and low  $^{44}\text{Ti}$  breakthrough, and selection of an appropriate eluent to obtain  $^{44}\text{Sc}$  in a chemical form suitable for subsequent radiolabeling

(i.e. high radioactive concentration (RAC), low pH, free from metallic impurities etc.). With an aim to tap the potential of  $^{44}\text{Ti}/^{44}\text{Sc}$  generator to avail  $^{44}\text{Sc}$  of requisite purity, several strategies have been explored [101] among which the method reported by Filosofov *et al.* [102] merits attention. This 185 MBq (5 mCi)  $^{44}\text{Ti}/^{44}\text{Sc}$  generator system has been studied in detail and has been successfully exploited for preclinical investigations.

The generator consists of a chromatography column containing Bio-Rad AG1  $\times$  8 (200-400 mesh, Br<sup>-</sup>-form), an anion-exchange resin, on to which purified  $^{44}\text{Ti}$  dissolved in 20 mL of 0.1 M  $\text{H}_2\text{C}_2\text{O}_4$  was loaded.  $^{44}\text{Sc}$  could be eluted with 20 mL of 0.005M  $\text{H}_2\text{C}_2\text{O}_4/0.07$  M HCl solution with > 97% elution yield and low  $^{44}\text{Ti}$  breakthrough ( $5 \times 10^{-5}\%$ ). The low RAC and the chemical composition of the generator eluate emerged as the major hindrances that thwarted efforts for fast, reliable and quantitative radiolabeling of nanomolar concentration of precursors. In order to enhance the RAC, fractionation of the elution of  $^{44}\text{Sc}$  was resorted to, but met with limited success, as the concentration of hydrochloric acid was too high for realizing direct radiolabeling.

## Radionuclide generators for PET imaging

With to the goal of enhancing RAC, reducing HCl concentration, and removing the oxalate anions, the prospect of using post elution processing was considered to be reliable and subsequently pursued [103]. In this procedure 0.005 M  $\text{H}_2\text{C}_2\text{O}_4$  / 0.07 M HCl solution was passed through the  $^{44}\text{Ti}/^{44}\text{Sc}$  generator to elute  $^{44}\text{Sc}$  adsorbs, which was again passed online through a small cation exchange column to retain  $^{44}\text{Sc}$ . The cation-exchange column was washed with 2-4 mL of  $\text{H}_2\text{O}$  to remove the remaining traces of the initial eluate solution.  $^{44}\text{Sc}$  retained by the cation exchange column was then eluted with 3 mL of 0.25 M ammonium acetate buffer, pH = 4.0. Reconditioning of the cation exchange cartridge was performed by passing 1 mL of 4 M HCl and finally by 1 mL  $\text{H}_2\text{O}$ . A schematic representation of the procedure is depicted in **Figure 9**. A 185 MBq (5 mCi) generator provides about 170 MBq of  $^{44}\text{Sc}$  after direct elution and about 150 MBq following online post-processing.

Scandium is chemically similar to  $\text{Y}^{3+}$  and lanthanides. While the ionic radius of  $\text{Sc}^{3+}$  (74.5 pm) is smaller than that of lanthanides, it is larger than any of the  $\text{M}^{3+}$  cations formed by the 3d transition metals. It has been established that  $\text{Sc}^{3+}$  in solution has a tendency to forms DOTA complexes with coordination number 8 and 9 similar to that  $\text{Y}^{3+}$  and  $\text{Lu}^{3+}$ , whereas  $\text{Ga}^{3+}$  forms 6 coordinated octahedral complexes [104].  $^{44}\text{Sc}^{3+}$  as a metallic cation is suitable for complexation with chelators alone or with BFCs (DOTA, DTPA, NOTA, etc) conjugated to peptides or other molecular targeting vectors similar to the currently-used, trivalent radionuclides such as  $^{68}\text{Ga}$ ,  $^{111}\text{In}$  or  $^{90}\text{Y}$  and  $^{177}\text{Lu}$  [105].

Recent studies on a series of polyamino-poly-carboxylate ligands has shown that Sc-8-dentate ethylene glycol-bis(2-aminoethylether)-N,N,N',N'-tetraacetic acid (EGTA) is a promising moiety for coupling  $^{47}\text{Sc}$  to proteins [106]. It has been demonstrated that DOTA is the most preferred chelator for  $^{44}\text{Sc}(\text{III})$  among a series of macrocyclic ligands [52]. All 4 amine and carboxyl groups of a DOTA chelator contribute to the complexation of  $^{44}\text{Sc}(\text{III})$ , resulting in a stability constant comparable to those of  $\text{Y}(\text{III})$  and lanthanides [52]. Also,  $^{44}\text{Sc}$ -DOTATATE has similar lipophilicity to that of  $^{177}\text{Lu}$ - and  $^{90}\text{Y}$ -DOTATATE [52]. Due to chemical similarity of  $\text{Sc}^{3+}$  with  $\text{Lu}^{3+}$  and  $\text{Y}^{3+}$  cations, it is anticipated that  $^{44}\text{Sc}$ -DOTA bioconjugates will have similar *in vivo* charac-

teristics (*i.e.* receptor affinity, kidney clearance) to the  $^{177}\text{Lu}$ - and  $^{90}\text{Y}$ -conjugates currently used in therapy.

The  $^{44}\text{Sc}$ -DOTA-conjugated tumor targeting vectors such as somatostatin analogs investigated so far are stable *in vitro* and *in vivo* [107, 108], and the data obtained reveal pharmacological parameters which are adequate for performing molecular imaging. Thus,  $^{44}\text{Sc}$  seems poised to become an alternative to  $^{68}\text{Ga}$  for imaging and dosimetry before  $^{177}\text{Lu}$ - or  $^{90}\text{Y}$ -radionuclide tumor therapy [101].

### $^{62}\text{Zn}/^{62}\text{Cu}$ generator

$^{62}\text{Cu}$  is a PET radionuclide with a half-life of 9.74 minutes, and decays 97.8% by  $\beta^+$  and 2.2% by EC to the ground state of stable  $^{62}\text{Ni}$ , with 99.6% of the  $\beta^+$  emissions having a 2.9 MeV positron  $E_{\text{max}}$  [109].

The 9.7 min half-life of  $^{62}\text{Cu}$  is long enough to facilitate radiopharmaceutical synthesis procedures and for image acquisition, while at the same time, it is short enough to afford favorable dosimetry.

The 9.7 min half-life of  $^{62}\text{Cu}$  enables serial imaging procedures in the same clinical visit without interference of  $^{62}\text{Cu}$  background activity from previous injections.

The versatile chemistry of copper provides the ability to prepare a wide range of  $^{62}\text{Cu}$ -labeled PET-radiopharmaceuticals for a variety of imaging applications.

The short half-life and high positron decay fraction (99.6%) of  $^{62}\text{Cu}$  make it suitable for characterizing the faster kinetics of smaller tracer molecules, such as Cu-PTSM or Cu-ATSM.

$^{62}\text{Cu}$  could be used as a PET-surrogate to therapeutic isotope  $^{67}\text{Cu}$ .

While the 9.7 min half-life of  $^{62}\text{Cu}$  restricts imaging to less than an hour following injection, this has the advantage of allowing several repeat scans in quick succession, which can be used to evaluate the response to a number of physiological or pharmacological stimuli.

The availability of  $^{62}\text{Zn}/^{62}\text{Cu}$  generators is often the ultimate limiting factor in realizing the benefit of  $^{62}\text{Cu}$ -radiopharmaceuticals. Evolution

## Radionuclide generators for PET imaging

and continued success of  $^{62}\text{Cu}$  in PET has been, in large part, due to development of the  $^{62}\text{Zn}/^{62}\text{Cu}$  generator (Figure 10). Advances in the development of  $^{62}\text{Zn}/^{62}\text{Cu}$  generator have contributed substantially to the deployment of  $^{62}\text{Cu}$ -radiopharmaceuticals in clinical PET.

Robinson et al. [110] prepared a  $^{62}\text{Zn}/^{62}\text{Cu}$  generator system based on "Dowex 1-X10" resin of 200-400 mesh [0.7 cm ( $\Phi$ )  $\times$  8.0 cm (l)] from which  $^{62}\text{Cu}$  could be eluted with 3.5 mL of 0.1 N HCl containing 100 mg/mL NaCl and 1  $\mu\text{g}/\text{mL}$   $\text{CuCl}_2$ , with 85% elution yield and with  $^{62}\text{Zn}$  breakthrough less than 0.001%. Fujibayashi et al. [111] has developed a generator based on a cation exchanger (CG-120, Amberlite), from which  $^{62}\text{Cu}$  is eluted in a glycine complex. While this system offers 70% elution efficiency, the  $^{62}\text{Zn}$  breakthrough was significantly high (2.2%). Zweit et al. [112] have developed a  $^{62}\text{Zn}/^{62}\text{Cu}$  generator based on anion-exchange resin from which  $^{62}\text{Cu}$  could be eluted in a solution of 0.3 M HCl/40% ethanol with greater than 90% elution yield in a 3-mL volume and with low  $^{62}\text{Zn}$  breakthrough ( $< 3 \times 10^{-7}\%$ ). Bormans et al. [113] have developed an improved  $^{62}\text{Cu}$ -generator system based on Dowex 1  $\times$  16, 200-400 mesh, from which  $^{62}\text{Cu}$  is eluted using a solution containing 1.7 M in NaCl/0.1 M in HCl. Fukumura et al. prepared an improved  $^{62}\text{Zn}/^{62}\text{Cu}$  using Sep-Pak plus CM cartridge, from which  $^{62}\text{Cu}$  was eluted with high elution efficiency (approximately 96%) using a small volume (ca. 3 mL) of a 200-mM glycine solution with a very low breakthrough of  $^{62}\text{Zn}$  ( $< 0.1\%$ ) [114]. El-Azony has reported a method based on a De-Acidite FF anion exchanger [115], from which  $^{62}\text{Cu}$  is eluted using a solution of 0.2 M HCl-60% acetone with an elution efficiency of 92.5%. As the 0.2 M HCl-60% acetone medium is unsuitable for medical use, it was evaporated and reconstituted in a chemical form suitable for radiolabeling.

The chemistry of copper is restricted to two principle oxidation states (I and II), and the relatively simple coordination and redox chemistry of copper is well documented [116]. Copper salts generally exists as  $[\text{Cu}(\text{OH})_6]^{2+}$  in aqueous solution. Compounds of the Cu(I) oxidation state are unstable in aqueous solution and readily oxidize to Cu(II) to form 4, 5, or 6 coordination bonds with ligands. The Cu(II) oxidation state has a pronounced tendency to form coordination

complexes with ligands that contain electron donor atoms, such as, N and S. Complex formation with chelating agents occurs at  $\text{pH} < 7$  since formation of insoluble  $\text{Cu}(\text{OH})_2$  at higher pH is a major concern [117]. The *in vivo* stability of the radio-copper complex is a critical factor for designing  $^{62}\text{Cu}$ -radiopharmaceuticals. Ligands that can form kinetically inert Cu(II) complexes are ideal since this is more significant than thermodynamic stability.

$^{62}\text{Cu}(\text{II})$  diacetyl-bis(N4-methylthiosemicarbazone), or  $^{62}\text{Cu}$ -ATSM, has emerged as an effective agent to image tissue hypoxia [118-120].  $^{62}\text{Cu}$ -ATSM is a neutral, lipophilic compound that can be readily diffuses into all the cells with perfusion. However, its structure changes due to the reduction of  $\text{Cu}^{2+}$  cation to  $\text{Cu}^+$  cation in hypoxic conditions resulting in accumulation in the hypoxic cell. The mechanism of  $^{62}\text{Cu}$ -ATSM retention in hypoxic tissues is ascribed mainly due to the low oxygen tensions and the subsequent altered redox environment of hypoxic tumors. Results from *in vivo* studies inferred that tissue Cu-ATSM uptake is dependent on oxygen concentration [121].  $^{62}\text{Cu}$ -ATSM has shown heterogeneous uptake in tumors with homogeneous perfusion images, strongly suggesting uptake reflecting hypoxic heterogeneity. Results from several studies demonstrated the utility of Cu-ATSM PET hypoxic imaging with improved prognosis and effectiveness of radiotherapy [122-128].

$^{62}\text{Cu}(\text{II})$  pyruvaldehyde bis(N4-methylthiosemicarbazone), or  $^{62}\text{Cu}$ -PTSM, is a promising tracer for myocardial, cerebral, renal, and tumor perfusion agents, and has attracted considerable interest [128-132].  $^{62}\text{Cu}$ -PTSM demonstrated a high, first-pass extraction along with prolonged tissue retention due to intracellular reductive decomposition of the lipophilic Cu-PTSM complex to liberate the  $^{62}\text{Cu}$  ion, with negligible washout from the myocardium cell, suggesting the ability of  $^{62}\text{Cu}$ -PTSM to quantify blood flow in organs such as the heart, brain, and kidneys [130, 133, 134].  $^{62}\text{Cu}$ -PTSM is reduced readily by the mitochondria, and is retained in most tissues, and thus can be used as a marker of tissue perfusion [135]. While Cu-ATSM and Cu-PTSM share the same molecular structural backbone, they have significantly different properties when utilized in PET imaging due to

the presence of an additional methyl group on the ligand backbone of Cu-ATSM [136].

Another agent in the bis (thiosemicarbazone) family which merits attention is the  $^{62}\text{Cu}$  ethylglyoxal bis (thiosemicarbazone), or Cu-ETS, which is under investigation in human studies. The  $^{62}\text{Cu}$ -ETS radiopharmaceutical exhibits properties similar to  $^{62}\text{Cu}$ -PTSM *in vivo* due to its structural similarity with  $^{62}\text{Cu}$ -PTSM, while avoiding limitations imposed by human albumin binding. This agent has shown more linear uptake at high blood flow rates and thus may provide a superior PET perfusion tracer for applications such as myocardial perfusion and renal blood flow measurements [137-139].

As blood flow and hypoxia are complex, inter-related factors of physiology, the prospect of using dual-tracer studies with  $^{62}\text{Cu}$ -PTSM (blood flow) and  $^{62}\text{Cu}$ -ATSM (hypoxia) affords the potential for characterizing both tumor blood flow and hypoxia in a single scan [120, 140, 141]. In this modality, dynamic signals from overlapping tracers with staggered injections are recovered using differences in tracer kinetics and decay. The multi-tracer PET imaging paradigm has great potential to avail complementary information that would help for treatment selection, planning, and early response monitoring.

Proportional Technologies, Inc. USA has developed a micro  $^{62}\text{Zn}/^{62}\text{Cu}$  generator to avail  $^{62}\text{Cu}$  tracer at very high isotonic concentration amenable for clinical use. Proportional Technologies, Inc. has also developed include  $\text{H}_2\text{PTSM}$ ,  $\text{H}_2\text{ETS}$  and  $\text{H}_2\text{TASM}$  kits available for both non-human studies and clinical investigation. Components in each injectable solution are described in **Table 6**.

Despite the many advantages, the utility of  $^{62}\text{Zn}/^{62}\text{Cu}$  generators comes with a few limitations. Currently,  $^{62}\text{Zn}/^{62}\text{Cu}$  generators are procured on an as-needed basis as they are relatively expensive and have a shelf life of 1-2 days, and patients must be scheduled several days in advance of imaging. The cost of  $^{62}\text{Zn}/^{62}\text{Cu}$  generator can be significantly off set if demand for the  $^{62}\text{Cu}$  compounds increases to the point at which generators can be produced for routine clinical use and the scheduling of several patients for  $^{62}\text{Cu}$  PET studies on the day of generator delivery. One generator will support 20 or more dose preparations during 1 day

of use, and these doses can be produced at frequent intervals of 30-45 minutes between elution. In this context use, of a lyophilized kit formulation seems poised to provide a practical means of producing  $^{62}\text{Cu}$ -PTSM,  $^{62}\text{Cu}$ -ATSM and  $^{62}\text{Cu}$ -ETS on-site and bring substantial benefits at lower cost, as is well known in radiopharmaceutical practice. Additionally, one of two distribution models for the  $^{62}\text{Zn}/^{62}\text{Cu}$  generator can be considered. Production of  $^{62}\text{Zn}$  can be carried out either in or near the  $^{18}\text{F}$  radiopharmacies using a 19 MeV cyclotron and  $^{62}\text{Zn}/^{62}\text{Cu}$  generator can then be delivered using the same local established delivery network already in place for  $^{18}\text{F}$ . Alternatively, the  $^{62}\text{Zn}$  parent can be produced using > 25 MeV cyclotrons and loaded into generators which can be shipped to the local radiopharmacies or hospital radiopharmacies.

### $^{72}\text{Se}/^{72}\text{As}$ generator

$^{72}\text{As}$  is a positron-emitting arsenic isotope with a half life of 1.08 d, with branching ratio of 88% and  $E_{\beta^+, \text{max}} = 2.49$  MeV. The chemical properties of  $^{72}\text{As}$  are amenable for the preparation of wide range of  $^{72}\text{As}$ -labelled PET radiopharmaceuticals. Interest in the use of a  $^{72}\text{Se}/^{72}\text{As}$  generator is primarily attributed to the following:

Its relatively high  $\beta^+$  abundance and hours-long half-life allows for imaging of slower biological processes.

The relatively long half-life of the parent  $^{72}\text{Se}$  ( $t_{1/2} = 8.4$  d) allows usage of the  $^{72}\text{Se}/^{72}\text{As}$  generator for 2-3 weeks.

The long physical half-life of 1.08 d may render  $^{72}\text{As}$  a PET radionuclide of choice for the quantitative imaging of biochemical and physiological processes with longer biological half-lives, e.g. immunoimaging and receptor mapping.

The longer half-life allows for more elaborate chemical modification and labeling methodologies.

The versatile chemistry of arsenic would permit the radiolabelling of a broad spectrum of potentially valuable pharmaceuticals.

$^{72}\text{Se}/^{72}\text{As}$  generators offer the prospect of availing  $^{72}\text{As}$  at the hospital radiopharmacies without dependence on an accelerator facility in close proximity.

Recognizing the potentially important role of the  $^{72}\text{Se}/^{72}\text{As}$  generator in NM, a wide range of adaptive separation strategies with an aim to obtain  $^{72}\text{As}$  in a suitable chemical form and of requisite purity have been reported. An ion-exchange chromatography  $^{72}\text{Se}/^{72}\text{As}$  generator based on Dowex 50 was developed by Al-Kouraiishi and Boswell [142]. In this process, cold selenous acid was added to  $^{72}\text{Se}$  solution containing sulfur to reduce Se which was obtained as a precipitate. This was then centrifuged, washed with deionized water, loaded onto the chromatography column containing cation exchanger column and held for 90 hours for the in-growth of the  $^{72}\text{As}$  daughter. It is possible to elute  $^{72}\text{As}$  from the column using deionized water with a 70% elution yield. Another generator system developed at Los Alamos National Laboratory was based on the addition of selenium carrier in the form of selenic acid and hydrazine for cyclic reduction of selenium to Se(0) followed by separation of  $^{72}\text{As}$  by filtration with subsequent oxidative dissolution of Se(0) using  $\text{H}_2\text{O}_2$  prior to each separation cycle [143]. A  $^{72}\text{Se}/^{72}\text{As}$  generator based on an electrochemical process with selective deposition of  $^{72}\text{Se}$  on Pt electrodes as  $\text{Cu}^{72}\text{Se}$  were also reported [144]. Jennewein et al. reported a  $^{72}\text{Se}/^{72}\text{As}$  generator based on distillation technique [145]. In this work,  $^{72}\text{As}$  produced by radioactive decay of  $^{72}\text{Se}$  was distilled off as the volatile  $\text{AsCl}_3$  at  $105^\circ\text{C}$  for 10 minutes in a gaseous HCl stream, and collected on a charcoal filter with a radiochemical yield  $> 99\%$  [145]. The same group of authors have reported a system based on a polystyrene solid support [Varian ENV solid phase extraction cartridge] to adsorb elemental  $^{72}\text{Se}$  (0) [146]. The in-grown  $^{72}\text{As}$  was then eluted using 2 mL of concentrated HF with a 50% elution yield [146]. Chajduk et al. have proposed a method based on extraction chromatography for isolation of arsenic from selenium [147]. In this method aromatic o-diamine extractant was impregnated into a polystyrene column matrix. The extractant selectively retains  $^{72}\text{Se}$  from which  $^{72}\text{As}$  could be selective eluted using 0.9% NaCl solution. The proposed separation procedure assures  $> 95\%$  elution yield with low ( $< 0.01\%$ )  $^{72}\text{Se}$  breakthrough [147]. A  $^{72}\text{Se}/^{72}\text{As}$  RNG system utilizing chelation and liquid-liquid extraction has been reported [148]. Despite the impressive progress, the promise to develop a commercial, clinical scale  $^{72}\text{Se}/^{72}\text{As}$  generator

amenable for use in a hospital radiopharmacy has not been fulfilled.

Arsenic forms stable covalent bonds with carbon and sulphur and can substitute phosphorus in certain compounds with minimal alteration of the biological activities of the parent molecule. Jennewein et al. has reported a method to radiolabel  $^{74}\text{As}$  with N-succinimidyl S-acetylthioacetate (SATA) derivitized bavituximab [149]. Arsenic has a high affinity to sulfur and As is able to bind covalently to sulfhydryl groups. In antibodies, the sulfur moieties are mainly associated with dithiol bridges. To increase the number of free thiols, conscious modification of antibodies with SATA (N-succinimidyl S-acetylthioacetate) seemed sagacious and was pursued [149]. It has been demonstrated that  $^{74}\text{As}$  labeled bavituximab-SATA-conjugate retained its immunoreactivity and exhibits favorable *in vitro* stability in fetal bovine serum. Biodistribution studies carried out with Dunning prostate R3327-AT1 tumor bearing rats reveal that tumors were clearly visible after 48 hours, exhibiting 8-fold higher uptake at 72 hours as compared to the control antibody [149, 150].

It is clear that  $^{72}\text{As}$  based radiopharmaceuticals for clinical PET are still in their infancy and their utility is limited by the commercial unavailability of  $^{72}\text{Se}/^{72}\text{As}$  generators as well as end-user radiolabeling techniques. Additional preclinical and clinical studies are warranted to exploit the full potential of  $^{72}\text{As}$ . Having established their importance in NM, the exploration of  $^{72}\text{As}$ -labeled PET tracers will continue to rise.

### $^{110}\text{Sn}/^{110\text{m}}\text{In}$ generator

$^{110\text{m}}\text{In}$  is a positron-emitting isotope of In, with a half-life of 69.1 min and branching ratio of 62% with  $E_{\beta^+, \text{max}} = 2.26$  MeV. This radioisotope is of interest as it would provide the scope of preparation of radiolabeled agents (analogous to SPECT tracers) to be quantified with PET and allow for sequential studies to be performed within a relatively short time. Potential use includes preparation of  $^{110\text{m}}\text{In}$  labeled leukocytes for infection/inflammation imaging [151] and  $^{110\text{m}}\text{In}$ -octreotide in clinical imaging of neuroendocrine tumors (NET) [152]. The prospect of using  $^{110\text{m}}\text{In}$ -labeled octreotide seemed to be an interesting proposition as it can better detect small tumors and might be able to more

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accurately quantify tumor uptake with PET than can  $^{111}\text{In}$ -labelled octreotide and SPECT. Due to the short half-life of the  $^{110\text{m}}\text{In}$ , use of the Octreoscan kit has been embraced by investigators [152]. Since octreotide is commercially available in the Octreoscan kit (Mallinckrodt Medical, St. Louis), an optimized procedure for labeling with  $^{110\text{m}}\text{In}$  could be routinely used, solving the problems associated with GMP production of the peptide-chelator conjugate. The 69-min half-life of  $^{110\text{m}}\text{In}$  matches the rapid kinetics of the octreotide well. Apart from enabling detection of smaller tumors,  $^{110\text{m}}\text{In}$ -octreotide-PET can also provide quantitative information about receptor kinetics and concentrations with better temporal and spatial resolution than  $^{111}\text{In}$ -octreotide-SPECT.

This generator was prepared using Kieselgel 40 (silica gel) conditioned with 0.02 M HCl [153].  $^{110}\text{Sn}$  was loaded in the column at 0.02 M HCl and elution of  $^{110\text{m}}\text{In}$  was performed using 0.02 M HCl [153]. Owing to the relatively short half-life of the parent,  $^{110}\text{Sn}$  ( $t_{1/2} = 4.9$  h), this generator has a limited shelf-life of 10-12 hours. The generator was eluted at 2 h interval with > 90% elution yield of  $^{110\text{m}}\text{In}$  and the level of  $^{110}\text{Sn}$  breakthrough was < 0.003%.

### $^{52}\text{Fe}/^{52\text{m}}\text{Mn}$ generator

$^{52\text{m}}\text{Mn}$  is a positron-emitting isotope which decays with a branching ratio of 98.3% with a 21.1 min half-life and with  $E_{\beta^+, \text{max}} = 2.631$  MeV. In addition to the annihilation radiation,  $^{52\text{m}}\text{Mn}$  also emits a 1434-keV gamma ray (98.3%). The remainder of the decay is by isomeric transition to  $^{52}\text{Mn}$ , which has a 5.59-day half-life. This PET isotope has been considered as a potential agent for myocardial imaging studies owing to the possibility to perform a number of studies in the course of a day [154-156]. The tremendous prospect associated with the use of  $^{52}\text{Fe}/^{52\text{m}}\text{Mn}$  generators in NM has led to the development of a number of strategies [155-159]. Due to the short half life of  $^{52}\text{Fe}$  ( $t_{1/2} = 8.27$  h) breakthrough up to 1% would not significantly alter the efficacy of the  $^{52\text{m}}\text{Mn}$  eluted. This generator has a very limited shelf life due to the short half life of  $^{52}\text{Fe}$ , the parent radioisotope.

Despite the favorable physical properties of  $^{52\text{m}}\text{Mn}^{2+}$  as an agent for myocardial imaging studies, results from pig model studies con-

cluded that  $^{52\text{m}}\text{Mn}$  allows the qualitative assessment of myocardial perfusion but does not meet the requirements of a quantitative myocardial perfusion agent [160]. The  $^{52}\text{Fe}/^{52\text{m}}\text{Mn}$  generator presents no chemical or practical advantages over the  $^{62}\text{Zn}/^{62}\text{Cu}$  generator, which has similar parent and daughter half-lives.

### $^{122}\text{Xe}/^{122}\text{I}$ generator

The use of  $^{122}\text{Xe}$  ( $t_{1/2} = 20.1$  h)/ $^{122}\text{I}$  ( $t_{1/2} = 3.6$  min;  $\beta^+ = 77\%$ , EC = 23%,  $E_{\beta^+, \text{max}} = 3.1$  MeV) generator system as a means of availing  $^{122}\text{I}$  for PET studies has caught the attention of NM clinicians and evoked excitement among radiopharmaceutical scientists.  $^{122}\text{I}$  is unique among all generator produced PET radionuclides in that it is not a metallic element and it is availed from a parent nuclide that is an inert gas. Due to the gaseous nature of the parent radionuclide, the customary use of column chromatography technique for the separation of daughter radionuclide will not be appropriate for this generator. In view of this, suitable alternative means for this separation have been described [161, 162].

While the 3.6-min half-life of  $^{122}\text{I}$ , as well as the versatile chemistry of iodine, are appealing for many PET applications, the chemistry of iodine is not particularly amenable to the rapid synthetic chemistry which is dictated by the physical half-life of this label. Nevertheless, a few attempts have already been made. Potential utility of  $^{122}\text{I}$  labeled Iodoperidol (IP), an iodinated analogue of the antipsychotic drug haloperidol, as a cerebral blood flow radiopharmaceutical for PET has been evaluated and showed promising results [163]. This study indicates that this class of compounds holds promise for development as perfusion radiopharmaceuticals.  $^{122}\text{I}$  has been successfully incorporated into an amphetamine analog, 2,4-dimethoxy-N,N-dimethyl-5-[ $^{122}\text{I}$ ]iodophenylisopropylamine (5-[ $^{122}\text{I}$ ]-2,4-DNNA), using a remote synthesis protocol and studied in dog models as a quantitative cerebral blood flow agent for PET [164].

### In vivo generators

This concept essentially consists of labeling of molecular carriers (complexes, peptides, monoclonal antibodies and their fragments, etc.)

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with intermediate half-life generator parents, which continuously decay and generate shorter half-life daughter radionuclides much more than the parent [165-167]. It is pertinent to note that the chemical binding of the daughter nuclide must be analogous to the parent one to preclude the release of daughter radionuclide from the original position. Owing to the decay kinetics, the daughter nucleus experiences some recoil. However, this is assumed to be negligible. This is the reverse of the usual use of a generator, where the daughter is initially separated from the parent prior to use. By contrast, with this strategy the daughter is removed from the parent using a chemical separation technique and the parent is then attached to tissue-specific therapeutic agents (complexes, chelate, peptides, monoclonal antibodies and their fragments, etc.) to be administered. While this innovative paradigm has been practiced in radionuclide therapy to minimize the radiation exposure to non-target tissues, this could be extended to imaging agents [168]. Such a strategy seemed appealing, as it has the potential for quantitative PET to inform on a more personalized treatment strategy, since the same carrier moiety can be radiolabeled with a suitable parent/daughter pair to deliver therapeutic or diagnostic imaging radionuclides. In this context two generators that merit attention for the “Theranostics” concept are:  $^{140}\text{Nd}/^{140}\text{Pr}$  and  $^{134}\text{Ce}/^{134}\text{La}$  generators [168].

### $^{140}\text{Nd}/^{140}\text{Pr}$ generator

$^{140}\text{Nd}$  decays 100% by EC with a half-life of 3.37 days to produce a short-lived positron emitter  $^{140}\text{Pr}$  which decays to stable  $^{140}\text{Ce}$  by positron emission with a branching ratio of 49 %, with  $E_{\beta^+, \text{max}} = 2.4 \text{ MeV}$  and with a 3.4 min half-life. This system shows potential as an RNG or as an *in vivo* generator system for PET [168].

A  $^{140}\text{Nd}/^{140}\text{Pr}$  RNG system based on physico-chemical transitions (hot-atom effects) of the daughter  $^{140}\text{Pr}$  following the electron capture process of  $^{140}\text{Nd}$  has been developed [169]. In this process  $^{140}\text{Nd}(\text{III})$ , in the form of  $^{140}\text{Nd}$ -DOTA-conjugated complexes, was quantitatively retained on a cation-exchange resin (Bio-Rad AG 50W-X8, 200-400 mesh, in hydrogen form).  $^{140}\text{Pr}$  was eluted using  $10^{-3} \text{ M}$  DTPA in  $> 93\%$  yield with negligible levels of  $^{140}\text{Nd}$  breakthrough.

### $^{134}\text{Ce}/^{134}\text{La}$ generator

$^{134}\text{Ce}$  is an Auger electron-emitting radionuclide which decays to  $^{134}\text{La}$  with a half-life of 3.16 d and the daughter nuclide  $^{134}\text{La}$  ( $t_{1/2} = 6.45 \text{ min}$ ) is a positron and Auger-electron emitter. While  $^{134}\text{La}$  was proposed as PET perfusion imaging agent [170], real practical applications have not yet been described. Both the low-energy Auger electrons, emitted in the  $^{134}\text{Ce}$  and  $^{134}\text{La}$  decays, as well as the high energy positrons emitted in the  $^{134}\text{La}$  decay, can be conscientiously exploited for radionuclide therapy. The kinetics of the positron-emitting daughter nuclide can be measured with PET and used for dosimetry.  $^{134}\text{Ce}/^{134}\text{La}$  absorbed doses to single cells were reported to be higher than absorbed doses from  $^{90}\text{Y}$  and  $^{111}\text{In}$  [170]. Further investigations are warranted to realize the full potential of this system.

### Production of parent radionuclide

Any advancement in PET RNGs will be largely dependent upon the availability of required quantity and quality of parent radionuclides. The major challenge for the production of parent radionuclide requires selection of the most economical processes from the pool of available options. Most of the parent radionuclides used in RNGs are produced using solid targets of metal-based materials (e.g. elemental metal or metal oxide) with the target either mounted to the cyclotron (under vacuum) or external to the cyclotron/accelerator. In each case, the target system needs to tolerate heat generated from the particle bombardment. Depending on the energy and current of the beam, the cooling systems can be quite elaborate. As the number of nuclear reactions in a given target material can be potentially large, one needs to design the target so that the preferred nuclear reaction dominates. This may be achieved in a number of ways:

Choice of beam incident particle [i.e. p, d, or  $\alpha$ ] energy of the beam, target material (i.e. natural or enriched isotope of target element).

Routine production of parent radionuclides for RNGs should meet the following requirements:

The production method, involving the bombardment as well as the radiochemical separation

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procedure for the isolation radionuclide of interest, must be economically viable.

Ability to isolate the radionuclide of interest in high specific activity, with acceptable radionuclidic, radiochemical and chemical impurities.

The radiochemical separation method selected must be as simple as possible to facilitate remote operation/automation within a hot cell to minimize radiation exposure to the operator.

The following section provides an overview of the issues associated with production of parent radionuclides which should be considered to identify recent advances in this field.

### <sup>68</sup>Ge

Two nuclear reactions have been utilized for the routine production of <sup>68</sup>Ge, namely, by <sup>66</sup>Zn( $\alpha$ ,2n)<sup>68</sup>Ge (<sup>66</sup>Zn natural abundance being 27.8%) giving a yield of up to 2  $\mu$ Ci.( $\mu$ A.h)<sup>-1</sup> (yield per  $\mu$ A beam current calculated for 1 h irradiation) at 35 MeV beam energy, or by <sup>69</sup>Ga(p,2n)<sup>68</sup>Ge (<sup>69</sup>Ga natural abundance being 60%) giving a yield of up to 20  $\mu$ Ci.( $\mu$ A.h)<sup>-1</sup> at 23 MeV beam energy [171]. Of the two reactions, <sup>69</sup>Ga(p,2n)<sup>68</sup>Ge has been regarded as the reaction of choice due to the higher yields obtained and ease of chemical separation. In this method, only two elements need to be separated from each other, where with the other reaction, a third element (Zn) needs to be taken into consideration [172].

When selecting the target, chemical, mechanical and thermal properties, and corrosion and radiation resistance need to be considered since the target will be exposed to high current irradiations and the power dissipated in the targets reaches values of about 300-1000 W or more. Target materials used for the production of <sup>68</sup>Ge include Ga<sub>2</sub>O<sub>3</sub>, Ga<sub>4</sub>Ni, GaAg and Ga metal. The use of encapsulated Ga<sub>2</sub>O<sub>3</sub> with high-current proton beams is precluded as the oxide changes from a hexagonal  $\alpha$ -form to a monoclinic  $\beta$ -form at about 600°C accompanied by a volume increase, which leads to capsule rupture. While the use of alloys as target material (Ga<sub>4</sub>Ni and GaAg) has the advantage of attaining good thermal conductivity, the requirement of an elaborated chemical separation procedure to make <sup>68</sup>Ge free from coproduced impurities discourage their use. The

prospect of using Ga<sub>2</sub>O<sub>3</sub> is prohibited by the difficulties encountered during the dissolution of irradiated target. In this regard, the idea of using Ga metal seemed attractive. As Ga metal is corrosive to Al, it is essential that it be encapsulated, using Nb for example, as Ga would not react with this encapsulation.

In order to avail satisfactory batch yields, proton energy > 20 MeV, high-current accelerators on the order of the mA's and long irradiation periods of several days duration are required. Hence there are very few suppliers of <sup>68</sup>Ge, despite huge demands. Four major centers which produce <sup>68</sup>Ge currently are: iThemba laboratories (South Africa), Brookhaven National Laboratory (USA), Los Alamos National Laboratory (USA) and Cyclotron Co Ltd (Obninsk, Russia) [171]. These centers report on production capacities of about 18.5 to 74 GBq (0.5 to 2 Ci) of <sup>68</sup>Ge per batch. Separation techniques used to isolate micro quantities of no-carried-added (NCA) <sup>68</sup>Ge from macro amount of irradiated target range from solvent extraction [173-176] and ion exchange chromatography, to using organic [177] and inorganic [172, 178, 179] materials, have been employed.

At BNL, production is carried out using <sup>nat</sup>Ga targets with ~45 MeV protons. For a typical batch production, 81 g of <sup>nat</sup>Ga metal encapsulated in a Nb container is used and irradiation was carried for period of 4 weeks (0.52 MBq. ( $\mu$ Ah)<sup>-1</sup>. <sup>68</sup>Ge is recovered from the target by extraction into 4 N HCl and 30% H<sub>2</sub>O<sub>2</sub> after two weeks cooling. Further purification is achieved by solvent extraction using carbon tetrachloride and back-extraction of <sup>68</sup>Ge into H<sub>2</sub>O. An overall recovery yields > 85% having a batch yields of 33.3-51.8 GBq (900-1400 mCi) with radionuclidic purity > 99.9%, and activity concentrations > 3.15 GBq/mL (85 mCi/mL) have been reported [180]. At the Los Alamos National Laboratory (LANL), 100 MeV protons are used [181]. For a typical batch production, 4 g of <sup>nat</sup>Ga metal encapsulated in a Nb container is used and irradiation was carried for period 16-20 days (1.18 MBq/ $\mu$ Ah). The batch yield at end of bombardment (EOB) is about 55-70 GBq. Chemical processing is carried out after two weeks of cooling using solvent extraction with CCl<sub>4</sub> and re-extraction of <sup>68</sup>Ge into water followed by an ion exchange purification step using alumina [182]. At the iThemba La-

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laboratories, a 66 MeV proton beam is used. For a typical batch production, 5 g of target with a production rate 1.18 MBq (0.032 mCi). ( $\mu\text{Ah}$ )<sup>-1</sup> is used. The radionuclidic purity of the processed <sup>68</sup>Ge is > 99.9% and the final product contains < 1  $\mu\text{g}$  of Ga per 37 MBq (1 mCi) of <sup>68</sup>Ge [183]. At the Cyclotron Co. Ltd. in Obninsk, Russian Federation, Ga-Ni alloy prepared on Cu backings is used as the target material. Irradiations are performed at a high proton beam intensity of several hundred microamperes of 23 MeV protons. <sup>68</sup>Ge of high specific activity [ $> 74 \text{ GBq} (> 2 \text{ Ci})/\text{mg}$ ] and 99.8% radionuclidic purity is obtained [184].

### <sup>82</sup>Sr

<sup>82</sup>Sr has been produced via several different reaction routes, as shown in **Table 7**. Each method presents different challenges for targetry, process chemistry, practical yield, radionuclidic purity, and availability. While the use of high energy spallation reactions with Mo or Y metal as the target constitutes a method for the production of <sup>82</sup>Sr [185-187], low reaction cross-sections and the requirement of an elaborate radiochemical procedure to isolate <sup>82</sup>Sr from other spallation products, as well as the bulk target material, emerged as the major impediments which continue to discourage this method's wide scale adaptability. In an attempt to produce <sup>82</sup>Sr, high energy <sup>3</sup>He and alpha particle irradiations of natural Kr have also been tried [188-190], but met with limited success due to low yields and the scarcity of operating accelerators capable of accelerating <sup>3</sup>He ions to the energies required. In this light, the <sup>nat</sup>Rb(p,xn)<sup>82</sup>Sr reaction seemed most attractive and thus stands as the technique of choice for large scale production [191-193].

The requirement to use high energy proton reactions leads to relatively large government owned accelerator facilities around the world, and poses challenges associated with irradiation scheduling (as these facilities have other missions and do not operate continuously year round) and timely transport of large quantities of radioactivity to the generator production site; these are some of the major road blocks that need to be surmounted for widespread use of <sup>82</sup>Sr for medical applications. As the potential for <sup>82</sup>Sr/<sup>82</sup>Rb generators is evident, several commercial companies have started producing

<sup>82</sup>Sr to meet the demand on a routine basis. Production details adopted by the current suppliers of <sup>82</sup>Sr are depicted in **Table 8**.

With the goal of undertaking a large scale production process using the <sup>nat</sup>Rb(p,xn)<sup>82</sup>Sr reaction, both RbCl and Rb metals have been used. The advantages of using RbCl are its commercial availability in high chemical and isotopic purity, resistance to corrosion, ability to be pressed into a pellet at near theoretical density, or melted and cast into a capsule, and easy dissolution of irradiated targets in water as well as common mineral acid. Limitations on the use of RbCl include hygroscopic behavior of the material and low thermal conductivity. The poor thermal conductivity requires careful target design and limits target thickness in order to withstand high beam current.

The use of Rb metal permit permits the use of very thick targets in order to increase batch quantities because of high thermal conductivity. Disadvantages of using Rb metal include commercial non-availability of very high purity material and the serious safety issues in handling metallic Rb, due to its susceptibility to ignite or explode upon exposure to air or moisture, and the subsequent requirement to perform initial irradiated target dissolution within an inert atmosphere (e.g. dry argon) using an anhydrous higher alcohol, typically propan-2-ol.

At BNL and LANL, processing of the irradiated RbCl target was carried out by removing the exterior of the target capsules with acid, followed by dissolution of irradiated RbCl pellet in water. <sup>82</sup>Sr<sup>2+</sup> was isolated using an ion exchange chromatography separation process using Chelex 100, wherein <sup>82</sup>Sr<sup>2+</sup> is chelated and retained on the resin while Rb<sup>+</sup> gets eluted. <sup>82</sup>Sr<sup>2+</sup> was eluted from the column using 6 M HCl and further purification of <sup>82</sup>Sr<sup>2+</sup> was carried out using ion exchange chromatography with AG 50W-X8 and Chelex 100 [171, 194]. At iThemba Labs, the irradiated target is dissolved in dilute ammonium chloride solution and <sup>82</sup>Sr is separated from the target material using column chromatographic methods with Purolite S950, a macroporous aminophosphonic acid chelating resin. Further purification of <sup>82</sup>Sr is carried out following column chromatography technique using AG MP-50 macroporous cation exchange resin. The final <sup>82</sup>Sr possesses high

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radionuclidic purity with negligible Rb and Fe chemical impurities [194].

Proton irradiated metallic Rb targets from Institute for Nuclear Research (INR) of the Russian Academy of Sciences, Russian Federation, are also processed at Los Alamos National Laboratory (USA) [195], as well as in Institute for Physics and Power Engineering (IPPE), Obninsk, Russia, using a patented method [196]. Pure  $^{82}\text{Sr}$  obtained in IPPE is then transported to the Russian Research Center of Radiology and Surgical Technologies (RRCRST), St. Petersburg, for loading the  $^{82}\text{Rb}$ -generator. Positron Corporation, USA has entered into a license agreement with INR to produce  $^{82}\text{Sr}$  in its proposed 70 MeV cyclotron and using the patented process technology of INR [197]. The rights to this patented technology have been awarded by INR to Positron Corporation.

Over the past decade, the growth of cardiac PET imaging has driven a significant increase in the use of  $^{82}\text{Sr}/^{82}\text{Rb}$  generators. Currently, the US Department of Energy (DOE) is the only supplier of  $^{82}\text{Sr}$  in the US. Positron Corp, U.S., is working with the US FDA for certification so it can begin its own production of  $^{82}\text{Sr}$ , through its subsidiary, Manhattan Isotope Technology (MIT), to provide a second source for  $^{82}\text{Sr}$  in the USA. In August 2012, MIT submitted its drug master file (DMF) with the US FDA and has begun production of active pharmaceutical ingredient (API) grade  $^{82}\text{Sr}$  at its Lubbock, Texas, facility with strontium received from iThemba South Africa.

### $^{44}\text{Ti}$

$^{44}\text{Ti}/^{44}\text{Sc}$  RNGs described in the literature thus far are all based on the  $^{44}\text{Ti}$  produced by proton irradiation of scandium, by the  $^{45}\text{Sc}(p,2n)^{44}\text{Ti}$  reaction. The long half-life of  $^{44}\text{Ti}$  (60 years) and a low cross-section necessitates the use of high proton flux and long-duration irradiations. The targets are prepared by melting Sc in 150-220  $\mu\text{m}$  thick layers onto copper backings, which themselves are covered by intermediate layers of Ag in order to reduce  $^{65}\text{Zn}$  coproduction. About 1.5 g Sc targets are subjected to proton currents of  $\sim 200 \mu\text{A}$  for  $\sim 10$  h at  $\sim 30$  MeV proton energy. Irradiated Sc target processing was carried out by dissolving the target in 18 mL of 2 M HCl. Separation of  $^{44}\text{Ti}$  from silver as well as co-produced  $^{65}\text{Zn}$  and  $^{109}\text{Cd}$

have been achieved following a multi-step ion-exchange chromatography separation, and purification procedures using AG 50W-X8, 200-400 mesh in  $\text{H}^+$ -form, as reported [101, 102]. Using the reported procedure, about 185 MBq (5 mCi) of  $^{44}\text{Ti}$  was successfully recovered.

### $^{62}\text{Zn}$

The common method for the production of the  $^{62}\text{Zn}$  parent is  $^{nat}\text{Cu}(p,xn)^{62}\text{Zn}$  using intermediate energy (30-60 MeV) proton accelerators [110, 112]. Using low-energy protons (5-14 MeV),  $^{62}\text{Cu}$  can be produced following  $^{62}\text{Ni}(p,n)^{62}\text{Cu}$  reaction [198, 199]. As reported, the  $^{nat}\text{Zn}(p,x)^{62}\text{Zn}$  process can be adopted as a production route if protons of energies higher than 50 MeV are available [200]. The radiochemical processing step involves dissolution of the irradiated target in concentrated  $\text{HNO}_3$ , reconstitution in 3 M HCl and separation from Cu using ion exchange chromatography (AG1-X8, Cl<sup>-</sup> form) [114].

### $^{72}\text{Se}$

Spurred by the perceived need to avail  $^{72}\text{Se}$  of requisite purity for the development of  $^{72}\text{Se}/^{72}\text{As}$  generators, a number of production strategies have been described in the literature [142, 146, 201-203] and are elaborated in **Table 9**. When preparing for the production of  $^{72}\text{Se}$ , following one of the different production pathways, a thorough assessment of the production yield, the ease of the required separation chemistry, and the radiochemical purity of the  $^{72}\text{Se}$  product needs to be considered. It is pertinent to point out that highest production yield for  $^{72}\text{Se}$  is achieved following the proton induced reaction paths using RbBr salt targets, although this production approach is associated with challenges to isolate  $^{72}\text{Se}$  owing to the complexity of the product mixture in dissolved solution. While the irradiation of As targets with intermediate energy protons offers the next best yields for  $^{72}\text{Se}$ , chemical processing of multi-gram production targets is not only challenging but also associated with radioactive waste disposal issues because of co-production of long lived  $^{75}\text{Se}$  ( $t_{1/2} = 120$  d).

Among the various possible routes to be considered for the production of  $^{72}\text{Se}$ , the use of alkaline bromide targets seems attractive, as they balance a relatively inexpensive and bio-

logically benign target material with sufficiently high yields for the production of  $^{72}\text{Se}$  [148]. Other advantages include ease of dissolution of the irradiated target due to high solubility in water, and a reasonably high thermal conductivity. The target processing step involves dissolution of the irradiated target in dilute HCl. Quantitative removal of bromide is achieved by oxidation to elemental bromine, followed by distillation. A liquid-liquid extraction system using dithiocarbamate/ethyl acetate is used to purify Se [148].

### $^{52}\text{Fe}$

A number of nuclear reactions using proton,  $^3\text{He}$  and  $\alpha$  particles have been studied for the  $^{52}\text{Fe}$  production:  $^{52}\text{Cr}(^3\text{He},3n)^{52}\text{Fe}$  [204],  $^{50}\text{Cr}(^4\text{He},2n)^{52}\text{Fe}$  [205],  $^{55}\text{Mn}(p,4n)^{52}\text{Fe}$  [157, 206, 207],  $^{nat}\text{Ni}(p,x)^{52}\text{Fe}$  [207]. While the  $^{55}\text{Mn}(p,4n)^{52}\text{Fe}$  [157, 206-208] route of production using a 65-70 MeV proton beam has been appealing, the beams available from most medical accelerators are below this energy. Therefore, attempts to prepare sufficient quantities of  $^{52}\text{Fe}$  following this path have met with limited success. The production of  $^{52}\text{Fe}$  by spallation suffers from the requirement of a high energy cyclotron and the coproduction of  $^{59}\text{Fe}$ , a troublesome contaminant with a 45 day half-life.

The irradiation of Mn with 65-70 MeV protons is expected to produce isotopes of Fe and Mn, and possibly of Cr with reasonable yield, while V and Ti radionuclides will be formed in very small quantities [206]. The irradiated target is dissolved in 6 N HCl containing  $\text{H}_2\text{O}_2$ . In order to avail  $^{52}\text{Fe}$  of required quality, these radionuclides were separated using an ion-exchange chromatography method with Dowex-1  $\times$  8, wherein the Fe gets trapped and the Mn, Na, Cr, and Al pass through the resin column with the 6 N HCl loading solution. Fe retained on the column is eluted with 0.5 N HCl. This step is repeated 2-3 times to obtain Fe of required purity [206]. One of the major limitations of this production route is that  $^{52}\text{Fe}$  produced is contaminated with  $^{55}\text{Fe}$  impurity.

The use of the  $^{50}\text{Cr}(^4\text{He},2n)^{52}\text{Fe}$  nuclear reaction with an enriched  $^{50}\text{Cr}$  target and an irradiation with an  $\sim 40$  MeV  $^4\text{He}$  beam seemed to be appealing option [209] as it precluded the production of the long-lived  $^{59}\text{Fe}$  isotope. However,

it requires the recycling of precious enriched  $^{50}\text{Cr}$  target in order to make the production cost effective. The irradiated target contains  $^{52}\text{Mn}$ ,  $^{54}\text{Mn}$ ,  $^{56}\text{Mn}$ ,  $^{49}\text{Cr}$ ,  $^{51}\text{Cr}$ ,  $^{48}\text{V}$  and  $^{55}\text{Fe}$  radionuclides in addition to the  $^{52}\text{Fe}$ . Separation of  $^{52}\text{Fe}$  from radioactive contaminants, as well as  $^{50}\text{Cr}$ , is achieved by solvent extraction of Fe(III) from 8 M HCl using di-isopropyl ether (DIPE) [209].

### $^{122}\text{Xe}$

The nuclear reactions used for the production of  $^{122}\text{Xe}$  are:  $^{120}\text{Te}(\alpha, 2n)^{122}\text{Xe}$ ,  $^{122}\text{Te}(\alpha, 4n)^{122}\text{Xe}$ ,  $^{124}\text{Xe}(p, 3n)^{122}\text{Cs}$  which decays to  $^{122}\text{Xe}$ ,  $^{124}\text{Xe}(p, p2n)^{122}\text{Xe}$  and  $^{127}\text{I}(p,6n)^{122}\text{Xe}$  [210]. The proton induced reaction using  $^{127}\text{I}$  is most abundantly used because the product and reactants are chemically different. The maximum cross-section for the  $^{127}\text{I}(p,6n)^{122}\text{Xe}$  reaction is expected to be in the 72-74 MeV energy range [162, 211]. While the use of a higher energy proton beam results in significantly higher  $^{122}\text{Xe}$  yields, it also leads to the production of other radioisotopes of iodine such as  $^{121}\text{I}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$  due to the decay of  $^{121}\text{Xe}$ ,  $^{123}\text{Xe}$ ,  $^{125}\text{Xe}$  coproduced in the same energy region. With the aim to reduce the radiation dose hazard and to minimize the level of radioiodine isotopic impurities, proton energy in the range of 72-74 MeV energy is desirable. However,  $^{123}\text{Xe}$  is also obtained as a byproduct of irradiation of NaI targets due to  $^{127}\text{I}(p, 5n)^{123}\text{Xe}$  reaction with 67.5 MeV proton beams and this is undesirable [211].  $^{124}\text{Xe}(p, 3n)^{122}\text{Cs}$  which decays to  $^{122}\text{Xe}$ , and  $^{124}\text{Xe}(p, p2n)^{122}\text{Xe}$  are not used for production for economic reasons due to the requirement of enriched and expensive target material which cannot be recovered for recycling as the separation of  $^{124}\text{Xe}$  from the  $^{122}\text{Xe}$  is not feasible.

While the use of  $^{120}\text{Te}(\alpha, 2n)^{122}\text{Xe}$  and  $^{122}\text{Te}(\alpha, 4n)^{122}\text{Xe}$  reactions offer the potential of availing  $^{122}\text{Xe}$ , the requirement of 30-40-MeV  $\alpha$  beams, expeditious as well as continuous removal of the radioxenons formed using solid/gas separation technique, and low natural abundances of  $^{120}\text{Te}$  (0.096%) and  $^{122}\text{Te}$  (2.60%) have emerged as the major impediments that discourage their large scale adaptability. Use of expensive enriched target material, the need to recover the target, and restricted availability of an accelerator to produce intense 30-40 MeV  $\alpha$  beams are other major hurdles that must be tackled while following this route [211].

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The production of  $^{122}\text{Xe}$  by spallation using CsI,  $\text{La}_2\text{O}_3$  or  $\text{BaCO}_3$  targets and protons of energies from 320 to 590 MeV has also been reported by Peek and Hegedus [212]. Production of many xenon isotopes, such as  $^{127}\text{Xe}$ ,  $^{125}\text{Xe}$ ,  $^{123}\text{Xe}$ ,  $^{121}\text{Xe}$ , during spallation and the requirement of > 200-MeV proton beams have emerged as the major deterrents that limit the utility of this production pathway.

### Radiation safety

Radiation safety is another important part of the RNG development process. Because of the recent advancements in cyclotron targetry, radiochemistry, and separation techniques, new RNGs capable of providing PET radionuclides with different decay characteristics are entering biomedical research and seem poised to enter into clinical practices. Therefore, there is a clear need to reconsider the radiation safety aspects in the development of PET RNGs. Most of the RNGs are appropriately placed in a shielded container, designed to enable elution of the daughter radionuclide. Meeting the regulatory requirements for safe operation is an expensive proposition, but constitutes a necessity. Careful planning with the design engineer, generator architect, and a qualified medical physicist is necessary to produce a cost-effective design while maintaining the radiation safety standard.

With the aim to minimize both manufacturing and transportation expenses, and to make the system portable, it is essential to design an RNG such that the amount of shielding can be kept as small as possible. Adequate shielding is essential to reduce the risk of radiation exposure to workers. The purpose of the RNG shielding is to attenuate radiation by absorption (and to some extent scattering). This protects radiation workers by reducing their exposure. The design of proper shielding requires the use of accurate  $\gamma$ -ray dose (C) constants and tenth value layers (TVLs). In order to achieve the greatest possible radiation safety, the amount of radiation exposure from RNGs should be kept below a safe limit following the "ALARA" (As Low As Reasonably Achievable) principle. Based on the type of PET radionuclide, the design and radiation safety features of RNGs need to be adjusted appropriately.

### Regulatory need

While the use of PET RNGs is a successful paradigm for ensuring sustained growth and future expansion of PET, their development and the possibility of their clinical translation have been stymied by a number of factors, such as: the complexity of pharmaceutical legislation and regulations, the lengthy process of obtaining a marketing authorization, and, in some cases, a limited return on investment, as well as lack of consensus. Despite the encouraging prospects and the favorable results of many PET RNGs, there is still quite a long way to go before any one of them become standard for widespread use in daily NM routine.

Among many other requirements, such as those relating to establishment of chemical and radionuclidic purity of the PET radionuclide obtained from an RNG, clinical use of RNGs is dependent on the condition that they are manufactured under conditions of good manufacturing practice (GMP). Radionuclides obtained from RNGs are considered as approved pharmaceutical ingredients (API) as they are used as a starting material for the preparation of radiopharmaceuticals for human use [213], and therefore subjected to regulatory approval to ensure both quality and safety. The emphasis on quality is most prominently manifested by the fact that not only do radionuclides obtained from the generators have to meet strict specifications but also the separation processes and associated accessories must fulfill the preset criteria.

Directive 2001/83 of European Union [214] states that all medicinal products must comply with the current standards of GMP. In Europe, these GMP rules have legal character as they are issued by the European Medicines Agency (EMA) and the DG Enterprise and Industry of the European Commission. They are published online in the Eudralex, a web-based compendium of European pharmaceutical legislation [215]. However, Directive 2001/83, the basis for European GMP as outlined in Eudralex, only has a mandate for the industrial manufacture of medicinal products and does not legally cover the small-scale, patient-specific preparation, e.g., in pharmacies. Similarly, the US FDA approved a set of regulations describing production of PET radiopharmaceuticals according

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to current good manufacturing practice (cGMP), outlined in the Code of Federal Regulations (21CFR212), [216]. Because of the differences and complexities of the regulatory machinery in different countries, it would be expected that each country is different, and the introduction of an RNG to avail PET radionuclides for routine PET imaging would, of course, depend on regional and country regulations. Use of PET RNGs in radiopharmacies requires either dedicated radionuclide specific radio-synthesizers or kit-based, micro-scale radio-synthesizers that offer fully integrated radiochemistry solutions on the bench top to synthesize the radio-tracers, and quality control (QC) testing equipment [e.g. gas chromatography (GC), analytical radio-high-performance liquid chromatography (radio-HPLC), dose calibrators, radio-thin layer chromatography (radio-TLC), etc.] to ensure the safety of the patient. Additionally, it also requires the availability specially trained and skilled personnel to operate the entire process, from generator elution to the aseptic dose preparation.

In light of the perceived need to address regulatory requirements and to achieve Current Good Manufacturing Practices (cGMP) compliance, the field of RNGs is increasingly migrating toward the use of automated systems. Automation offers several advantages, including providing robust, repeatable processes, reducing the radiation dose to operators, offering consistent performance of the generator system, ability to handle and distribute multiple doses daily, and providing a log of the steps performed in the elution of the medical radionuclide [217]. Automation also facilitates regulatory compliance through manufacturer design qualification/operational qualification/performance qualifications and scheduled maintenance protocols performed on automated RNGs by trained service engineers.

Due to the short half-life of most of the generator produced radionuclides, the prospect of using kit-type formulation strategies seemed sagacious, as it would reduce reagent preparation and setup time, curtail human errors, eliminate the possibility of contamination, facilitate cleanup, and simplify operation. A further advantage of kits is the simplification of reagent handling. Rather than individually managing multiple reagents, the radiopharmacy need

only to manage the kit as a single unit, greatly simplifying compliance with FDA regulations concerning production of PET tracers for injection into humans. Kit formulation strategies are beginning to put the capability to make PET tracers directly into the hands of the scientists and clinicians who need them.

### Summary and outlook

A review of the current use and potential applications of PET RNGs indicates that this dynamic field is evolving rapidly from being an “art rather than a science”, to a radionuclide delivery system. This multidisciplinary technological paradigm, which resides at the intersection of radiochemistry and chemical separation techniques, has undergone a tremendous metamorphosis and is destined to bring perpetual changes in clinical PET practices. New PET generators are emerging persistently, taking shape progressively and after maturation, steadily migrating towards clinical practice. The relentless parade of new PET generators, destined to unfold on many new fronts in clinical PET, harbor boundless possibilities and a wellspring to spur myriad applications in clinical PET. Almost every advance in PET RNGs is billed as a breakthrough, and the list of “next generation generators” grows longer every day. While the potential benefits of the new PET generators are tremendous, so are the challenges of bringing them from laboratory research to clinical practice for their impact.

RNGs have their roots in NM, and progress is inextricably linked to the continued research and advancements of PET imaging in NM. As PET is moving to the forefront of NM, demands for new radionuclides are emerging far more quickly than they did over the past decade. Because of the pace at which the PET scene is evolving, RNG strategies need a vision for today and tomorrow. Given the importance of PET in molecular imaging, paradigm-changing PET RNGs are quick to grab the headlines.

The advances made so far are exciting and efforts to develop new generators for use in clinical practices are evolving persistently. While the clinical realization of any of these paradigm-changing new PET RNGs would be expected to revitalize current PET practices and provide myriad opportunities to instill new possibilities to reshape the clinical PET of today

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and tomorrow, it requires effective harnessing of emerging technology and inspired vision from clinical as well as industrial partners to provide functional systems in appropriate volumes at the right cost. In this premise, each new generator and associated daughter PET radionuclide must be evaluated on the basis of their performance, affordability, cost effectiveness, and propitious clinical outcome. “Synergy, understanding, and collaboration” have emerged as the three most common descriptors that underpin their survival and growth.

Much has been written about the  $^{82}\text{Sr}/^{82}\text{Rb}$  generator due to its dominance in the field of cardiac PET, but this example should really be viewed largely as a model that can be copied for several alternative PET RNGs. They deserve greater attention not only because a greater range of PET radionuclides will be needed, but also for the adaptability to use different radionuclides for different applications. With a better understanding of the properties, including the physical and chemical properties of each of the radionuclides, a wide range of PET radiopharmaceuticals can be prepared which can be effectively used for molecular imaging of targets for a broad range of biological or disease processes. Despite being a late entrant to PET, the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator has not only consolidated its presence but also established a strong foothold at the forefront of PET. In a relatively short time-span,  $^{68}\text{Ga}$  has virtually pervaded all areas of PET and has become a key PET radionuclide of choice for the foreseeable future. It may be surmised that diffusion of  $^{68}\text{Ga}$  tracers seem poised to bring spectacular developments and serve as the springboard to spur new breakthroughs in PET imaging.

The restricted clinical utility of PET in diagnostic NM is mainly due to limited availability of this technology, its cost, and limited published data supporting its use. In recent years, PET imaging has moved from an exotic diagnostic modality for very few patients to a mainstream modality. The future of generator derived PET radionuclides is, of course, difficult to predict, and there will be surprising inventions, as in the past, in which PET radionuclides availed from a generator may have an unexpected application that will continue to fuel development the field. Healthcare service providers should seize the opportunity by keeping their organizational

strategies updated in the face of continually evolving PET radiotracer technologies and ensure that their organizations continue to pursue optimum PET radiotracers as well as innovative technologies in an effort to reduce the gap between requirements and capabilities.

In spite of the huge potential of PET RNGs, cost-effective availability of parent radionuclides is one major challenge which currently obstructs the path for their widespread progress. To traverse these obstacles, a constant and reliable supply of parent radionuclides of the required quality in the desired quantities needs to be assured. Owing to the inherent requirement of capital intensive installation of cyclotrons, significant expertise, skilled manpower and adequate resources to undertake regular production of radionuclides, the number of commercial radioisotope suppliers remains finite and their current production capabilities remain limited. Additional research efforts and large resources are warranted to undertake their production on a regular basis to meet the current and foreseeable demands.

There are several reasons why marketing authorization of PET RNGs are not attractive. First, the economic investment costs for a PET RNG with a very small potential market cannot be recouped. Second, an RNG housing a short-lived parent radionuclide is unattractive and the investment required for its large-scale production would usually require the availability of targets as well as high energy accelerators. Furthermore, such short-lived parent radionuclides would have to be produced regularly to replenish the generators. This demands extremely efficient logistics for the overall process of availing the proven benefit of PET tracers.

The clinical success of a new RNG largely depends on its application, cost-effective availability of the parent radionuclide, the overall cost associated with its GMP production, and the process of obtaining regulatory approval, which is gradually increasing. The process of converting a promising RNG for the clinical application is rife with scientific and regulatory obstacles. In order to surmount the regulatory barrier and become accepted in daily clinical practice, PET RNGs will likely need a strong cor-

porate sponsor willing to invest. Industry sponsorship is possible in this era because academic inventors now routinely secure strong intellectual property rights on RNGs. If strong intellectual property rights are secured and industry makes a substantial investment, the cost of new PET RNGs will be significantly high, which may lead to few early users and consequently inhibit their widespread use as well as convergence into standard clinical practice. In order to mitigate such unforeseen situations, a more holistic, pragmatic and outcome-oriented regulatory approach is required. NM needs leaders who are capable of managing both technical and non-technical issues, whether in academia, business, government or the medical sector. It is the responsibility of all the stake holders, including research scientists, clinicians, radiopharmacists, hospitals and industries to share a common platform to convince regulatory authorities of the need for change to address the challenges in an ever-demanding regulatory environment. While the utility of generator derived PET tracers has passed many milestones and made considerable inroads into the arena of PET imaging, but without a doubt this is just the tip of the iceberg and further excitement in this field is promised in the foreseeable future.

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### Disclosure of conflict of interest

None.

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### References

- [1] Castello A, Olivari L and Lopci E. Adenoid cystic carcinoma: focus on heavy ion therapy and molecular imaging. *Am J Nucl Med Mol Imaging* 2018; 8: 1-14.
- [2] Davidson CQ, Phenix CP, Tai TC, Khaper N and Lees SJ. Searching for novel PET radiotracers: imaging cardiac perfusion, metabolism and inflammation. *Am J Nucl Med Mol Imaging* 2018; 8: 200-227.
- [3] Filippi L, Chiaravallotti A, Bagni O and Schillaci O.  $^{18}\text{F}$ -labeled radiopharmaceuticals for the molecular neuroimaging of amyloid plaques in Alzheimer's disease. *Am J Nucl Med Mol Imaging* 2018; 8: 268-281.
- [4] Hagemann CE, Ghotbi AA, Kjaer A and Hasbak P. Quantitative myocardial blood flow with Rubidium-82 PET: a clinical perspective. *Am J Nucl Med Mol Imaging* 2015; 5: 457-468.
- [5] Houshmand S, Salavati A, Hess S, Ravina M and Alavi A. The role of molecular imaging in diagnosis of deep vein thrombosis. *Am J Nucl Med Mol Imaging* 2014; 4: 406-425.
- [6] Jensen MM and Kjaer A. Monitoring of anti-cancer treatment with  $^{18}\text{F}$ -FDG and  $^{18}\text{F}$ -FLT PET: a comprehensive review of pre-clinical studies. *Am J Nucl Med Mol Imaging* 2015; 5: 431-456.
- [7] Karakatsanis NA, Fokou E and Tsoumpas C. Dosage optimization in positron emission tomography: state-of-the-art methods and future prospects. *Am J Nucl Med Mol Imaging* 2015; 5: 527-547.
- [8] Keiding S, Sorensen M, Frisch K, Gormsen LC and Munk OL. Quantitative PET of liver functions. *Am J Nucl Med Mol Imaging* 2018; 8: 73-85.
- [9] Li F, Joergensen JT, Hansen AE and Kjaer A. Kinetic modeling in PET imaging of hypoxia. *Am J Nucl Med Mol Imaging* 2014; 4: 490-506.
- [10] Lopci E, Grassi I, Chiti A, Nanni C, Cicoria G, Toschi L, Fonti C, Lodi F, Mattioli S and Fanti S. PET radiopharmaceuticals for imaging of tumor hypoxia: a review of the evidence. *Am J Nucl Med Mol Imaging* 2014; 4: 365-384.
- [11] Sarikaya I. PET studies in epilepsy. *Am J Nucl Med Mol Imaging* 2015; 5: 416-430.
- [12] Vali R, Loidl W, Pirich C, Langesteger W and Beheshti M. Imaging of prostate cancer with PET/CT using  $^{18}\text{F}$ -Fluorocholine. *Am J Nucl Med Mol Imaging* 2015; 5: 96-108.
- [13] Chakravarty R, Goel S, Hong H, Chen F, Valdivinos HF, Hernandez R, Barnhart TE and Cai W. Hollow mesoporous silica nanoparticles for tumor vasculature targeting and PET image-guided drug delivery. *Nanomedicine (Lond)* 2015; 10: 1233-1246.

## Radionuclide generators for PET imaging

- [14] Chakravarty R, Hong H and Cai W. Positron emission tomography image-guided drug delivery: current status and future perspectives. *Mol Pharm* 2014; 11: 3777-3797.
- [15] Quarles van Ufford HM, Quekel LG, van Waes PF, de Haas PJ and de Klerk JM. Diagnostic evaluation of separately acquired PET and CT images by nuclear medicine physicians and radiologists in cancer patients. *Hell J Nucl Med* 2007; 10: 105-108.
- [16] Grammaticos P, Zerva C, Asteriadis I, Trontzos C and Hatzioannou K. Is hybridic positron emission tomography/computerized tomography the only option? The future of nuclear medicine and molecular imaging. *Hell J Nucl Med* 2007; 10: 74-76.
- [17] Townsend DW. Positron emission tomography/computed tomography. *Semin Nucl Med* 2008; 38: 152-166.
- [18] Cho MW and Chin BB.  $^{18}\text{F}$ -FDG PET/CT findings in hepatosplenic Gamma-Delta T-cell lymphoma: case reports and review of the literature. *Am J Nucl Med Mol Imaging* 2018; 8: 137-142.
- [19] Eary JF, Hawkins DS, Rodler ET and Conrad EU.  $^{18}\text{F}$ -FDG PET in sarcoma treatment response imaging. *Am J Nucl Med Mol Imaging* 2011; 1: 47-53.
- [20] Usmani S, Sit C, Gnanasegaran G, den Wyngaert TV and Marafi F. Pictorial atlas of symptomatic accessory ossicles by  $^{18}\text{F}$ -Sodium Fluoride (NaF) PET-CT. *Am J Nucl Med Mol Imaging* 2017; 7: 275-282.
- [21] Vallabhajosula S, Solnes L and Vallabhajosula B. A broad overview of positron emission tomography radiopharmaceuticals and clinical applications: what is new? *Semin Nucl Med* 2011; 41: 246-264.
- [22] Mankoff DA and Katz SI. PET imaging for assessing tumor response to therapy. *J Surg Oncol* 2018; 118: 362-373.
- [23] Chakraborty S, Chakravarty R, Sarma HD, Dash A and Pillai MR. The practicality of nanoceria-PAN-based  $^{68}\text{Ge}/^{68}\text{Ga}$  generator toward preparation of  $^{68}\text{Ga}$ -labeled cyclic RGD dimer as a potential PET radiotracer for tumor imaging. *Cancer Biother Radiopharm* 2013; 28: 77-83.
- [24] Chakravarty R, Chakraborty S, Ram R, Vatsa R, Bhusari P, Shukla J, Mittal BR and Dash A. Detailed evaluation of different  $^{68}\text{Ge}/^{68}\text{Ga}$  generators: an attempt toward achieving efficient  $^{68}\text{Ga}$  radiopharmacy. *J Labelled Comp Radiopharm* 2016; 59: 87-94.
- [25] Chakravarty R, Chakraborty S, Shukla R, Bahadur J, Ram R, Mazumder S, Dev Sarma H, Tyagi AK and Dash A. Mechanochemical synthesis of mesoporous tin oxide: a new generation nanosorbent for  $^{68}\text{Ge}/^{68}\text{Ga}$  generator technology. *Dalton Trans* 2016; 45: 13361-13372.
- [26] Chakravarty R, Dash A and Pillai MR. Availability of yttrium-90 from strontium-90: a nuclear medicine perspective. *Cancer Biother Radiopharm* 2012; 27: 621-641.
- [27] Chakravarty R, Dash A and Pillai MR. Electrochemical separation is an attractive strategy for development of radionuclide generators for medical applications. *Curr Radiopharm* 2012; 5: 271-287.
- [28] Chakravarty R, Ram R, Pillai KT, Pamale Y, Kamat RV and Dash A. Ammonium molybdophosphate impregnated alumina microspheres as a new generation sorbent for chromatographic  $^{137}\text{Cs}/^{137\text{m}}\text{Ba}$  generator. *J Chromatogr A* 2012; 1220: 82-91.
- [29] Chakravarty R, Shukla R, Ram R, Venkatesh M, Tyagi AK and Dash A. Exploitation of nano alumina for the chromatographic separation of clinical grade  $^{188}\text{Re}$  from  $^{188}\text{W}$ : a renaissance of the  $^{188}\text{W}/^{188}\text{Re}$  generator technology. *Anal Chem* 2011; 83: 6342-6348.
- [30] Chakravarty R and Dash A. Nanomaterial-based adsorbents: the prospect of developing new generation radionuclide generators to meet future research and clinical demands. *J Radioanal Nucl Chem* 2014; 299: 741-757.
- [31] Dash A and Chakravarty R. Pivotal role of separation chemistry in the development of radionuclide generators to meet clinical demands. *RSC Adv* 2014; 4: 42779-42803.
- [32] Dash A, Knapp FF Jr and Pillai MR.  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  separation: an assessment of technology options. *Nucl Med Biol* 2013; 40: 167-176.
- [33] Amor-Coarasa A, Schoendorf M, Meckel M, Vallabhajosula S and Babich JW. Comprehensive Quality control of the ITG  $^{68}\text{Ge}/^{68}\text{Ga}$  generator and synthesis of  $^{68}\text{Ga}$ -DOTATOC and  $^{68}\text{Ga}$ -PSMA-HBED-CC for clinical imaging. *J Nucl Med* 2016; 57: 1402-1405.
- [34] Maecke HR, André JP.  $^{68}\text{Ga}$ -PET radiopharmacy: a generator-based alternative to  $^{18}\text{F}$ -radiopharmacy. *Ernst Schering Res Found Workshop* 2007; 215-242.
- [35] Martiniova L, Palatis L, Etchebehere E and Ravizzini G. Gallium-68 in medical imaging. *Curr Radiopharm* 2016; 9: 187-207.
- [36] Prata MI. Gallium-68: a new trend in PET radiopharmacy. *Curr Radiopharm* 2012; 5: 142-149.
- [37] Velikyan I and Lindhe O. Preparation and evaluation of a  $^{68}\text{Ga}$ -labeled RGD-containing octapeptide for noninvasive imaging of angiogenesis: biodistribution in non-human primate. *Am J Nucl Med Mol Imaging* 2018; 8: 15-31.
- [38] Velikyan I, Rosenstrom U and Eriksson O. Fully automated GMP production of [ $^{68}\text{Ga}$ ]Ga-DO3A-VS-Cys(40)-Exendin-4 for clinical use. *Am J Nucl Med Mol Imaging* 2017; 7: 111-125.

## Radionuclide generators for PET imaging

- [39] Rosch F. Past, present and future of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators. *Appl Radiat Isot* 2013; 76: 24-30.
- [40] Roesch F. Maturation of a key resource - the germanium-68/gallium-68 generator: development and new insights. *Curr Radiopharm* 2012; 5: 202-211.
- [41] Gleason GI. A positron cow. *Int J Appl Radiat Isot* 1960; 8: 90-94.
- [42] Greene MW and Tucker WD. An improved gallium-68 cow. *Appl Radiat Isot* 1961; 12: 62-63.
- [43] Kopecký P and Mudrová B.  $^{68}\text{Ge}/^{68}\text{Ga}$  generator for the production of  $^{68}\text{Ga}$  in an ionic form. *Appl Radiat Isot* 1974; 25: 263-268.
- [44] Malyshev KV and Smirnov VV. A generator of gallium-68 based on zirconium hydroxide. *Radiokhimiya* 1975; 17: 137-140.
- [45] Arino H, Skraba WJ and Kramer HH. A new  $^{68}\text{Ge}/^{68}\text{Ga}$  radioisotope generator system. *Appl Radiat Isot* 1978; 29: 117-120.
- [46] Loc'h C, Maziere B and Comar D. A new generator for ionic gallium-68. *J Nucl Med* 1980; 21: 171-173.
- [47] Neirinckx RD and Davis MA. Potential column chromatography generators for ionic Ga-68. I. Inorganic substrates. *J Nucl Med* 1979; 20: 1075-1079.
- [48] Neirinckx RD and Davis MA. Potential column chromatography for ionic Ga-68. II: organic ion exchangers as chromatographic supports. *J Nucl Med* 1980; 21: 81-83.
- [49] McElvany KD, Hopkins KT and Welch MJ. Comparison of  $^{68}\text{Ge}/^{68}\text{Ga}$  generator systems for radiopharmaceutical production. *Appl Radiat Isot* 1984; 35: 521-524.
- [50] Ambe S.  $^{68}\text{Ge}/^{68}\text{Ga}$  generator with alpha-ferric oxide support. *Appl Radiat Isot* 1988; 39: 49-51.
- [51] Razbash AA, Sevastianov YG, Krasnov NN, Leonov AI and Panickin VE. Germanium-68 row of products. In: *Proceedings of the 5<sup>th</sup> International Conference on Isotopes 51Cl*, Brussels, Belgium, April 25-29, 2005; 147-151.
- [52] Majkowska-Pilip A and Bilewicz A. Macrocyclic complexes of scandium radionuclides as precursors for diagnostic and therapeutic radiopharmaceuticals. *J Inorg Biochem* 2011; 105: 313-320.
- [53] Eppard E, Wuttke M, Nicodemus PL and Rosch F. Ethanol-based post-processing of generator-derived  $^{68}\text{Ga}$  toward kit-type preparation of  $^{68}\text{Ga}$ -radiopharmaceuticals. *J Nucl Med* 2014; 55: 1023-1028.
- [54] Zheronosekov KP, Filosofov DV, Baum RP, Aschoff P, Bihl H, Razbash AA, Jahn M, Jennewein M and Rosch F. Processing of generator-produced  $^{68}\text{Ga}$  for medical application. *J Nucl Med* 2007; 48: 1741-1748.
- [55] Asti M, De Pietri G, Fraternali A, Grassi E, Sghedoni R, Fioroni F, Roesch F, Versari A and Salvo D. Validation of  $^{68}\text{Ge}/^{68}\text{Ga}$  generator processing by chemical purification for routine clinical application of  $^{68}\text{Ga}$ -DOTATOC. *Nucl Med Biol* 2008; 35: 721-724.
- [56] Mueller D, Klette I, Baum RP, Gottschaldt M, Schultz MK and Breeman WA. Simplified NaCl based  $^{68}\text{Ga}$  concentration and labeling procedure for rapid synthesis of  $^{68}\text{Ga}$  radiopharmaceuticals in high radiochemical purity. *Bioconjug Chem* 2012; 23: 1712-1717.
- [57] Loktionova NS, Belozub AN, Filosofov DV, Zheronosekov KP, Wagner T, Turler A and Rosch F. Improved column-based radiochemical processing of the generator produced  $^{68}\text{Ga}$ . *Appl Radiat Isot* 2011; 69: 942-946.
- [58] Rosch F. Post-processing via cation exchange cartridges: versatile options. *Recent Results Cancer Res* 2013; 194: 33-42.
- [59] Mueller D, Klette I and Baum RP. Purification and labeling strategies for  $^{68}\text{Ga}$  from  $^{68}\text{Ge}/^{68}\text{Ga}$  generator eluate. *Recent Results Cancer Res* 2013; 194: 77-87.
- [60] Velikyan I. Prospective of  $^{68}\text{Ga}$ -radiopharmaceutical development. *Theranostics* 2013; 4: 47-80.
- [61] Chakravarty R, Shukla R, Ram R, Venkatesh M, Dash A and Tyagi AK. Nanoceria-PAN composite-based advanced sorbent material: a major step forward in the field of clinical-grade  $^{68}\text{Ge}/^{68}\text{Ga}$  generator. *ACS Appl Mater Interfaces* 2010; 2: 2069-2075.
- [62] Chakravarty R, Chakraborty S, Ram R, Dash A and Pillai MR. Long-term evaluation of 'BARC  $^{68}\text{Ge}/^{68}\text{Ga}$  generator' based on the nanoceria-polyacrylonitrile composite sorbent. *Cancer Biother Radiopharm* 2013; 28: 631-637.
- [63] Chakravarty R, Shukla R, Ram R, Tyagi AK, Dash A and Venkatesh M. Development of a nano-zirconia based  $^{68}\text{Ge}/^{68}\text{Ga}$  generator for biomedical applications. *Nucl Med Biol* 2011; 38: 575-583.
- [64] Bartholomä MD. Recent developments in the design of bifunctional chelators for metal-based radiopharmaceuticals used in Positron Emission Tomography. *Inorganica Chimica Acta* 2012; 389: 36-51.
- [65] Chakravarty R, Chakraborty S, Radhakrishnan ER, Kamaleshwaran K, Shinto A and Dash A. Clinical  $^{68}\text{Ga}$ -PET: is radiosynthesis module an absolute necessity? *Nucl Med Biol* 2017; 46: 1-11.
- [66] Abongwa C, Mott S, Schafer B, McNeely P, Abusin G, O'Dorisio T, Zamba G, O'Dorisio MS and Menda Y. Safety and accuracy of  $^{68}\text{Ga}$ -DOTATOC PET/CT in children and young adults with solid tumors. *Am J Nucl Med Mol Imaging* 2017; 7: 228-235.
- [67] Afzelius P, Nielsen OL, Alstrup AK, Bender D, Leifsson PS, Jensen SB and Schonheyder HC.

- Biodistribution of the radionuclides  $^{18}\text{F}$ -FDG,  $^{11}\text{C}$ -methionine,  $^{11}\text{C}$ -PK11195, and  $^{68}\text{Ga}$ -citrate in domestic juvenile female pigs and morphological and molecular imaging of the tracers in hematogenously disseminated *Staphylococcus aureus* lesions. *Am J Nucl Med Mol Imaging* 2016; 6: 42-58.
- [68] Esfahani SA, Salcedo S, Heidari P, Catalano OA, Pauplis R, Hesterman J, Kronauge JF and Mahmood U. A phase one, single-dose, open-label, clinical safety and PET/MR imaging study of  $^{68}\text{Ga}$ -DOTATOC in healthy volunteers. *Am J Nucl Med Mol Imaging* 2017; 7: 53-62.
- [69] Madru R, Tran TA, Axelsson J, Ingvar C, Bibic A, Stahlberg F, Knutsson L and Strand SE.  $^{68}\text{Ga}$ -labeled superparamagnetic iron oxide nanoparticles (SPIONs) for multi-modality PET/MR/Cherenkov luminescence imaging of sentinel lymph nodes. *Am J Nucl Med Mol Imaging* 2013; 4: 60-69.
- [70] Mojtahedi A, Alavi A, Thamake S, Amerinia R, Ranganathan D, Tworowska I and Delpassand ES. Assessment of vulnerable atherosclerotic and fibrotic plaques in coronary arteries using  $^{68}\text{Ga}$ -DOTATATE PET/CT. *Am J Nucl Med Mol Imaging* 2015; 5: 65-71.
- [71] Olsen IH, Langer SW, Federspiel BH, Oxbol J, Loft A, Berthelsen AK, Mortensen J, Oturai P, Knigge U and Kjaer A.  $^{68}\text{Ga}$ -DOTATOC PET and gene expression profile in patients with neuroendocrine carcinomas: strong correlation between PET tracer uptake and gene expression of somatostatin receptor subtype 2. *Am J Nucl Med Mol Imaging* 2016; 6: 59-72.
- [72] Retamal J, Sorensen J, Lubberink M, Suarez-Sipmann F, Borges JB, Feinstein R, Jalkanen S, Antoni G, Hedenstierna G, Roivainen A, Larsson A and Velikyan I. Feasibility of  $^{68}\text{Ga}$ -labeled Siglec-9 peptide for the imaging of acute lung inflammation: a pilot study in a porcine model of acute respiratory distress syndrome. *Am J Nucl Med Mol Imaging* 2016; 6: 18-31.
- [73] Selvaraju RK, Bulenga TN, Espes D, Lubberink M, Sorensen J, Eriksson B, Estrada S, Velikyan I and Eriksson O. Dosimetry of [ $^{68}\text{Ga}$ ]Ga-DO3A-VS-Cys(40)-Exendin-4 in rodents, pigs, non-human primates and human - repeated scanning in human is possible. *Am J Nucl Med Mol Imaging* 2015; 5: 259-269.
- [74] Decristoforo C, Pickett RD and Verbruggen A. Feasibility and availability of  $^{68}\text{Ga}$ -labelled peptides. *Eur J Nucl Med Mol Imaging* 2012; 39 Suppl 1: S31-40.
- [75] Win Z, Al-Nahhas A, Rubello D and Gross MD. Somatostatin receptor PET imaging with Gallium-68 labeled peptides. *Q J Nucl Med Mol Imaging* 2007; 51: 244-250.
- [76] Persson M, Madsen J, Ostergaard S, Ploug M and Kjaer A.  $^{68}\text{Ga}$ -labeling and in vivo evaluation of a uPAR binding DOTA- and NODAGA-conjugated peptide for PET imaging of invasive cancers. *Nucl Med Biol* 2012; 39: 560-569.
- [77] Mojtahedi A, Thamake S, Tworowska I, Ranganathan D and Delpassand ES. The value of  $^{68}\text{Ga}$ -DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. *Am J Nucl Med Mol Imaging* 2014; 4: 426-434.
- [78] Wild D, Bomanji JB, Benkert P, Maecke H, Ell PJ, Reubi JC and Caplin ME. Comparison of  $^{68}\text{Ga}$ -DOTANOC and  $^{68}\text{Ga}$ -DOTATATE PET/CT within patients with gastroenteropancreatic neuroendocrine tumors. *J Nucl Med* 2013; 54: 364-372.
- [79] FDA grants orphan drug designation for  $^{68}\text{Ga}$ -DOTATOC. *J Nucl Med* 2014; 55: 10N.
- [80] Jensen RT, Battey JF, Spindel ER and Benya RV. International Union of Pharmacology. LXVIII. Mammalian bombesin receptors: nomenclature, distribution, pharmacology, signaling, and functions in normal and disease states. *Pharmacol Rev* 2008; 60: 1-42.
- [81] Kahkonen E, Jambor I, Kemppainen J, Lehtio K, Gronroos TJ, Kuisma A, Luoto P, Sipila HJ, Tolvanen T, Alanen K, Silen J, Kallajoki M, Roivainen A, Schafer N, Schibli R, Dragic M, Johayem A, Valencia R, Borkowski S and Minn H. In vivo imaging of prostate cancer using [ $^{68}\text{Ga}$ ]-labeled bombesin analog BAY86-7548. *Clin Cancer Res* 2013; 19: 5434-5443.
- [82] Tateishi U, Oka T and Inoue T. Radiolabeled RGD peptides as integrin  $\alpha_v\beta_3$ -targeted PET tracers. *Curr Med Chem* 2012; 19: 3301-3309.
- [83] Sun Y, Zeng Y, Zhu Y, Feng F, Xu W, Wu C, Xing B, Zhang W, Wu P, Cui L, Wang R, Li F, Chen X and Zhu Z. Application of  $^{68}\text{Ga}$ -PRGD<sub>2</sub> PET/CT for  $\alpha_v\beta_3$ -integrin imaging of myocardial infarction and stroke. *Theranostics* 2014; 4: 778-786.
- [84] Banerjee SR, Pullambhatla M, Byun Y, Nimmagadda S, Green G, Fox JJ, Horti A, Mease RC and Pomper MG.  $^{68}\text{Ga}$ -labeled inhibitors of prostate-specific membrane antigen (PSMA) for imaging prostate cancer. *J Med Chem* 2010; 53: 5333-5341.
- [85] Eder M, Schafer M, Bauder-Wust U, Hull WE, Wangler C, Mier W, Haberkorn U and Eisenhut M.  $^{68}\text{Ga}$ -complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. *Bioconjug Chem* 2012; 23: 688-697.
- [86] Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, Holland-Letz T, Hadaschik BA, Giesel FL, Debus J and Haberkorn U. Comparison of PET imaging with a  $^{68}\text{Ga}$ -labelled PSMA ligand and  $^{18}\text{F}$ -choline-

## Radionuclide generators for PET imaging

- based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* 2014; 41: 11-20.
- [87] Kilian K.  $^{68}\text{Ga}$ -DOTA and analogs: current status and future perspectives. *Rep Pract Oncol Radiother* 2014; 19: S13-S21.
- [88] Doughton JA, Hofman MS, Eu P, Hicks RJ and Williams SG. A first-in-man study of  $^{68}\text{Ga}$ -nanocolloid PET-CT sentinel lymph node imaging in prostate cancer demonstrates aberrant lymphatic drainage pathways. *J Nucl Med* 2018; 59: 1837-1842.
- [89] Evertsson M, Kjellman P, Cinthio M, Andersson R, Tran TA, In't Zandt R, Grafstrom G, Toftvall H, Fredriksson S, Ingvar C, Strand SE and Jansson T. Combined magnetomotive ultrasound, PET/CT, and MR imaging of  $^{68}\text{Ga}$ -labelled superparamagnetic iron oxide nanoparticles in rat sentinel lymph nodes in vivo. *Sci Rep* 2017; 7: 4824.
- [90] Yoshinaga K, Klein R and Tamaki N. Generator-produced rubidium-82 positron emission tomography myocardial perfusion imaging-from basic aspects to clinical applications. *J Cardiol* 2010; 55: 163-173.
- [91] Alvarez-Diez TM, deKemp R, Beanlands R and Vincent J. Manufacture of strontium-82/rubidium-82 generators and quality control of rubidium-82 chloride for myocardial perfusion imaging in patients using positron emission tomography. *Appl Radiat Isot* 1999; 50: 1015-1023.
- [92] N JE, Benelfassi A, R SBB and DeKemp RA. An  $^{82}\text{Rb}$  infusion system for quantitative perfusion imaging with 3D PET. *Appl Radiat Isot* 2004; 60: 921-927.
- [93] Klein R, Adler A, Beanlands RS and DeKemp RA. Precision-controlled elution of a  $^{82}\text{Sr}/^{82}\text{Rb}$  generator for cardiac perfusion imaging with positron emission tomography. *Phys Med Biol* 2007; 52: 659-673.
- [94] Machac J. Cardiac positron emission tomography imaging. *Semin Nucl Med* 2005; 35: 17-36.
- [95] Bateman TM, Heller GV, McGhie AI, Friedman JD, Case JA, Bryngelson JR, Hertenstein GK, Moutray KL, Reid K and Cullom SJ. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. *J Nucl Cardiol* 2006; 13: 24-33.
- [96] Sampson UK, Dorbala S, Limaye A, Kwong R and Di Carli MF. Diagnostic accuracy of rubidium-82 myocardial perfusion imaging with hybrid positron emission tomography/computed tomography in the detection of coronary artery disease. *J Am Coll Cardiol* 2007; 49: 1052-1058.
- [97] Lortie M, Beanlands RS, Yoshinaga K, Klein R, Dasilva JN and DeKemp RA. Quantification of myocardial blood flow with  $^{82}\text{Rb}$  dynamic PET imaging. *Eur J Nucl Med Mol Imaging* 2007; 34: 1765-1774.
- [98] Gould KL, Goldstein RA, Mullani NA, Kirkeeide RL, Wong WH, Tewson TJ, Berridge MS, Bolomey LA, Hartz RK, Smalling RW, Fuentes F and Nishikawa A. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. VIII. Clinical feasibility of positron cardiac imaging without a cyclotron using generator-produced rubidium-82. *J Am Coll Cardiol* 1986; 7: 775-789.
- [99] Merhige ME, Breen WJ, Shelton V, Houston T, D'Arcy BJ and Perna AF. Impact of myocardial perfusion imaging with PET and  $^{82}\text{Rb}$  on downstream invasive procedure utilization, costs, and outcomes in coronary disease management. *J Nucl Med* 2007; 48: 1069-1076.
- [100] Groves AM, Speechly-Dick ME, Dickson JC, Kayani I, Endozo R, Blanchard P, Shastry M, Prvulovich E, Waddington WA, Ben-Haim S, Bomanji JB, McEwan JR and Ell PJ. Cardiac  $^{82}\text{Rb}$  PET/CT: initial European experience. *Eur J Nucl Med Mol Imaging* 2007; 34: 1965-1972.
- [101] Roesch F. Scandium-44: benefits of a long-lived PET radionuclide available from the  $^{44}\text{Ti}/^{44}\text{Sc}$  generator system. *Curr Radiopharm* 2012; 5: 187-201.
- [102] Filosofov DV, Loktionova NS and Rosch F. A  $^{44}\text{Ti}/^{44}\text{Sc}$  radionuclide generator for potential nuclear-medical application of  $^{44}\text{Sc}$ -based PET-radiopharmaceuticals. *Radiochim Acta* 2010; 98: 149-156.
- [103] Pruszyński M, Loktionova NS, Filosofov DV and Rosch F. Post-elution processing of  $^{44}\text{Ti}/^{44}\text{Sc}$  generator-derived  $^{44}\text{Sc}$  for clinical application. *Appl Radiat Isot* 2010; 68: 1636-1641.
- [104] Viola-Villegas N and Doyle RP. The coordination chemistry of 1,4,7,10-tetraazacyclododecane- $\text{N},\text{N}',\text{N}'',\text{N}'''$ -tetraacetic acid ( $\text{H}_4\text{DOTA}$ ): structural overview and analyses on structure-stability relationships. *Coord Chem Rev* 2009; 253: 1906-1925.
- [105] Mausner LF, Joshi V, Kolsky KL, Meinken GE, Mease RC, Sweet MP and Srivastava SC. Evaluation of chelating agents for radioimmunotherapy with scandium-47. *J Nucl Med* 1995; 36: 104.
- [106] Polosak M, Piotrowska A, Krajewski S and Bilewicz A. Stability of  $^{47}\text{Sc}$ -complexes with acyclic polyamino-polycarboxylate ligands. *J Radioanal Nucl Chem* 2013; 295: 1867-1872.
- [107] Pruszyński M, Majkowska-Pilip A, Loktionova NS, Eppard E and Roesch F. Radiolabeling of

## Radionuclide generators for PET imaging

- DOTATOC with the long-lived positron emitter  $^{44}\text{Sc}$ . *Appl Radiat Isot* 2012; 70: 974-979.
- [108] Muller C, Bunka M, Reber J, Fischer C, Zher-nosekov K, Turler A and Schibli R. Promises of cyclotron-produced  $^{44}\text{Sc}$  as a diagnostic match for trivalent beta-emitters: in vitro and in vivo study of a  $^{44}\text{Sc}$ -DOTA-folate conjugate. *J Nucl Med* 2013; 54: 2168-2174.
- [109] Laforest R, Dehdashti F, Lewis JS and Schwarz SW. Dosimetry of  $^{60/61/62/64}\text{Cu}$ -ATSM: a hypoxia imaging agent for PET. *Eur J Nucl Med Mol Imaging* 2005; 32: 764-770.
- [110] Robinson GD Jr, Zielinski FW and Lee AW. The zinc-62/copper-62 generator: a convenient source of copper-62 for radiopharmaceuticals. *Int J Appl Radiat Isot* 1980; 31: 111-116.
- [111] Fujibayashi Y, Matsumoto K, Yonekura Y, Koni-shi J and Yokoyama A. A new zinc-62/cop-per-62 generator as a copper-62 source for PET radiopharmaceuticals. *J Nucl Med* 1989; 30: 1838-1842.
- [112] Zweit J, Goodall R, Cox M, Babich JW, Potter GA, Sharma HL and Ott RJ. Development of a high performance zinc-62/copper-62 radionu-clide generator for positron emission tomogra-phy. *Eur J Nucl Med* 1992; 19: 418-425.
- [113] Bormans G, Janssen A, Adriaens P, Crombez D, Witsenboer A, de Goeij J, Mortelmans L and Verbruggen A. A  $^{62}\text{Zn}/^{62}\text{Cu}$  generator for the routine production of  $^{62}\text{Cu}$ -PTSM. *Appl Radiat Isot* 1992; 43: 1437-1441.
- [114] Fukumura T, Okada K, Suzuki H, Nakao R, Mu-kai K, Szelecsenyi F, Kovacs Z and Suzuki K. An improved  $^{62}\text{Zn}/^{62}\text{Cu}$  generator based on a cat-ion exchanger and its fully remote-controlled preparation for clinical use. *Nucl Med Biol* 2006; 33: 821-827.
- [115] El-Azony KM. Improving the separation of Cu(II) from Zn(II) based on an anion exchanger for the preparation a  $^{62}\text{Zn}/^{62}\text{Cu}$  generator. *Appl Radiat Isot* 2011; 69: 1176-1180.
- [116] Wadas TJ, Wong EH, Weisman GR and Ander-son CJ. Copper chelation chemistry and its role in copper radiopharmaceuticals. *Curr Pharm Des* 2007; 13: 3-16.
- [117] Szymanski P, Fraczek T, Markowicz M and Mi-kiciuk-Olasik E. Development of copper based drugs, radiopharmaceuticals and medical ma-terials. *Biometals* 2012; 25: 1089-1112.
- [118] Lewis JS, Sharp TL, Laforest R, Fujibayashi Y and Welch MJ. Tumor uptake of copper-diacetyl-bis(N(4)-methylthiosemicarbazone): effect of changes in tissue oxygenation. *J Nucl Med* 2001; 42: 655-661.
- [119] Obata A, Yoshimi E, Waki A, Lewis JS, Oyama N, Welch MJ, Saji H, Yonekura Y and Fujibayashi Y. Retention mechanism of hypoxia selective nuclear imaging/radiotherapeutic agent cu-di-acetyl-bis(N4-methylthiosemicarbazone) (Cu-ATSM) in tumor cells. *Ann Nucl Med* 2001; 15: 499-504.
- [120] Wong TZ, Lacy JL, Petry NA, Hawk TC, Sporn TA, Dewhirst MW and Vlahovic G. PET of hypoxia and perfusion with  $^{62}\text{Cu}$ -ATSM and  $^{62}\text{Cu}$ -PTSM using a  $^{62}\text{Zn}/^{62}\text{Cu}$  generator. *AJR Am J Roent-genol* 2008; 190: 427-432.
- [121] O'Donoghue JA, Zanzonico P, Pugachev A, Wen B, Smith-Jones P, Cai S, Burnazi E, Finn RD, Burgman P, Ruan S, Lewis JS, Welch MJ, Ling CC and Humm JL. Assessment of regional tu-mor hypoxia using  $^{18}\text{F}$ -fluoromisonidazole and  $^{64}\text{Cu}$ (II)-diacetyl-bis(N4-methylthiosemicarba-zone) positron emission tomography: compar-ative study featuring microPET imaging, Po2 probe measurement, autoradiography, and fluorescent microscopy in the R3327-AT and FaDu rat tumor models. *Int J Radiat Oncol Biol Phys* 2005; 61: 1493-1502.
- [122] Dehdashti F, Grigsby PW, Lewis JS, Laforest R, Siegel BA and Welch MJ. Assessing tumor hy-poxia in cervical cancer by PET with  $^{60}\text{Cu}$ -la-beled diacetyl-bis(N4-methylthiosemicarbazone). *J Nucl Med* 2008; 49: 201-205.
- [123] Dehdashti F, Grigsby PW, Mintun MA, Lewis JS, Siegel BA and Welch MJ. Assessing tumor hy-poxia in cervical cancer by positron emission tomography with  $^{60}\text{Cu}$ -ATSM: relationship to therapeutic response-a preliminary report. *Int J Radiat Oncol Biol Phys* 2003; 55: 1233-1238.
- [124] Lewis JS, Laforest R, Dehdashti F, Grigsby PW, Welch MJ and Siegel BA. An imaging compari-son of  $^{64}\text{Cu}$ -ATSM and  $^{60}\text{Cu}$ -ATSM in cancer of the uterine cervix. *J Nucl Med* 2008; 49: 1177-1182.
- [125] Lohith TG, Kudo T, Demura Y, Umeda Y, Kiyono Y, Fujibayashi Y and Okazawa H. Pathophy-siologic correlation between  $^{62}\text{Cu}$ -ATSM and  $^{18}\text{F}$ -FDG in lung cancer. *J Nucl Med* 2009; 50: 1948-1953.
- [126] Minagawa Y, Shizukuishi K, Koike I, Horiuchi C, Watanuki K, Hata M, Omura M, Odagiri K, Toh-nai I, Inoue T and Tateishi U. Assessment of tumor hypoxia by  $^{62}\text{Cu}$ -ATSM PET/CT as a pre-dictor of response in head and neck cancer: a pilot study. *Ann Nucl Med* 2011; 25: 339-345.
- [127] Tateishi K, Tateishi U, Nakanowatari S, Ohtake M, Minamimoto R, Suenaga J, Murata H, Kubo-ta K, Inoue T and Kawahara N.  $^{62}\text{Cu}$ -diacetyl-bis (N(4)-methylthiosemicarbazone) PET in hu-man gliomas: comparative study with [ $^{18}\text{F}$ ] fluorodeoxyglucose and L-methyl- [ $^{14}\text{C}$ ]methio-nine PET. *AJNR Am J Neuroradiol* 2014; 35: 278-284.
- [128] Herrero P, Hartman JJ, Green MA, Anderson CJ, Welch MJ, Markham J and Bergmann SR. Re-gional myocardial perfusion assessed with generator-produced copper-62-PTSM and PET. *J Nucl Med* 1996; 37: 1294-1300.
- [129] Haynes NG, Lacy JL, Nayak N, Martin CS, Dai D, Mathias CJ and Green MA. Performance of a  $^{62}\text{Zn}/^{62}\text{Cu}$  generator in clinical trials of PET per-

## Radionuclide generators for PET imaging

- fusion agent  $^{62}\text{Cu}$ -PTSM. *J Nucl Med* 2000; 41: 309-314.
- [130] Herrero P, Markham J, Weinheimer CJ, Anderson CJ, Welch MJ, Green MA and Bergmann SR. Quantification of regional myocardial perfusion with generator-produced  $^{62}\text{Cu}$ -PTSM and positron emission tomography. *Circulation* 1993; 87: 173-183.
- [131] Wallhaus TR, Lacy J, Whang J, Green MA, Nickles RJ and Stone CK. Human biodistribution and dosimetry of the PET perfusion agent copper-62-PTSM. *J Nucl Med* 1998; 39: 1958-1964.
- [132] Tadamura E, Tamaki N, Okazawa H, Fujibayashi Y, Kudoh T, Yonekura Y, Magata Y, Nohara R, Sasayama S and Konishi J. Generator-produced copper-62-PTSM as a myocardial PET perfusion tracer compared with nitrogen-13-ammonia. *J Nucl Med* 1996; 37: 729-735.
- [133] Shelton ME, Green MA, Mathias CJ, Welch MJ and Bergmann SR. Assessment of regional myocardial and renal blood flow with copper-PTSM and positron emission tomography. *Circulation* 1990; 82: 990-997.
- [134] Mathias CJ, Welch MJ, Raichle ME, Mintun MA, Lich LL, McGuire AH, Zinn KR, John EK and Green MA. Evaluation of a potential generator-produced PET tracer for cerebral perfusion imaging: single-pass cerebral extraction measurements and imaging with radiolabeled Cu-PTSM. *J Nucl Med* 1990; 31: 351-359.
- [135] Green MA, Mathias CJ, Welch MJ, McGuire AH, Perry D, Fernandez-Rubio F, Perlmutter JS, Raichle ME and Bergmann SR. Copper-62-labeled pyruvaldehyde bis(N4-methylthiosemicarbazone)copper(II): synthesis and evaluation as a positron emission tomography tracer for cerebral and myocardial perfusion. *J Nucl Med* 1990; 31: 1989-1996.
- [136] Tateishi K, Tateishi U, Sato M, Yamanaka S, Kanno H, Murata H, Inoue T and Kawahara N. Application of  $^{62}\text{Cu}$ -diacetyl-bis (N4-methylthiosemicarbazone) PET imaging to predict highly malignant tumor grades and hypoxia-inducible factor-1 $\alpha$  expression in patients with glioma. *AJNR Am J Neuroradiol* 2013; 34: 92-99.
- [137] Fletcher JW, Logan TF, Eitel JA, Mathias CJ, Ng Y, Lacy JL, Hutchins GD and Green MA. Whole-body PET/CT evaluation of tumor perfusion using generator-based  $^{62}\text{Cu}$ -ethylglyoxal bis (thiosemicarbazone) copper (II): validation by direct comparison to  $^{15}\text{O}$ -water in metastatic renal cell carcinoma. *J Nucl Med* 2015; 56: 56-62.
- [138] Green MA, Mathias CJ, Willis LR, Handa RK, Lacy JL, Miller MA and Hutchins GD. Assessment of Cu-ETS as a PET radiopharmaceutical for evaluation of regional renal perfusion. *Nucl Med Biol* 2007; 34: 247-255.
- [139] Ng Y, Lacy JL, Fletcher JW and Green MA. Performance of a  $^{62}\text{Zn}/^{62}\text{Cu}$  microgenerator in kit-based synthesis and delivery of [ $^{62}\text{Cu}$ ]Cu-ETS for PET perfusion imaging. *Appl Radiat Isot* 2014; 91: 38-43.
- [140] Black NF, McJames S, Rust TC and Kadrmas DJ. Evaluation of rapid dual-tracer  $^{62}\text{Cu}$ -PTSM+  $^{62}\text{Cu}$ -ATSM PET in dogs with spontaneously occurring tumors. *Phys Med Biol* 2008; 53: 217-232.
- [141] Rust TC and Kadrmas DJ. Rapid dual-tracer PTSM+ ATSM PET imaging of tumour blood flow and hypoxia: a simulation study. *Phys Med Biol* 2006; 51: 61-75.
- [142] Al-Kouraiishi SH and Boswell GGJ. An isotope generator for  $^{72}\text{As}$ . *Int J Appl Radiat Isot* 1978; 29: 607-609.
- [143] Phillips DR. Chemistry and concept for an automated  $^{72}\text{Se}/^{72}\text{As}$  generator. United States Patent No. 5,371,372 (1994).
- [144] Phillips DR, Hamilton VT, Taylor MD, Farnham JE, Emran AM, Rowe RW and Pattel D. Generator-produced arsenic-72 in positron emission tomography. *Radioact Radiochem* 1992; 3: 53-58.
- [145] Jennewein M, Schmidt A, Novgorodov AF, Qaim SM and Rösch F. A no-carrier-added  $^{72}\text{Se}/^{72}\text{As}$  radionuclide generator based on distillation. *Radiochim Acta* 2004; 92: 245-249.
- [146] Jennewein M, Qaim SM, Kulkarni PV, Mason RP, Hermanne A and Roesch F. A no-carrier-added  $^{72}\text{Se}/^{72}\text{As}$  radionuclide generator based on solid phase extraction. *Radiochim Acta* 2005; 93: 579-583.
- [147] Chajduk E, Doner K, Polkowska-Motrenko H and Bilewicz A. Novel radiochemical separation of arsenic from selenium for  $^{72}\text{Se}/^{72}\text{As}$  generator. *Appl Radiat Isot* 2012; 70: 819-822.
- [148] Ballard B, Wycoff D, Birnbaum ER, John KD, Lenz JW, Jurisson SS, Cutler CS, Nortier FM, Taylor WA and Fassbender ME. Selenium-72 formation via nat Br(p,x) induced by 100 MeV protons: steps towards a novel  $^{72}\text{Se}/^{72}\text{As}$  generator system. *Appl Radiat Isot* 2012; 70: 595-601.
- [149] Jennewein M, Hermanne A, Mason RP, Thorpe PE and Rösch F. A new method for the labelling of proteins with radioactive arsenic isotopes. *Nucl Instrum Methods Phys Res A* 2006; 569: 512-517.
- [150] Jennewein M, Lewis MA, Zhao D, Tsyganov E, Slavine N, He J, Watkins L, Kodibagkar VD, O'Kelly S, Kulkarni P, Antich PP, Hermanne A, Rosch F, Mason RP and Thorpe PE. Vascular imaging of solid tumors in rats with a radioactive arsenic-labeled antibody that binds exposed phosphatidylserine. *Clin Cancer Res* 2008; 14: 1377-1385.

## Radionuclide generators for PET imaging

- [151] Lundqvist H, Scott-Robson S, Einarsson L and Malmberg P.  $^{110}\text{Sn}/^{110}\text{In}$ —a new generator system for positron emission tomography. *Int J Rad Appl Instrum A* 1991; 42: 447-450.
- [152] Lubberink M, Tolmachev V, Widstrom C, Bruskin A, Lundqvist H and Westlin JE.  $^{110\text{m}}\text{In}$ -DTPA-D-Phe1-octreotide for imaging of neuroendocrine tumors with PET. *J Nucl Med* 2002; 43: 1391-1397.
- [153] Rösch F, Qaim SM, Novgorodov AF and Ying-Ming T. Production of positron-emitting  $^{110\text{m}}\text{In}$  via the  $^{110}\text{Cd}(3\text{He}, 3\text{n})^{110}\text{Sn}\rightarrow^{110\text{m}}\text{In}$  process. *Appl Radiat Isot* 1997; 48: 19-26.
- [154] Atkins HL, Som P, Fairchild RG, Hui J, Schachner E, Goldman A and Ku T. Myocardial positron tomography with manganese-52m. *Radiology* 1979; 133: 769-774.
- [155] Atcher RW, Friedman AM, Huizenga JR, Rayudu GV, Silverstein EA and Turner DA. Manganese-52m, a new short-lived, generator-produced radionuclide: a potential tracer for positron tomography. *J Nucl Med* 1980; 21: 565-569.
- [156] Herscheid JD, Vos CM and Hoekstra A. Manganese-52m for direct application: a new  $^{52}\text{Fe}/^{52\text{m}}\text{Mn}$  generator based on a hydroxamate resin. *Int J Appl Radiat Isot* 1983; 34: 883-886.
- [157] Ku TH, Richards P, Stang LG Jr and Prach T. Preparation of  $^{52}\text{Fe}$  and its use in a  $^{52}\text{Fe}/^{52\text{m}}\text{Mn}$  generator. *Radiology* 1979; 132: 475-477.
- [158] Atcher RW, Friedman AM and Huizenga JR. Production of  $^{52}\text{Fe}$  for use in a radionuclide generator system. *Int J Nucl Med Biol* 1980; 7: 75-78.
- [159] Blauenstein P, Pellikka R and Schubiger PA. Reinvestigation of a physiological eluate of the  $^{52}\text{Fe}/^{52\text{m}}\text{Mn}$  generator. *Appl Radiat Isot* 1997; 48: 1097-1101.
- [160] Buck A, Nguyen N, Burger C, Ziegler S, Frey L, Weigand G, Erhardt W, Senekowitsch-Schmidtke R, Pellikka R, Blauenstein P, Locher JT and Schwaiger M. Quantitative evaluation of manganese-52m as a myocardial perfusion tracer in pigs using positron emission tomography. *Eur J Nucl Med* 1996; 23: 1619-1627.
- [161] Richards P and Ku TH. The  $^{122}\text{Xe}/^{122\text{I}}$  system: a generator for the 3.62-min positron emitter,  $^{122\text{I}}$ . *Int J Appl Radiat Isot* 1979; 30: 250-252.
- [162] Mathis CA, Lagunas-Solar MC, Sargent T 3rd, Yano Y, Vuletich A and Harris LJ. A  $^{122}\text{Xe}$ - $^{122\text{I}}$  generator for remote radio-iodinations. *Int J Rad Appl Instrum A* 1986; 37: 258-260.
- [163] Moerlein SM, Mathis CA, Brennan KM and Budinger TF. Synthesis and in vivo evaluation of  $^{122\text{I}}$ - and  $^{131\text{I}}$ -labelled iodoperidol, a potential agent for the tomographic assessment of cerebral perfusion. *Int J Rad Appl Instrum B* 1987; 14: 91-98.
- [164] Mathis CA, Sargent T 3rd and Shulgin AT. Iodine-122-labeled amphetamine derivative with potential for PET brain blood-flow studies. *J Nucl Med* 1985; 26: 1295-1301.
- [165] Borchardt PE, Yuan RR, Miederer M, McDevitt MR and Scheinberg DA. Targeted actinium-225 in vivo generators for therapy of ovarian cancer. *Cancer Res* 2003; 63: 5084-5090.
- [166] Knapp FF Jr and Mirzadeh S. The continuing important role of radionuclide generator systems for nuclear medicine. *Eur J Nucl Med* 1994; 21: 1151-1165.
- [167] Edem PE, Fonslet J, Kjaer A, Herth M and Severin G. In Vivo Radionuclide generators for diagnostics and therapy. *Bioinorg Chem Appl* 2016; 2016: 6148357.
- [168] Rosch F and Baum RP. Generator-based PET radiopharmaceuticals for molecular imaging of tumours: on the way to THERANOSTICS. *Dalton Trans* 2011; 40: 6104-6111.
- [169] Zhernosekov KP, Filosofov DV, Qaim SM and FR. A  $^{140}\text{Nd}/^{140}\text{Pr}$  radionuclide generator based on physico-chemical transitions in  $^{140}\text{Pr}$  complexes after electron capture decay of  $^{140}\text{Nd}$ -DOTA. *Radiochim Acta* 2007; 95: 319-327.
- [170] Lubberink M, Lundqvist H and Tolmachev V. Production, PET performance and dosimetric considerations of  $^{134}\text{Ce}/^{134}\text{La}$ , an Auger electron and positron-emitting generator for radionuclide therapy. *Phys Med Biol* 2002; 47: 615-629.
- [171] Production of long lived parent radionuclides for generators:  $^{68}\text{Ge}$ ,  $^{82}\text{Sr}$ ,  $^{90}\text{Sr}$ , and  $^{188}\text{W}$ , International Atomic Energy Agency (IAEA) publication 10-00628, Vienna, Austria, 2010.
- [172] Pao PJ, Silvester DJ and Waters SL. A new method for the preparation of  $^{68}\text{Ga}$ -generators following proton bombardment of gallium oxide targets. *J Radioanal Nucl Chem* 1981; 64: 267-272.
- [173] Loc'h C, Maziere B, Comar D and Knipper R. A new preparation of germanium 68. *Int J Appl Radiat Isot* 1982; 33: 267-270.
- [174] van der Walt TN and Vermeulen C. Thick targets for the production of some radionuclides and the chemical processing of these targets at iThemba LABS. *Nucl Instrum Methods Phys Res A* 2004; 521: 171-175.
- [175] Fassbender M, Nortier FM, Phillips DR, Hamilton VT, Heaton C, Jamriska DJ, Kitten JJ, Pitt LR, Salazar LL, Valdez FO and Peterson EJ. Some nuclear chemical aspects of medical generator nuclide production at the Los Alamos hot cell facility. *Radiochim Acta* 2004; 92: 237-243.
- [176] Ehrhardt GJ and Welch MJ. A new germanium-63/gallium-68 generator. *J Nucl Med* 1978; 19: 925-929.

## Radionuclide generators for PET imaging

- [177] Naidoo C, van der Walt TN and Raubenheimer HG. Cyclotron production of  $^{68}\text{Ge}$  with a  $\text{Ga}_2\text{O}$  target. *J Radioanal Nucl Chem* 2002; 253: 221-225.
- [178] Cheng WL, Jao Y, Lee CS and Lo AR. Preparation of  $^{68}\text{Ge}/^{68}\text{Ga}$  generator with a binary Ga/Ag electrodepositions as solid target. *J Radioanal Nucl Chem* 2000; 245: 25-30.
- [179] Schuhmacher J and Maier-Borst W. A new  $^{68}\text{Ge}/^{68}\text{Ga}$  radioisotope generator system for production of  $^{68}\text{Ga}$  in dilute HCl. *Int J Appl Radiat Isot* 1981; 32: 31-36.
- [180] Meinken GE, Kurczak S, Mausner LF, Kolsky KL and Srivastava SC. Production of high specific activity  $^{68}\text{Ge}$  at Brookhaven National Laboratory. *J Radioanal Nucl Chem* 2005; 263: 553-557.
- [181] Peterson EJ. Accelerator radioisotopes save lives: the isotope production facility at Los Alamos, Los Alamos Science No. 30, 2006; Available at: <http://lansce.lanl.gov/news/docs/LA%20Science.pdf>.
- [182] Phillips DR. Radioisotope production at Los Alamos National Laboratory, presented at Specialization School on Health Physics, Milan, 2002. Available at: [www.mi.infn.it/conferences/phillips/Lanl.pdf](http://www.mi.infn.it/conferences/phillips/Lanl.pdf).
- [183] The National Isotope Development Center (NIDC) Product Catalog, Available at [http://www.isotopes.gov/catalog/product.php?element=Titanium&type=rad&rad\\_product\\_index=61](http://www.isotopes.gov/catalog/product.php?element=Titanium&type=rad&rad_product_index=61).
- [184] Alenitzky YG, Novgorodov AF, Skripnik AV, Filosofov DV, Skripnik AV, Kaplun VG, Suzikov AG, Eliseev IA and Rösch F.  $^{44}\text{Ti}$ : investigation of target preparation, irradiation and yields in the  $^{45}\text{Sc}(p,2n)$  process. In: Annual report. Institute of Nuclear Chemistry, University of Mainz, 2005. Available at [http://www.kernchemie.uni-mainz.de/Dateien/b3\\_05.pdf](http://www.kernchemie.uni-mainz.de/Dateien/b3_05.pdf).
- [185] Caretto AA and Wiig EO. Interaction of yttrium with protons of energy between 60 and 240 MeV. *Phys Rev* 1959; 115: 1238-1242.
- [186] Grant PM, Erdal BR and O'Brien HA. Medium-energy spallation cross sections. 2. Mo irradiation with 800-MeV protons. *Int J Appl Radiat Isot* 1983; 34: 1631-1632.
- [187] Thomas KE. Isotope production from molybdenum targets. *Radiochim Acta* 1984; 37: 137-141.
- [188] Tárkányi F, Qaim SM and Stöcklin G. Excitation functions of high-energy  $^3\text{He}$ - and alpha-particle induced nuclear reactions on natural krypton with special reference to the production of  $^{82}\text{Sr}$ . *Appl Radiat Isot* 1990; 41: 91-95.
- [189] Tarkanyi F, Qaim SM and Stoecklin G. Excitation-functions of He-3-particle and alpha-particle induced nuclear-reactions on enriched Kr-82 and Kr-83. *Radiochim Acta* 1988; 43: 185-189.
- [190] Tárkányi F, Qaim SM and Stöcklin G. Production of  $^{82}\text{Sr}$  via the  $^{82}\text{Kr}(3\text{He},3n)$ -process at a compact cyclotron. *J Label Compd Radiopharm* 1989; 26: 153-154.
- [191] Buthelezi EZ, Nortier FM and Schroeder IW. Excitation functions for the production of  $^{82}\text{Sr}$  by proton bombardment of natRb at energies up to 100 MeV. *Appl Radiat Isot* 2006; 64: 915-924.
- [192] Qaim SM, Steyn GF, Spahn I, Spellerberg S, van der Walt TN and Coenen HH. Yield and purity of  $^{82}\text{Sr}$  produced via the natRb(p,xn)  $^{82}\text{Sr}$  process. *Appl Radiat Isot* 2007; 65: 247-252.
- [193] Cackette MRC, Ruth TJ and Vincent JS.  $^{82}\text{Sr}$  production from metallic Rb targets and development of an  $^{82}\text{Rb}$  generator system. *Appl Radiat Isot* 1993; 44: 917-922.
- [194] Meulen NP, Walt TN, Steyn GF and Raubenheimer HG. The production of  $^{82}\text{Sr}$  using larger format RbCl targets. *Appl Radiat Isot* 2013; 72: 96-99.
- [195] Phillips DR, Peterson EJ, Taylor WA, Jamriska DJ, Hamilton VT, Kitten JJ, Valdez FO, Salazar LL, Pitt LR, Heaton RC, Kolsky KL and Mausner LF. Production of strontium-82 for the CardioGen® PET generator: a project of the Department of Energy Virtual Isotope Center. *Radiochim Acta* 2000; 88: 149-155.
- [196] Zhuikov BL, Ermolaev SV and Kokhanyuk VM. Method for producing radiostrontium. Russian Patent 2356113 (2009).
- [197] Institute for Nuclear Research of the Russian Academy of Sciences granted U.S. Patent for radiostrontium production technology included in licensing agreement with Positron Corporation. Available at: <http://money.cnn.com/news/newsfeeds/articles/prnewswire/AQ116-23.htm>.
- [198] Piel H, Qaim SM and Stöcklin G. Excitation functions of (p,xn)-reactions on natNi and highly enriched  $^{62}\text{Ni}$ : possibility of production of medically important radioisotope  $^{62}\text{Cu}$  at a small cyclotron. *Radiochim Acta* 1992; 57: 1-5.
- [199] Szelecsényi F, Suzuki K, Kovács Z, Takei M and Okada K. Production possibility of  $^{60,61,62}\text{Cu}$  radioisotopes by alpha induced reactions on cobalt for PET studies. *Nucl Instrum Methods Phys Res B* 2002; 187: 153-163.
- [200] Szelecsényi F, Kovács Z, van der Walt TN, Steyn GF, Suzuki K and Okada K. Investigation of the natZn(p,x) $^{62}\text{Zn}$  nuclear process up to 70MeV: a new  $^{62}\text{Zn}/^{62}\text{Cu}$  generator. *Appl Radiat Isot* 2003; 58: 377-384.
- [201] Mushtaq A, Qaim SM and Stöcklin G. Production of  $^{73}\text{Se}$  via (p, 3n) and (d, 4n) reactions on arsenic. *Appl Radiat Isot* 1988; 39: 1085-1091.

## Radionuclide generators for PET imaging

- [202] Fassbender M, de Villiers D, Nortier M and van der Walt N. The  $^{nat}\text{Br}(p,x)^{73,75}\text{Se}$  nuclear processes: a convenient route for the production of radioselenium tracers relevant to amino acid labelling. *Appl Radiat Isot* 2001; 54: 905-913.
- [203] Phillips DR, Moody DC, Taylor WA, Segura NJ and Pate BD. Electrolytic separation of selenium isotopes from proton irradiated RbBr targets. *Appl Radiat Isot* 1987; 38: 521-525.
- [204] Dahl JR and Tilbury RS. The use of a compact, multi-particle cyclotron for the production of  $^{52}\text{Fe}$ ,  $^{67}\text{Ga}$ ,  $^{111}\text{In}$  and  $^{123}\text{I}$  for medical purposes. *Int J Appl Radiat Isot* 1972; 23: 431-437.
- [205] Thakur ML, Nunn AD and Waters SL. Iron-52: Improving its recovery from cyclotron targets. *Int J Appl Radiat Isot* 1971; 22: 481-483.
- [206] Saha GB and Farrer PA. Production of  $^{52}\text{Fe}$  by the  $^{55}\text{Mn}(p,4n)^{52}\text{Fe}$  reaction for medical use. *Int J Appl Radiat Isot* 1971; 22: 495-498.
- [207] Steyn GF, Mills SJ, Nortier FM, Simpson BR and Meyer BR. Production of  $^{52}\text{Fe}$  via proton-induced reactions on manganese and nickel. *Int J Rad Appl Instrum A* 1990; 41: 315-325.
- [208] Suzuki K. Production of  $^{52}\text{Fe}$  by the  $^{55}\text{Mn}(p,4n)^{52}\text{Fe}$  reaction and milking of  $^{52m}\text{Mn}$  from  $^{52}\text{Fe}$ . *Radioisotopes* 1985; 34: 537-542.
- [209] Zweit J, Downey S and Sharma H. A method for the production of iron-52 with a very low iron-55 contamination. *Int J Rad Appl Instrum A* 1988; 39: 1197-1201.
- [210] Tárkányi F, Qaim SM, Stöcklin G, Sajjad M and Lambrecht RM. Nuclear reaction cross sections relevant to the production of the  $^{122}\text{Xe} \rightarrow ^{122}\text{I}$  generator system using highly enriched  $^{124}\text{Xe}$  and a medium-sized cyclotron. *Appl Radiat Isot* 1991; 42: 229-233.
- [211] Lagunas-Solar MC, Carvacho OF, Harris LJ and Mathis CA. Cyclotron production of  $^{122}\text{Xe}$  (20.1 h)  $\rightarrow ^{122}\text{I}$  ( $\beta^+$  77%; EC 23%; 3.6 min) for positron emission tomography. Current methods and potential developments. *Appl Radiat Isot* 1986; 37: 835-842.
- [212] Peek NF and Hegedüs F. The production of xenon isotopes with protons of energies from 320 to 590 MeV. *Int J Appl Radiat Isot* 1979; 30: 631-635.
- [213] Guideline on Radiopharmaceuticals, CHMP, EMEA/CHMP/QWP/306970/2007 (draft released for consultation). Available at: <http://www.emea.europa.eu/pdfs/human/qwp/30697007en.pdf>.
- [214] Directive 2001/83/EC of the European Parliament and the Council of November 6, 2001 on the community code relating to medicinal products for human use. Available at: [https://ec.europa.eu/health/sites/health/files/files/eudralex/vol/dir\\_2001\\_83\\_cons2009/2001\\_83\\_cons2009\\_en.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol/dir_2001_83_cons2009/2001_83_cons2009_en.pdf).
- [215] EudraLex. The Rules Governing Medicinal Products in the European Union. Available at: [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm)
- [216] Current good manufacturing practice for positron emission tomography drugs. Final rule. Available at: <http://www.gpo.gov/fdsys/pkg/FR-2009-12-10/pdf/E9-29285.pdf>.
- [217] Shimchuk G, Gr S, Pakhomov G, Avalishvili G, Zavrzhnov G, Polonsky-Byslaev I, Fedotov A and Polozov P. Generators and automated generator systems for production and on-line injections of PET radiopharmaceuticals. *J Phys Conf Ser* 2017; 784: 012059.