40 Radionuclide Generators

F. Rösch[1] · *F. F. (Russ) Knapp*[2]
[1]Johannes Gutenberg-University Mainz, Mainz, Germany
[2]Nuclear Science and Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN, USA

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Abstract: Radionuclide generator systems continue to play a key role in providing both diagnostic and therapeutic radionuclides for various applications in nuclear medicine, oncology, and interventional cardiology. Although many parent/daughter pairs have been evaluated as radionuclide generator systems, there are a relatively small number of generators, which are currently in routine clinical and research use. Essentially every conceivable approach has been used for parent/separation strategies, including sublimation, thermochromatographic separation, solvent extraction, and adsorptive column chromatography. The most widely used radionuclide generator for clinical applications is the ^{99}Mo/^{99m}Tc generator system, but recent years have seen an enormous increase in the use of generators to provide therapeutic radionuclides, which has paralleled the development of complementary technologies for targeting agents for therapy and in the general increased interest in the use of unsealed therapeutic radioactive sources. More recently, use of the ^{68}Ge/^{68}Ga generator is showing great potential as a source of positron-emitting ^{68}Ga for positron emission tomography (PET)/CT imaging. Key advantages for the use of radionuclide generators include reasonable costs, the convenience of obtaining the desired daughter radionuclide on demand, and availability of the daughter radionuclide in high specific activity, no-carrier added form.

40.1 Introduction

40.1.1 Historical Perspective

A radionuclide generator is a concept defined as an effective radiochemical separation of decaying parent and daughter radionuclides such that the daughter is obtained in a pure radionuclidic and radiochemical form. Radionuclide generators were historically called "cows" since the daughter radioactivity was "milked" (i.e., removed) from its precursor and the parent then generated a fresh supply of the daughter.

Generator parent radionuclides are obtained from uranium fission products (i.e., ^{99}Mo and ^{90}Sr) or as decay products from ^{233}U (^{229}Th/^{225}Ac), or are produced directly in nuclear reactors (^{188}W, etc.) or at accelerators (^{82}Rb, ^{62}Zn, etc.).

Compared to in-house radionuclide production facilities such as accelerators or nuclear reactors, the availability of short-lived radionuclides from radionuclide generators provides an inexpensive and convenient alternative. The development of radionuclide generators over the past 3 decades was primarily motivated by the increasing spectrum of applications of radionuclides and labeled compounds in the life sciences, in particular for diagnostic applications in nuclear medicine. In the last years, however, promising applications of generator-derived therapeutic radionuclides have been developed in the fields of nuclear medicine, oncology, and interventions cardiology. This increasing importance of radionuclide generators has initiated a broad development for radionuclide production of the generator parent radionuclide, for sophisticated radiochemical separations as well as reliable technical design of the generator systems.

The first generator for life sciences application was developed in 1920, providing ^{222}Rn ($T_{½}$ = 3.825 d) to obtain radon seeds for radiation therapy as a daughter of ^{226}Ra ($T_{½}$ = 1.60 × 10^3 a) (Failla 1920). However, practical importance of radionuclide generators was achieved in 1951 by the ^{132}Te ($T_{½}$ = 3.26 d)/^{132}I ($T_{½}$ = 1.39 h) generator (Winsche et al. 1951), and, much more, in 1957 by the pioneering development of the ^{99}Mo/^{99m}Tc generator at

Brookhaven National Laboratory (BNL) (Stang et al. 1954, 1957). The technetium daughter radionuclide was soon envisioned for medical use (1960), and indeed its first clinical application was reported in 1961 (Richards 1960; Harper et al. 1962) and has revolutionized radiopharmaceutical chemistry and nuclear medicine. Since that time, various other generator systems have been developed, and some of them received significant practical application.

The broad use of the ^{99}Mo/^{99m}Tc generator system in nuclear medicine is a key example, which has been crucial for more than 2 decades for the hospital or central radiopharmacy preparation of a wide variety of diagnostic agents for applications in nuclear medicine and oncology. Over 35,000 diagnostic procedures are estimated to be currently conducted daily in the USA. (>16 million studies per year) with ^{99m}Tc. This reliance on the availability of ^{99m}Tc clearly underscores the crucial importance of the continued and reliable ^{99}Mo production and processing facilities to ensure the uninterrupted supply of the generator parent radionuclide required for fabrication of these generator systems.

These developments have been reviewed (Brucer 1965; Stang 1969; Lebowitz and Richards 1974; Lieser 1976; Yano 1978; Boyd et al. 1984; Paras and Thiessen 1985; Boyd 1986; Mani 1987; Lambrecht and Sajjad 1988; Ruth et al. 1989; Knapp et al. 1992; Knapp and Mirzadeh 1994; Mirzadeh and Knapp 1996; Lambrecht et al. 1997). Detailed reviews have addressed the following topics: parent–daughter half-lives (Finn et al. 1983), reactor-produced generators (Mani 1987), accelerator-produced generators (Lambrecht 1983), cyclotron production of generator parent nuclides (Qaim 1987), ultra short-lived generator-produced radionuclides (Guillaume and Brihaye 1986, 1987), generator-derived positron-emitting radionuclides (Knapp et al. 1992), and clinical applications (Knapp and Butler 1984; Knapp and Mirzadeh 1994). In addition to the generators discussed here in a clinical context, a significant number of other generator pairs exist. Many of those cases have been identified by Lieser (1976) for example, but there still may be other parent/daughter radionuclide pairs whose potential feasibility for generators has not yet been considered.

40.1.2 Equations of Radioactive Decay and Growth

The exponential laws of radioactive-series decay and growth of radionuclides were first formulated by Rutherford and Soddy in 1902, to explain their results (Rutherford and Soddy 1902, 1903) on the thorium series of radionuclides. In 1910, Bateman (Bateman 1910) derived generalized mathematical expressions that were used to describe the decay and growth of the naturally occurring actinium, uranium, and thorium series until the discovery of nuclear fission and other new radioactive decay series were found in the 1940s. For the description of half-lives and decay constants, activities and number of radionuclides involved in the decay of two radionuclides, Friedlander et al. (1981) have given a representative overview (see also Chap. 5 in Vol. 1).

A radioactive nuclide decays according to an exponential law:

$$N = N_0 e^{-\lambda t} \text{ or } A = A_0 e^{-\lambda t} \tag{40.1}$$

where N and A represent the number of atoms and the activity, respectively, at time t, and N_0 and A_0 the corresponding quantities when $t = 0$, and λ is the decay constant for the radionuclide. The half-life $T_{½}$ is related to the decay constant

$$T_{1/2} = \frac{\ln 2}{\lambda} \approx \frac{0.69315}{\lambda}. \tag{40.2}$$

The general case for the generation of a second radioactive nuclide from the decay of a first one must consider the decay parameters of the first radioactive nuclide, denoted by subscript 1 (parent), as well as the parameters of the produced second radioactive nuclide, denoted by subscript 2 (daughter). The behavior of N_1 is

$$-(\mathrm{d}N_1/\mathrm{d}t) = \lambda_1 N_1, \text{and } N_1 = N_1^0 \mathrm{e}^{-\lambda_1 t} \tag{40.3}$$

where N_1^0 represents the value of N_1 at $t = 0$. The second radionuclide is formed at the rate at which the first decays, $\lambda_1 N_1$, and itself decays at the rate $\lambda_2 N_2$:

$$\frac{\mathrm{d}N_2}{\mathrm{d}t} = \lambda_1 N_1 - \lambda_2 N_2 \tag{40.4}$$

or

$$\frac{\mathrm{d}N_2}{\mathrm{d}t} = \lambda_2 N_2 - \lambda_1 N_1^0 \mathrm{e}^{-\lambda_1 t} = 0. \tag{40.5}$$

Equations (40.4) and (40.5) represent linear differential equations of the first order and solutions obtained by standard methods lead to

$$N_2 = \frac{\lambda_1}{\lambda_2 - \lambda_1} N_1^0 (\mathrm{e}^{-\lambda_1 t} - \mathrm{e}^{-\lambda_2 t}) + N_2^0 \mathrm{e}^{-\lambda_2 t} \tag{40.6}$$

where N_2^0 is the value of N_2 at $t = 0$. The first group of terms reflects the growth of a "daughter" radionuclide 2 from a "parent" radionuclide 1 and the decay of these "daughter" radionuclides, while the second term gives the contribution at any time from the "daughter" radionuclides initially present.

Radionuclide generations are distinguished according to the half-lives of the parent and daughter radionuclides. Depending on which of the two radionuclides has the longer half-life, three principal cases occur: (1) parent is longer-lived, but not more than by a factor of about 100, i.e., $T_{½,2} < T_{½,1} < 100\ T_{½,2}$, *transient equilibrium*, (2) parent is much longer-lived than the daughter ($T_{½,1} \gg T_{½,2}$, i.e., $\lambda_1 \ll \lambda_2$), *secular equilibrium*, (3) parent is shorter-lived than the daughter ($T_{½,1} < T_{½,2}$, i.e., $\lambda_1 > \lambda_2$), *no equilibrium*.

Because in some cases daughter radionuclides are relevant, which are generated via one or more intermediate radionuclides from an original parent, also decay chains must be considered.

40.1.2.1 Transient Equilibrium

Suppose the parent is longer-lived than the daughter ($T_{½,1} > T_{½,2}$, i.e., $\lambda_1 < \lambda_2$), Eq. (40.6) reaches the form of Eq. (40.7)

$$N_2 = \frac{\lambda_1}{\lambda_2 - \lambda_1} N_1^0 \mathrm{e}^{-\lambda_1 t} \tag{40.7}$$

($\mathrm{e}^{-\lambda_2 t}$ is negligible compared with $\mathrm{e}^{-\lambda_1 t}$ after t becomes sufficiently large, and $N_2^0 \mathrm{e}^{-\lambda_2 t}$ also becomes negligible). Since $N_1 = N_1^0 \mathrm{e}^{-\lambda_1 t}$, the ratio of the numbers of the two radionuclides is

$$\frac{N_1}{N_2} = \frac{\lambda_2 - \lambda_1}{\lambda_1}, \tag{40.8}$$

and, consequently, the ratio of the absolute activities of the two radionuclides is

$$\frac{A_1}{A_2} = \frac{(\lambda_2 - \lambda_1)}{\lambda_2} = 1 - \frac{\lambda_1}{\lambda_2}. \tag{40.9}$$

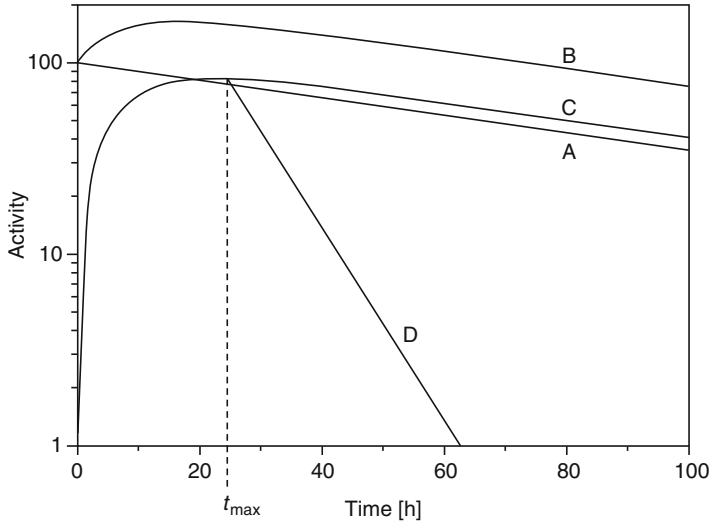
This ratio of the two activities may thus have any value between 0 and 1, depending on the ratio of λ_1 to λ_2. Consequently, in equilibrium the daughter activity will be greater than the parent activity by the factor $\lambda_2/(\lambda_2 - \lambda_1)$. Starting with an initially pure parent fraction, the sum of the parent and daughter disintegration rates goes through a maximum before transient equilibrium is achieved. In equilibrium, both activities decay with the parent's half-life. The corresponding kinetics are illustrated in *Fig. 40.1*, giving an example of the transient equilibrium for the most prominent medical radionuclide generator ^{99}Mo ($T_{½}$ = 65.945 h)/^{99m}Tc ($T_{½}$ = 6.006 h). The ratio between the half-lives is 11. The curves represent variations with time of the parent activity and the activity of a freshly isolated daughter fraction, the growth of daughter activity in a freshly purified parent fraction, and other relations (*Fig. 40.2*). *Figure 40.2* illustrates the general regime of subsequent separations of the daughter nuclide and shows the ingrowth of the daughter activity within the generators systems after each separation cycle.

40.1.2.2 Secular Equilibrium

The limiting case of radioactive equilibrium at $\lambda_1 \ll \lambda_2$ is called secular equilibrium. In this case, the parent activity does not decrease measurably during many daughter half-lives.

Fig. 40.1

Transient radionuclide generator kinetics for the system ^{99}Mo/^{99m}Tc. A, independent activity of the parent nuclide; B, growth of cumulative parent and daughter activity in a pure parent fraction; C, growth of daughter activity in a pure parent fraction; D, independent decay of the separated pure daughter fraction at maximum of generated activity



Equations (40.8) and (40.9) reduce to $N_1/N_2 = \lambda_2/\lambda_1$ and $A_1 = A_2$. In these equilibria, the daughter activity will not exceed the parent activity. This characteristic, different from the transient equilibrium shown in *Fig. 40.1*, is illustrated for the $^{68}Ge/^{68}Ga$ radionuclide generator in *Fig. 40.3*. The ratio between the mother and daughter half-lives in this case is 270.8 × 24 h/1.135 h = 5726.

Fig. 40.2

Illustration of daughter (A_2) in growth and parent (A_1) decay for four successive elution cycles

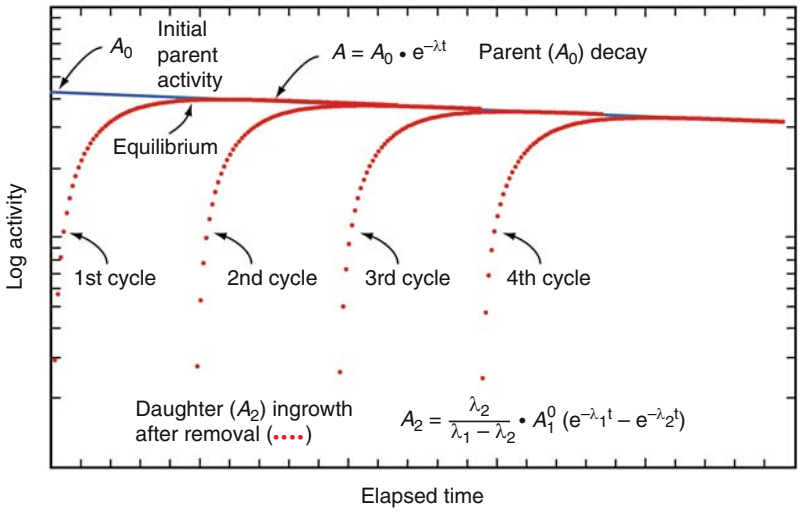
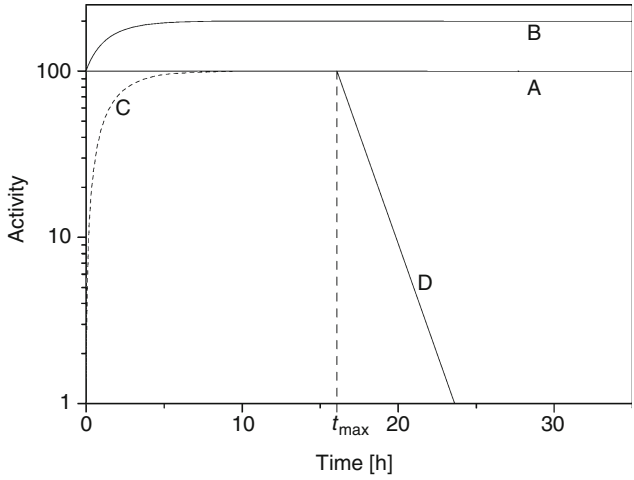


Fig. 40.3

Secular radionuclide generator kinetics for the system $^{68}Ge/^{68}Ga$. A, independent activity of the parent nuclide; B, growth of cumulative parent and daughter activity in a pure parent fraction; C, growth of daughter activity in a pure parent fraction; D, independent decay of the separated pure daughter fraction at maximum of generated activity



In the case of $T_{½,1} \gg T_{½,2}$ the maximum activity of the daughter occurs at the time, t, which is calculated by Eq. (40.10):

$$t = \frac{1}{\lambda_2 - \lambda_1} \ln \frac{\lambda_2}{\lambda_1}. \tag{40.10}$$

With the ^{68}Ge/^{68}Ga system, the theoretical maximum of generated activity is reached after 14.1 h. However, in the case of secular equilibria cyclic separations are performed much more frequently than that, e.g., after three half-lives of ^{68}Ga already (i.e., about 3.4 h after the preceding elution), when about 90% of the theoretical maximum is generated. In a clinical context, this may allow three individual elutions per day.

40.1.2.3 No Equilibrium

If the parent is shorter-lived than the daughter ($T_{½,1} < T_{½,2}$, i.e., $\lambda_1 > \lambda_2$), it is evident that no equilibrium is attained at any time. If the parent is made initially free of the daughter, then as the parent decays the amount of daughter will rise, pass through a maximum, and eventually decay with the characteristic half-life of the daughter.

40.1.2.4 Decay Chains: Many Successive Decays

The radionuclide of interest might not be produced by a direct generation from a parent radionuclide exclusively. Instead, it might be a product of a decay chain involving more than one parent radionuclide. If a chain of three or more radioactive products needs to be considered, the equations derived for N_1 and N_2 as functions of time are valid as well, and N_3 for example may be found by solving a new differential equation:

$$\frac{dN_3}{dt} = \lambda_2 N_2 - \lambda_3 N_3. \tag{40.11}$$

Mathematical treatments of this equation and for $n \geq 4$ members of a decay chain were developed (Bateman 1910). Moreover, for many decay chains, the case of branching decay needs to be considered. When a nuclide A can decay by more than one mode (e.g., by β^- decay generating the radionuclide B and by α decay generating the radionuclide C) the two partial decay constants λ_B and λ_C must be considered, cf. the generator systems with the ^{213}Bi parent. The considerations for branching decay, of course, are valid as well for a single, i.e., non-decay-chain decay.

40.1.3 Classifications

Generally, the decay of a radioactive nuclide results in a longer-lived or even stable daughter nuclide. In this respect, radionuclide generator systems where the daughter nuclide presents a shorter half-life are a welcome exception from the general properties of β decay. In particular, for a clinical application, a state of a "radioactive equilibrium" is mandatory. Thus, mainly the transient and secular equilibria of radionuclide generations are relevant for

application of the radionuclide pairs discussed in this chapter. There appears to be some relevancy for application of so-called in vivo radionuclide generator, which will be discussed as well.

There is another unique property of a "medical" radionuclide generator: The daughter nuclide is generated at a no-carrier-added concentration. It thus ideally meets the criteria of Hevesy's tracer concept, which entail the application of labeled compounds at almost negligible concentrations, completely irrelevant for pharmacodynamic interactions with the human body.

In addition, radionuclide generators intended for applications in life science, in particular in the context of routine clinical use, must meet strict regulatory and quality control requirements. The production of the radionuclide generator parent, its separation from the target material, the chemical and technical construction of the separation of the radionuclide generator daughter are factors, which in totality shall finally result in an efficient and easy handling. They are discussed below.

1. The production of the radionuclide generator parent: This includes the route of parent nuclide availability, i.e., reactor or accelerator production or usage of decay chains of "naturally" occurring radioisotopes or of reactor-generated ones; the investigation of precise nuclear data, which is mandatory for optimum production parameters providing the corresponding thick target yields and radionuclidic purities; high-flux irradiations with sophisticated target design at adequate irradiation facilities (including cost of irradiations); costs of target materials and if the use of enriched target material is required; specific activity of the parent isotope (no-carrier-added vs. carrier-added). Reactor and cyclotron-based production of the parent nuclides is discussed in detail in Chaps. 38 and 39 of this Volume.
2. The selection of a separation method of the parent nuclide from the target material: Investigation of the optimum chemical form of the target material and the principal separation methods (ion exchange, extraction, volatilization, precipitation, etc.) allowing high chemical yields of the parent nuclide; recovery of enriched target materials, etc.
3. The chemical and technical concept of the separation of the radionuclide generator daughter: Development of the optimum separation method (most often ion exchange or extraction; for in-house use ion exchange chromatography almost exclusively) providing high yield of the daughter nuclide in minimum volumes and highest radionuclidic purity (i.e., lowest breakthrough of parent nuclide); selection of solutions used, etc.
4. The efficient and easy handling: Experimental vs. routine build-up of the final generator, consideration of the activity scale with regard to radiation stability (radiolysis) and radiation safety; regulatory requirements and commercial logistics; eventual recovery of the parent nuclide, etc.

A significant number of generator radionuclide pairs have been discussed over the last decades, most of which are summarized in *Table 40.1*. This table also indicates the main production route of the parent radionuclide, i.e., whether the parent nuclide is accelerator or reactor produced or is made available via nuclear decay chains. According to their application for PET imaging, single photon emission computer tomography (SPECT), and photon imaging or for therapy, for various individual generators a short review is provided on the medical potential of the generator, the production routes of the parent nuclide, the chemical concepts of generator pair separations, and on some examples of state-of-the-art application of the daughter nuclide.

Table 40.1

Radionuclide generator systems relevant for life-sciences application

Generator system	Parent nuclide			Daughter nuclide		
	$T_{½}$	Main production route	Main decay	$T_{½}$	Main emission	Application
$^{42}Ar/^{42}K$	32.9 a	Reactor	β^-	12.36 h	β^-	Chemistry
$^{47}Ca/^{47}Sc$	4.536 d	Reactor	β^-	3.341 d	γ, β^-	ERT
$^{44}Ti/^{44}Sc$	60.3 a[a]	Accelerator	EC	3.927 h	β^+	PET
$^{52}Fe/^{52m}Mn$	8.28 h	Accelerator	β^+	21.1 min	β^+	PET
$^{66}Ni/^{66}Cu$	2.28 d	Reactor	β^-	5.10 min	γ, β^-	in vivo; ERT
$^{62}Zn/^{62}Cu$	9.26 h	Accelerator	EC	9.74 min	β^+	PET
$^{68}Ge/^{68}Ga$	270.8 d	Accelerator	EC	1.135 h	β^+	PET
$^{72}Se/^{72}As$	8.4 d	Accelerator	EC	1.083 d	β^+	PET
$^{77}Br/^{77m}Se$	2.377 d	Accelerator	EC	17.4 s	γ	FPRNA
$^{80m}Br/^{80}Br$	4.42 h	Reactor	IT	17.68 min	γ	Chemistry
$^{81}Rb/^{81m}Kr$	4.58 h	Accelerator	EC	13 s	γ	SPECT
$^{83}Rb/^{83m}Kr$	86.2 d	Accelerator	EC	1.86 h	γ	Chemistry/ RPC
$^{82}Sr/^{82}Rb$	25.6 d	Accelerator	EC	1.273 min	β^+	PET
$^{90}Sr/^{90}Y$	28.5 a	Reactor, f	β^-	2.671 d	β^-	ERT
$^{87}Y/^{87m}Sr$	3.35 d	Accelerator	EC	2.80 h	γ	Chemistry
$^{89}Zr/^{89m}Y$	3.268 d	Accelerator	EC	16.1 s	γ	Chemistry
$^{97}Zr/^{97}Nb$	16.90 h	Accelerator	β^-	1.20 h	γ, β^-	Chemistry
$^{99}Mo/^{99m}Tc$	2.7477 d	Reactor, f	β^-	6.006 h	γ	SPECT
$^{103}Ru/^{103m}Rh$	39.25 h	Reactor, f	β^-	56.12 min	γ, Ae	ERT
$^{103}Pd/^{103m}Rh$	16.97 d	Reactor, Acc.	EC	56.12 min	γ, Ae	Chemistry
$^{112}Pd/^{112}Ag$	21.04 h	Reactor, f	β^-	3.14 h	γ, β^-	in vivo, ERT
$^{109}Cd/^{109m}Ag$	1.267 a	Accelerator	EC	39.6 s	γ	FPRNA
$^{115}Cd/^{115m}In$	2.228 d	Reactor	β^-	4.486 h	γ, β^-	Chemistry/ RPC
$^{110}Sn/^{110m}In$	4.1 h	Accelerator	EC	1.15 h	β^+	PET
$^{113}Sn/^{113m}In$	115.1 d	Reactor	EC	1.658 h	γ	Chemistry/ RPC
$^{118}Te/^{118}Sb$	6.00 d	Accelerator	EC	3.6 m	β^+	PET
$^{132}Te/^{132}I$	3.26 d	Reactor (f)	β^-	2.284 h	γ, β^-	Therapy
$^{122}Xe/^{122}I$	20.1 h	Accelerator	EC	3.6 min	β^+	PET

Table 40.1 (Continued)

Generator system	Parent nuclide			Daughter nuclide		
	$T_{½}$	Main production route	Main decay	$T_{½}$	Main emission	Application
$^{137}Cs/^{137m}Ba$	30.0 a	Reactor, f	β^-	2.552 min	γ	in vivo, Diagnosis
$^{128}Ba/^{128}Cs$	2.43 d	Accelerator	EC	3.62 min	β^+	PET
$^{140}Ba/^{140}La$	12.75 d	Accelerator	β^-	1.678 d	γ, β^-	Chemistry/ RPC
$^{134}Ce/^{134}La$	3.16 d	Accelerator	EC	6.4 min	β+	PET
$^{144}Ce/^{144}Pr$	284.9 d	Reactor, f	β^-	17.3 min	γ	Chemistry/ RPC
$^{140}Nd/^{140}Pr$	3.37 d	Accelerator	EC	3.39 min	β^+, Aε	PET
$^{166}Dy/^{166}Ho$	3.400 d	Reactor	β^-	1.117 d	β^-	ERT
$^{166}Yb/^{166}Tm$	2.362 d	Accelerator	EC	17.70 h	γ	Chemistry/ RPC
$^{167}Tm/^{167m}Er$	9.24 d	Accelerator	EC	2.28 s	γ	Chemistry/ RPC
$^{172}Hf/^{172}Lu$	1.87 a	Accelerator	EC	6.70 d	γ	Chemistry/ RPC
$^{178}W/^{178m}Ta$	21.5 d	Accelerator	EC	9.31 min	γ	FPRNA
$^{188}W/^{188}Re$	69.4 d	Reactor	β^-	16.98 h	β^-	ERT
$^{191}Os/^{191m}Ir$	15.4 d	Reactor	β^-	4.94 s	γ	FPRNA
$^{194}Os/^{194}Ir$	6.0 a	Reactor	β^-	19.15 s	γ, β^-	FPRNA
$^{195m}Hg/^{195m}Au$	1.73 d	Accelerator	EC	30.5 s	γ	FPRNA
$^{197m}Hg/^{197m}Au$	2.67 d	Accelerator	EC	7.8 s	γ	FPRNA
$^{212}Pb/^{212}Bi$	10.64 h	Decay chain	β^-	1.009 h	β^-, α	ERT
$^{213}Bi/^{209}Pb$	45.6 min	Decay chain	β^-, α	3.253 h	β^-	ERT
$^{211}Rn/^{211}At$	14.6 h	Accelerator	α, EC	7.21 h	α, ε	ERT
$^{226}Ra/^{222}Rn$	1.6 × 103 a	Decay chain	α	3.825 d	α	ERT
$^{225}Ac/^{213}Bi$	10.0 d	Decay chain	α	45.6 min	β^-, α	ERT
$^{227}Ac/^{227}Th$-/^{223}Ra	21.77 d	Decay chain	α	11.43 d	α	ERT

[a] Mean value of most recent various literature data.

EC, electron capture; IT, isomeric transition; β^+, if EC < 50%; f, fission; Ae, atomic electrons; PET, positron emission tomography; SPECT, single photon emission computer tomography; FPRNA, first-pass radionuclide angiography; RPC, radiopharmaceutical chemistry; ERT, endoradiotherapy.

Nuclear decay data from: Browne and Firestone (1986)

40.2 Generator-Produced Positron Emitters

40.2.1 Overview

Among the generator pairs relevant for quantitative PET (Table 40.2), all parent nuclides are neutron deficient and are thus produced at accelerators. All daughter nuclides are positron emitters and provide a significant positron branching, although in some cases the decay is accompanied by high-energy photons, which might require careful adoption of PET scanners.

The generators can be categorized according to the half-life of the daughter nuclide. The short-lived daughters cover half-lives of a few minutes. As the short half-lives do not allow radiochemical synthesis, these systems are relevant for perfusion imaging exclusively. The generator design must allow for direct application of the separated daughter for human use.

The longer-lived daughter nuclides, on the other hand, provide a potential for the development of labeled radiopharmaceuticals. However, due to the long half-life and the low cross sections, in particular for the parent nuclides ^{44}Ti, ^{68}Ga, and ^{82}Sr, the production rates are relatively low and require long high-current irradiations. Although this results in rather high cost per generator, the number of PET scans achievable lowers the costs per individual patient investigation.

40.2.2 Generators with Potential Medical Application

Some generator pairs have been proposed decades ago and have continuously been improved radiochemically. In many cases, however, there was no parallel development of medical

Table 40.2

Generator-produced positron emitters with potential for positron emission tomography (PET) imaging

	Parent	Daughter			
Generator system	$T_{½}$	$T_{½}$	β_{branch}^{+} (%)	E_{β}+ (MeV)	Application
^{82}Sr/^{82}Rb	25.6 d	1.27 min	95.0	1.41	Perfusion
^{140}Nd/^{140}Pr	3.37 d	3.39 min	51.0	0.544	Perfusion
^{118}Te/^{118}Sb	6.00 d	3.6 min	74.0	0.882	Perfusion
^{122}Xe/^{122}I	20.1 h	3.6 min	77.0	1.09	(Labeling)
^{128}Ba/^{128}Cs	2.43 d	3.62 min	69.0	0.869	Perfusion
^{134}Ce/^{134}La	3.16 d	6.4 min	63.0	0.756	Perfusion
^{62}Zn/^{62}Cu	9.26 h	9.74 min	97.0	1.28	Labeling; Perfusion
^{52}Fe/^{52m}Mn	8.28 d	21.1 min	97.0	1.13	Perfusion
^{68}Ge/^{68}Ga	270.8 d	1.135 h	89.0	0.74	Labeling; Perfusion
^{110}Sn/^{110m}In	4.1 h	1.15 h	62.0	0.623	Labeling
^{44}Ti/^{44}Sc	60.3*a	3.927 h	94.0	0.597	Labeling
^{72}Se/^{72}As	8.4 d	1.083 d	88.0	1.02	Labeling

*Mean value of most recent various literature data.

application of the generator daughter nuclides due to various reasons, which might had led to a current routine application of the generator. On the other hand, although not yet accepted for routine clinical use, some generator pairs offer a significant potential for application in diagnostic nuclear medicine using PET due to the promising nuclear data of both the parent and daughter.

^{44}Ti ($T_{½}$ = 60 a)/^{44}Sc ($T_{½}$ = 3.927 h). Compared to the chemically similar system ^{68}Ge/^{68}Ga, this generator provides a much longer-lived daughter for extended PET/CT measurements. Also for the mother nuclide, the half-life is even longer than for ^{68}Ge. Although ^{44}Ti half-life values found in the literature vary significantly, most recent values average 60 ± 3 years. ^{44}Ti is produced by the ^{45}Sc(p,2n) reaction and by proton-induced spallation on V or Cr targets (Lambrecht and Lynn 1976; Sajjad and Lambrecht 1986; Zaitseva et al. 1994). The production rates are low and require long high-current irradiations. Dowex-1 and 0.1 M oxalic acid in 0.2 M HCl (Greene and Hillman 1967) provided a 60–70% radiochemical yield of ^{44}Sc in 30–50 mL of eluent, while the initial breakthrough of 10^{-3}% increased to 10^{-1}% after eluent volume of up to 2 L. With zirconium oxide as an analogue of Ti(IV) used as the support, and 0.01 M HCl as eluent, Seidl and Lieser (1973) reported a 42–46% radiochemical yield and a decontamination factor of 5×10^4. A solvent extraction technique with an organic phase of 1% 1-phenyl-3-methyl-4-capryl-pyrazolone-5 in methyl isobutyl ketone led to >90% recovery of Sc in <10 mL with a Ti contamination of $<10^{-6}$ (Mirza and Aziz 1969).

The first 5 mCi high activity level generator was described recently (Filosofov et al. 2010). ^{44}Ti/^{44}Sc radionuclide generators are of interest for molecular imaging. In this study, 185 MBq of ^{44}Ti were obtained via the Sc(p,2n) nuclear reaction. The separation of microscopic levels of ^{44}Ti from the macroscopic levels of scandium represents a significant challenge. The ^{44}Ti was separated from 1.5 g of massive scandium targets in multi-step procedures, including exchange chromatography on a cation column (AG 50W-X8, 200–400 mesh, H^+-form). In order to design a robust ^{44}Ti/^{44}Sc generator concept, distribution coefficients of Ti(IV) and Sc(III) on both AG 1-X8 (200–400 mesh, Cl^--form) and AG 50W-X8 (200–400 mesh, H^+-form) resins eluted with HCl and HCl/$H_2C_2O_4$ solution of various concentrations were investigated systematically. Optimal conditions for efficient separations of both radionuclides have been determined for AG 1-X8 resin and mixtures of 0.07 M HCl and 0.005 M $H_2C_2O_4$. The 5 mCi generator was prepared on a column (H = 150 mm, D = 3 mm, V_0 = 0.55 mL) made of radiation resistant PEEK polymer (polyetheretherketone). The system achieved elution of 180 MBq ^{44}Sc in 20 mL of eluate solution. The breakthrough of ^{44}Ti was 90 Bq. This corresponds to an excellent separation factor of 2×10^6. In the context of long-term stability of ^{44}Ti/^{44}Sc generators, a "reverse" type of washing steps after each elution using 0.07 M HCl/0.005 M $H_2C_2O_4$ mixtures appeared to be essential. To allow efficient ^{44}Sc labeling, a post-elution processing of initial ^{44}Sc generator eluates was investigated in order to reduce its volume, for HCl concentration and to remove the oxalate anions (Pruszyński et al. 2010). The online adsorption of ^{44}Sc on cationic resin AG 50W-X8 (200–400 mesh, H^+-form) is achieved with >98% efficacy. Subsequently, the purified ^{44}Sc is desorbed by using 3 mL of 0.25 M ammonium acetate (pH = 4.0). The post-processing requires only 10 min. The overall yield of the post-processing reached 90% of the ^{44}Sc obtained from the ^{44}Ti/^{44}Sc generator. In addition to the chemical purification, the content of ^{44}Ti breakthrough was further reduced by one order of magnitude. The generator finally provides 150 MBq of ^{44}Sc containing <10 Bq of ^{44}Ti ready for radiolabeling chemistry.

Syed and Hosain (1975) proposed ^{44}Sc as a positron-emitting radionuclide for studying bone disease with positron emission tomography. Due to the increasing medical applications

of trivalent radiometals in diagnosis and therapy, the generator could possibly provide an interesting route for PET-imaging using ^{44}Sc-labeled analogues. As a proof-of-principle, ^{44}Sc-DOTA-TOC was synthesized and somatostatin G-protein coupled receptor (GPCR) localization was verified in patient studies (Rösch and Baum 2009, unpublished data). High-quality PET/CT images have been recorded even 18 h post injection. The unique application will focus on the quantitative measurement of uptake kinetics of, e.g., ^{44}Sc-DOTA-TOC in primary and metastatic neuroendocrine tumors in order to estimate the optimum radiation dose the individual patient will receive in a subsequent therapeutic application of biologically and chemically analogue compounds, e.g., ^{90}Y-DOTA-TOC or ^{177}Lu-DOTA-TOC.

^{52}Fe ($T_{½}$ = 8.28 h)/^{52m}Mn ($T_{½}$ = 21.1 min). Lyster et al. (1982) and Tendov et al. (1988) have reviewed the production and purification of ^{52}Fe by the ^{50}Cr(^{4}He,2n), ^{52}Cr(^{3}He,3n), ^{55}Mn(p,4n), ^{54}Fe(γ,2n), and Ni(p,s) reactions. Experimental thick target yields for the ^{52}Cr(^{3}He,3n) and the ^{55}Mn(p,4n) reactions are 1.85 and 3.6 MBq μA^{-1} h^{-1}, respectively, while the proton-induced spallation reaction Ni(p,3p*x*n) provides 24 MBq μA^{-1} h^{-1}. A projected half-saturation yield of 307 GBq (end of bombardment, EOB) was considered (Grant et al. 1979), and Ku et al. (1979a) reported a yield of 2.6 GBq (EOB) following irradiation of 0.45 g·cm^{-2} of Ni at 200 MeV with 70 μA for 15 h. Recent studies thus concentrated on the latter process, also showing lower ^{55}Fe ($T_{½}$ = 2.6 a) impurities. Although providing lower yields of 3.7 MBq h^{-1} at 5 μA beam, 0.008% ^{55}Fe and 1.67 MBq μA^{-1} h^{-1}, the ^{52}Cr(^{3}He,3n) (Fessler et al. 1994), and ^{50}Cr(α,2n) processes on enriched chromium targets (Zweit et al. 1988) could be an alternative concerning the radionuclidic impurity of ^{55}Fe. Conventional anion exchange chromatography using 8 M HCl was applied for the isolation of the short-lived daughter onto Dowex 1 columns (Atcher et al. 1978, 1980) or AGI-X8 (Ku et al. 1979b). To avoid hydrochloric solutions either 2 M tartrate solutions were used to eluate ^{52m}Mn (Schwarzbach et al. 1991) or a 5% glucose solution (Bläuenstein et al. 1997) from Dowex 1, the later approach providing 90% elution yields with a <0.3% ^{52}Fe contamination. A hydroxamate resin allowed elution of ^{52m}Mn with acetate buffer or physiological saline (Herscheid et al. 1983). Based on early tissue distribution studies with ^{54}Mn^{2+} (Chauncey et al. 1977), this generator had received some attention because of the high heart uptake of Mn, and the possibility of using ^{52m}Mn or ^{51}Mn in combination with positron emission tomography for evaluation of myocardial perfusion (Lambrecht and Wolf 1970; Atkins et al. 1979; Atcher et al. 1980).

^{72}Se ($T_{½}$ = 8.4 d)/^{72}As ($T_{½}$ = 1.083 d). This generator could provide a long-lived positron emitter with significant (88%) positron branching. Both deuteron- or proton-induced reactions on arsenic targets and α- or ^{3}He-induced reaction on germanium targets have been investigated, mainly in the context of ^{73}Se production (Nozaki et al. 1979; Mushtaq et al. 1988; Mushtaq and Qaim 1990). Alternatively, ^{72}Se was obtained via proton-induced spallation of RbBr. Al-Kouraishi and Boswell (1978) were able to obtain a 70% elution yield of ^{72}As from a coagulated form of carrier-added ^{72}Se on a Dowex 50 column in 15 mL of water. Electrolytic generators based on ^{72}Se deposited on Pt electrodes as Cu^{72}Se were reported (Phillips and Nix 1989). Another process using addition of selenium carrier consists of cyclic reduction of selenium to Se^{0} and a separation of ^{72}As by filtration with subsequent oxidative dissolution of Se^{0} using H_2O_2. For generators using no-carrier-added ^{72}Se, Novgorodov et al. (2001) described the distillation of $AsCl_3$, while Se remains in nonvolatile compounds in the residue. Jennewein et al. (2004) developed a solid phase extraction system with ^{72}Se fixed as metallic Se; the daughter ^{72}As is eluted by protic solvents. Systematic chemical investigations on the labeling chemistry of no-carrier-added radioarsenic, however, are required prior to the application of ^{72}As labeled compounds (Brockmann et al. 1999a, b). In this context, a new method

was developed (Jennewein et al. 2006) for labeling monoclonal antibodies, i.e., proteins, with radioactive arsenic isotopes via the labeling synthon [*As]AsI_3. Arsenic has a high affinity to sulfur and [*As]AsI_3 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, the antibodies were modified with SATA (*N*-succinimidyl *S*-acetylthioacetate). At least for the mAb (monoclonal antibody) used in this work, this route of radioarsenic labeling does not affect the immunoreactivity of the product. The arsenic label was stable for up to 72 h at the molecular mass of the monoclonal antibody, which is particularly relevant because of the molecular imaging strategy, namely to follow the pharmacology and pharmacokinetics of the labeled mAb for several days. Tarvacin^{TM}, a chimeric monoclonal antibody that binds anionic phospholipids in the presence of serum or β2-glycoprotein 1, was labeled using trivalent radioarsenic and tested for its ability to image Dunning prostate R3227–AT1 tumors growing subcutaneously in rats (Jennewein et al. 2008). [^{72,74}As]Tarvacin^{TM} localized specifically to tumor vascular endothelial cells after injection into tumor-bearing rats. Clear images of the tumors were obtained using planar γ-scintigraphy and positron emission tomography, confirming the utility of the arsenic radioisotopes for molecular imaging. Biodistribution studies confirmed the specific localization of [^{72,74}As]Tarvacin^{TM} to the tumors. The tumor-to-liver ratio 72 h after injection was 22 for [^{72,74}As]Tarvacin^{TM} as compared with 1.5 for an isotype-matched control chimeric antibody of irrelevant specificity, demonstrating the potential merits of this promising approach.

^{110}Sn ($T_{½}$ = 4.1 h)/^{110m}In ($T_{½}$ = 1.15 h). Positron-emitting ^{110m}In could be a choice for quantitative imaging of analogous ^{111}In SPECT compounds (Tsai et al. 1997, Lubberink et al. 2002b). The direct production of ^{110m}In via ^{110}Cd(p,n)-, ^{107}Ag(α,n)-, and ^{109}Ag(^{3}He,2n)-processes, however, leads to the co-formation of the ground state isomer ^{110g}In ($T_{½}$ = 4.9 h). Isotopically pure ^{110m}In could only be prepared via the generator system ^{110}Sn/^{110m}In (Tsai et al. 1997). ^{110}Sn was produced via the ^{110}Cd(^{3}He,3n) reaction with 36 → 25 MeV ^{3}He particles and $^{110}SnCl_4$ was isolated thermochromatographically from the enriched target material. The generator itself was designed by adsorption of ^{110}Sn on a small Kieselgel 40 column and ^{110m}In was eluted quantitatively within 1 mL 0.02 M HCl. However, the short half-life of ^{110}Sn resulting in short useful generator shelf life would possibly limit a wide application of the generator system.

^{118}Te ($T_{½}$ = 6.00 d)/^{118}Sb ($T_{½}$ = 3.6 min). The production of ^{118}Te via ^{123}Sb(p,6n)- and ^{121}Sb(p,4n)-processes was initially reported by Lindner and Perlman (1950) and Fink et al. (1961), while excitation functions were measured by Lagunas-Solar et al. (1990). Batch yields of ^{118}Te in a Ci-scale, however, would be accompanied by significant ^{119m,g}Te impurities resulting in ^{119}Sb ($T_{½}$ = 38.1 h) impurities. Alternatively, the ^{116}Sn(α,2n) reaction holds promise for the production of isotopically more pure ^{118}Te if an enriched ^{116}Sn target would be used (Yano et al. 1989). These authors used SnO_2 and Al_2O_3 type generators to elute ^{118}Sb with tartrate and citrate solutions.

^{122}Xe ($T_{½}$ = 20.1 h)/^{122}I ($T_{½}$ = 3.6 min). Various positron-emitting nuclides of iodine have been proposed to obtain more precise data on localization, quantification, and dosimetry of these compounds using PET. ^{122}I represents one important example providing a 77% β^+ branching. The availability via the generator was investigated as a by-product during the production of the ^{123}Xe/^{123}I generator by the ^{127}I(p,6n)^{122}Xe reaction with 70 MeV protons (Diksic and Yaffe 1977; Richards and Ku 1979; Mathis et al. 1986; Lagunas-Solar et al. 1986) or analogously via the (d,7n) channel (Weinreich et al. 1974) and the ^{124}Xe(p,3n) process

(Tárkányi et al. 1991). Amphetamine analogues and iodoperidol were successfully labeled with ^{122}I to measure brain blood flow with PET (Braun et al. 1978; Mathis et al. 1985; Moerlein et al. 1987). Not only rapid iodination chemistry is required to make use of the short-lived iodine positron emitter, but also the short physical half-life might not correspond to longer-lasting physiological requirements.

^{128}Ba ($T_{½}$ = 2.43 d)/^{128}Cs ($T_{½}$ = 3.62 min). The accelerator production of ^{128}Ba has been evaluated with the ^{133}Cs(p,*x*n) reactions at $E_p = 67 \rightarrow 54$ MeV (Lagunas-Solar et al. 1982), and 111 MBq μA^{-1} h^{-1} experimental thick target yields were reported. The Xe(α,*x*n) reactions seem to be possible as well. Elution yields of ^{128}Cs from a Chelex 100 column ranging from 60–80% were obtained with 5–10 mL of 0.9% NaCl pH 9 solutions. Bievelez and Jacquemin (1982) loaded $^{128}Ba^{2+}$ onto Chelex 100 from a solution of NH_4OH (pH 9.25–9.3) in a buffer of 0.1 M NH_4Cl. Transition between the buffer and an elution medium of 0.1 M NH_4OH and 0.06 M NaCl/HCl at pH 10 was done by successive washings, which resulted in <0.5% loss of the initial ^{128}Ba. ^{128}Cs yields of 75 and 90% were obtained and the breakthrough was 1.1×10^{-3}% per mL. The ^{128}Ba/^{128}Cs generator is of medical interest, since ^{128}Cs might be applied to blood flow measurements. Bievelez and Jacquemin (1982) attempted to image the heart of rabbits and dogs, but concluded that ^{128}Cs is not compatible with the relatively slow muscle absorption kinetics of Cs.

^{134}Ce ($T_{½}$ = 3.16 d)/^{134}La ($T_{½}$ = 6.4 min). ^{134}Ce is produced via the ^{139}La(p,6n) route within an optimum energy of $61 \rightarrow 53$ MeV resulting in a thick target yield of 85 MBq μA^{-1} h^{-1}. Of several inorganic materials tested, manganese dioxide provided the best adsorption for ^{134}Ce, and ^{134}La was eluted with 85% yield in 1.6 mL of 0.5 M NaCl (Lubberink et al. 2002a). The ^{134}La was proposed as PET perfusion imaging (Zweit et al. 1994). The generator may have, in addition, potential for in vivo application with ^{134}Ce-labeled radiopharmaceuticals.

^{140}Nd ($T_{½}$ = 3.37 d)/^{140}Pr ($T_{½}$ = 3.39 min). This generator also provides a short-lived positron-emitting radiolanthanide nuclide and could have some potential as an in vivo generator. The parent nuclide is produced via the ^{140}Ce(α,2n) or (^{3}He,3n) reactions (Rösch et al. 1999, 2000) but also via the ^{140}Pr(p,2n) reaction (Zeisler and Becker 1999). The parent nuclide is radiochemically isolated from the target materials by ion exchange chromatography. Chemical isolation of ^{140}Nd(III) from macro amounts of Ce(III) was performed by cation exchanger chromatography (two purification steps) with an overall separation yield of > 95% ^{140}Nd, overall decontamination factor for cerium of $\sim 10^8$ and with reduction of contaminations of coproduced Pr(III) isotopes of up to 0.5% (Rösch et al. 2003).

The radiochemical principle of separation of the generator mother and daughter nuclides is based on physical–chemical transitions of ^{140}Pr following the electron capture process. A significant separation effect was observed when the parent nuclide ^{140}Nd was coordinated to a DOTA-conjugated peptide or octylamine, which were absorbed on resins. The thermodynamically and kinetically stable complex binds ^{140}Nd while the released ^{140}Pr is kinetically hindered to form similar complexes with the macrocyclic ligand. The ^{140}Nd-DOTA absorption on the solid phase remains stable within at least three half-lives of ^{140}Nd. ^{140}Pr is eluted with a yield >93% if optimized eluent systems such as 10^{-3} M DTPA are applied with negligible levels of ^{140}Nd breakthrough. For 100 MBq of ^{140}Nd-DOTA-like activity and 0.5 h between two subsequent elutions (half an hour is enough for the accumulation of 100% of ^{140}Pr activity), a breakthrough of about 25 kBq of ^{140}Nd (~0.025%) could be expected (Zhernosekov et al. 2007b).

40.2.3 Key Examples of Generator-Derived Positron-Emitting Radionuclides

^{62}Zn ($T_{½}$ = 9.26 h)/^{62}Cu ($T_{½}$ = 9.74 min). The parent ^{62}Zn can be produced with a significant thick-target yield via the (p,2n) reaction on ^{63}Cu (Robinson et al. 1980) or via the ^{60}Ni(α,2n) process (Neirinckx 1977; Zweit et al. 1992). Anion exchange chromatography is clearly the method of choice for this generator system. To adsorb no-carrier-added $^{62}Zn^{2+}$, Dowex 1 was used and Cu^{2+} is eluted with hydrochloric acid (Yagi and Kondo 1979; Fujibayashi et al. 1989; Green et al. 1990). CG-120 Amberlite resin provided an elution of ^{62}Cu in 70% yield with a glycine solution (Fujibayashi et al. 1989) allowing subsequent ligand exchange reactions. For elution, other ligands (Okazawa et al. 1994) or HCl/ethanol (Zweit et al. 1992) solutions were also introduced. The ^{62}Cu was chelated to human serum albumin (HSA) (Fujiyabasyi et al. 1990) and benzyl-TETA-HSA (Mathias et al. 1991b) used for blood pool imaging (Herrero et al. 1996). Several hypoxia and perfusion ^{62}Cu-complexes have been developed and applied for PET studies such as [^{62}Cu]ATSM (diacetyl-bis(N^4-methylthiosemicarbazone)) (Fujibayashi et al. 1997) and [^{62}Cu]PTSM (pyruvaldehyde bis(N^4-methylthiosemicarbazone)) (see, e.g., Green et al. 1990; Mathias et al. 1990; Shelton et al. 1989, 1990; Bormans et al. 1992; Taniuchi et al. 1997). Human biodistribution and dosimetry studies of the perfusion agent [^{62}Cu]PTSM were investigated and this tracer was recommended for repeated studies of myocardial imaging in the same patient (Wallhaus et al. 1998) as well as for quantification of the cerebral blood flow (Okazawa et al. 1994). The clinical performance of the ^{62}Zn/^{62}Cu generator and results of initial evaluation of [^{62}Cu]PTSM) in 68 patients have been described (Haynes et al. 2000), and demonstrated that this generator system is easily manufactured and transported, and is an inexpensive source of the ^{62}Cu positron-emitter for in-house radiopharmaceutical preparation. The compound was also applied for the assessment of angiotensin II-induced blood flow changes in patients with colorectal liver metastases (Flower et al. 2001). The detection of coronary artery disease with [^{62}Cu]PTSM has been reported in 47 patients (Wallhaus et al. 2001). In addition, the successful use of ^{62}Cu liquid-filled angioplasty balloons for the inhibition of coronary restenosis has been reported in a swine coronary overstretch model (Chan et al. 2001). A recent publication (Fukumura et al. 2006), described further refinement of this generator, and focused on high activity (1.8–3.5 GBq) loading of the $^{62}Zn^{2+}$ on a Sep-Pak™ "plus" CM weak acidic cation exchanger column with a high ^{62}Cu elution yield of ~96% with a low 3 mL volume of 200 mM glycine solution. The Zn parent breakthrough is <0.1%. Semi-automated syringe pump systems were designed for separated hot cell separation system and dispensing systems.

^{68}Ge ($T_{½}$ = 270.8 d)/^{68}Ga ($T_{½}$ = 68 min). The first compilation of the data relevant to ^{68}Ge/^{68}Ga generator systems was published in 1996 (Mirzadeh and Lambrecht, 1996). The IAEA has recently initiated comprehensive review of the production of several generator mother nuclides including a chapter on ^{68}Ge (Rösch and Filosofov 2009).

Integral ^{68}Ge thick targets yields have been calculated (Horiguchi et al. 1982) for accelerator-based nuclear reactions on natural metallic germanium and zinc, and Ga_2O_3 targets. The yields for the proton-induced reactions on Ga are larger than those on Ge in the region lower than 60 MeV, although the latter become larger above 60 MeV. The thick target yields for the Ga (p,2n) reactions have been recently validated (IAEA 2001). The (p,2n) reaction on gallium targets (Ga_2O_3 or Ga_4Ni) provides significant cross sections. Experimental thick-target yields – calculated for a 1 h irradiation as well as for saturation – amount to 0.96/0.53 MBq μA^{-1} h^{-1}

at this energy, but reach values of >2/>1 MBq μA^{-1} h^{-1} already at 25 MeV, respectively. Proton-induced spallation reactions on Rb, Br, or As target materials give about one tenth of that yield. The $^{nat}Zn(\alpha,xn)$ reactions show similar low cross sections (Hagebo et al. 1984). Due to the long half-life of ^{68}Ge, high-current accelerators are required for sufficient (about 3.7 GBq batch yields) of the parent nuclide. Routine production is established at Brookhaven National Laboratory (BNL) and Los Alamos National Laboratory (LANL), USA, iThemba Laboratories/NAC, Faure, Republic of South Africa, and Obninsk, Russian Federation. These production centers report on production capacities of about 18.5 to 74 GBq (0.5 to 2 Ci) ^{68}Ge per batch. At the Cyclotron Co., Ltd., Obninsk, Russian Federation, gallium–nickel alloys are used as target material, prepared on copper backings. Irradiations are performed at rather high proton beam intensity of several hundred μA at 23 MeV proton energy. ^{68}Ge of high specific activity of >74 GBq (>2 Ci)/mg and 99.8% radionuclidic purity is obtained (Razbash et al. 2005).

Early attempts to adopt liquid–liquid extraction chemistry for the routine generator use were not sustainable (Gleason 1960; Erhardt and Welch 1978). The first column-based generator systems separated ^{68}Ga using 0.005 N EDTA from ^{68}Ge, absorbed on alumina or zirconium oxides (Greene and Tucker 1961; Yano and Anger 1964) and this neutral [^{68}Ga]EDTA solution was directly used in an attempt to image tumors. Analogously, ^{68}Ge was retained on antimony oxide Sb_2O_5 and ^{68}Ga was eluted with oxalate solutions (Arino et al. 1978). Anion exchange resins using dilute hydrofluoric acid solutions as eluents allowed high-purity separations due to the significant differences of distribution coefficients of the elements (Neirinckx and Davis 1980). The breakthrough of ^{68}Ge was $<10^{-4}$ for up to 600 elutions, and the ^{68}Ga yield >90%. In all these cases, however, further application of the generator eluate for ^{68}Ga labeling reactions was not possible.

Consequently, $^{68}Ge/^{68}Ga$ generators were developed to avoid the formation of stable ^{68}Ga-ligand complex in the eluate system. This strategy is achieved for eluates providing both $^{68}Ga(OH)_4^-$ and $^{68}Ga^{3+}$. Indeed, ^{68}Ga has been eluted in 0.1 M NaOH solution as gallate anion from alumina columns (Lewis and Camin 1960). A comparison of performances of alumina/EDTA, alumina/NaOH, and tin oxide/HCl generators (McElvany et al. 1984), however, indicated superior characteristics for the latter system in terms of ^{68}Ge breakthrough (10^{-6}–10^{-5}% per bolus) and $^{68}Ga^{3+}$ elution (70–80%) in 1 M hydrochloric acid (Loc'h et al. 1980). In other cases, ^{68}Ge was absorbed on inorganic matrices such as alumina, $Al(OH)_3$, and $Fe(OH)_3$ (Kopecky et al. 1973; Kopecky and Mudrova 1974), SnO_2, ZrO_2, TiO_2 (Malyshev and Smirnov 1975), and CeO_2 (Ambe 1988; Bao and Song 1996).

As Ge(IV) is known to form very stable complexes with phenolic groups (Kurnevich et al. 1974), its adsorption on a 1,2,3-trihydroxybenzene (pyrogallol)-formaldehyde resin was utilized (Schumacher and Maier-Borst 1981; Neirinckx et al. 1982). Average yields of ^{68}Ga of 75% during a period of 250 days were reported (Schumacher and Maier-Borst, 1981). The Ge breakthrough was <0.5 ppm with no detectable radiolytic by-products for a 370 MBq (10 mCi) generator. The pyrogallol-formaldehyde resin was found to be resistant to dissociation from radiation. An organic macroporous styrene-divinylbenzene copolymer containing *N*-methylglucamine groups was developed to provide ^{68}Ga with a solution of a low-affinity gallium-chelating ligand such as citric acid or phosphoric acid. The ^{68}Ge breakthrough was less than 0.0004% of the ^{68}Ge adsorbed on the resin (Nakayama et al. 2003).

For commercial generator productions, however, Me(IV)-oxide-based matrices were preferred. A modified TiO_2 phase has been used by the pioneers in this field at the Cyclotron Ltd., Obninsk, Russian Federation, since about 2000 (Razbash et al. 2005). These generators are

eluted with 0.1 N HCl and show initial ^{68}Ga elution yields of about 80% with ^{68}Ge breakthrough of about 1×10^{-3}%. These values decrease over time (e.g., after about 1 year) or with increasing number of elutions (e.g., 200), approaching values of about 50% of ^{68}Ga elution and about 10^{-2}% of ^{68}Ge breakthrough. A similar generator is available as "IGG 100" providing improved elution characteristics. Another system is produced at iThemba Laboratories, Republic South Africa, using a SnO_2-based solid phase. Optimum ^{68}Ge elution efficacy is reported at 0.6 N HCl, decreasing at lower HCl concentration.

However, all commercially available generators need further improvement to be acceptable for regulatory approval for routine medical use (Breeman and Verbruggen 2007). The ^{68}Ge/^{68}Ga radionuclide generator systems used today are not necessarily optimally designed for direct syntheses of radiopharmaceuticals for human use. The eluates still contain measurable activities of long-lived ^{68}Ge. In addition, the rather large volume and the relatively high concentration of hydrochloric acid in many cases prevent the direct use for labeling reactions. Furthermore, labeling yields and specific activities might not reach maximum values due to the presence of metallic impurities. For example, significant amounts of Zn(II) are generated from the decay of ^{68}Ga. For a "fresh" 1110 MBq ^{68}Ge generator, the number of stable ^{68}Zn atoms generated within 1 day after an elution amounts to 9×10^{13} (i.e., 10 ng of Zn(II)) as compared to about 5×10^{12} atoms of ^{68}Ga in 800 MBq of the ^{68}Ga eluted. In the case of "fresh" generators, amounts of stable ^{71}Ga as generated from the ^{71}Ge decay may be one order of magnitude higher than those of stable ^{68}Zn. In addition, Ti(IV) or other residuals from the generator column material and Fe(III) are present in the eluate. All these metallic impurities will adversely affect the ^{68}Ga-labeling yields as well as the specific activity of the labeled product. Thus, dedicated procedures to process the eluate from the radionuclide generator, ideally including labeling and purification of ^{68}Ga radiopharmaceuticals need to be developed.

Anion exchange chromatography: Following the concept of Schumacher and Maier-Borst (1981) of processing 1 N HCl eluates (Meyer et al. 2004) adopted this approach for 0.1 N HCl eluates. The initial volume of 10 mL of the 0.1 N HCl eluate is transferred to a vial containing 15 mL of 9.5 N HCl to obtain a final hydrochloric acid concentration of 5.5 M. Under these conditions ^{68}Ga can be adsorbed on a strong anion exchanger as anionic chloro complexes of ^{68}Ga(III). Following a washing step with 1 mL of 5.5 N HCl, the resin is flushed with a stream of nitrogen and then ^{68}Ga is eluted with H_2O in small volumes. This strategy separates ^{68}Ge, but does not allow *direct* loading of ^{68}Ga(III) on the anion exchange resin from 0.1 N HCl and does not purify Ga(III) from Zn(II) and Fe(III) impurities either. A final yield of 46 ± 5% for the ^{68}Ga-labeled DOTA-conjugated octreotide is reported (Meyer et al. 2004; Velikyan et al. 2004; Meyer et al. 2005; Decristoforo et al. 2005).

Fractionation (Breeman et al. 2005): The concept utilizes the fact that the eluted ^{68}Ga activity peaks within ~1–2 mL, representing about 2/3 of the total activity. If this fraction is isolated from the eluate, the contents of ^{68}Ge and metallic impurities are lowered because of the lower eluate volume used. When synthesizing ^{68}Ga-labeled compounds, decay-corrected yields of ^{68}Ga radiopharmaceuticals cannot exceed 60–70% and effective yields of labeled DOTA-conjugated peptides like ^{68}Ga-DOTATOC amount to about 50% (Decristoforo et al. 2005).

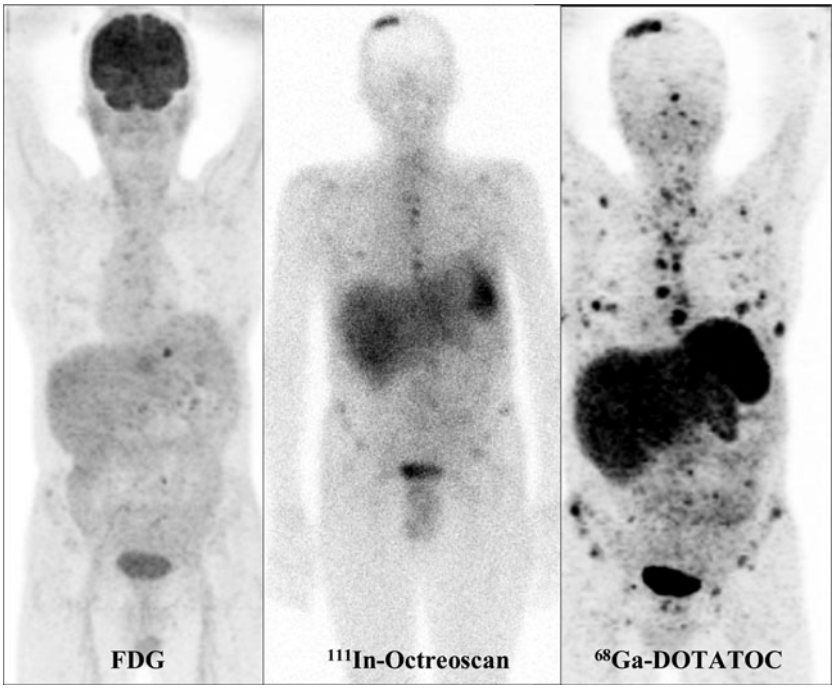
Cation exchange chromatography: The key step in this procedure is the direct transfer of the initial 0.1 N HCl ^{68}Ga eluate to a cation exchanger. Due to high distribution coefficients, ^{68}Ga is quantitatively adsorbed on only about 50 mg of the resin directly from the generator eluate. This effect also occurs with higher concentrations of HCl, e.g., 0.6 N HCl, as used for SnO_2-based ^{68}Ge/^{68}Ga generators. Low volumes of 0.4–1.0 mL of hydrochloric acid/acetone mixtures

are applied to purify ^{68}Ga from Ge(IV), Ti(IV), Zn(II), and Fe(III). This procedure leads to almost complete removal of metallic impurities including ^{68}Ge breakthrough, thus providing the purified ^{68}Ga in a form useful for direct labeling with acceptable pH, volume, and purity. The post-processing takes 4 min with overall ^{68}Ga recovery yields of 97 ± 2% (Zhernosekov et al. 2007; Asti et al. 2008). The above method is adapted for the preparation of a chemistry module, which is commercially used for the preparation of injectable ^{68}Ga-labeled radiopharmaceuticals.

^{68}Ga had some earlier application as [^{68}Ga]BAT-TECH agent for myocardial perfusion (Mathias et al. 1991a), but significant potential has been developed since about 2000 for imaging neuroendocrine tumors using [^{68}Ga]DOTA-DPhe^{1}-Tyr^{3}-octreotide ([^{68}Ga]DOTATOC) and PET (Hofmann et al. 2001). This octapeptide shows high affinity to the sstr2 subtype of somatostatin receptor expressing tumors, and the conjugated macrocyclic bifunctional chelator DOTA binds the trivalent ^{68}Ga^{3+} with high thermodynamic and kinetic stability. Despite the short ^{68}Ga half-life, this tracer allows excellent visualization of tumors and small metastases (Al-Nahhas et al. 2007; Decristoforo et al. 2007; Dimitrakopoulou-Strauss et al. 2006; von Falck et al. 2007; Gabriel et al. 2007, 2009; Henze et al. 2004, 2005; Khan et al. 2009; Koukouraki et al. 2006a, b; Lopci et al. 2008; Luboldt et al. 2010; Maecke et al. 2005; Milker-Zabel et al. 2006; Nyuki et al. 2010; Putzer et al. 2009; Win et al. 2007). This diagnosis, in particular if carried out using PET/CT imaging, is superior to any other imaging approach (*Fig. 40.4*). Systematic

Fig. 40.4

[^{68}Ga]DOTA-DPhe^{1}-Tyr^{3}-octreotide imaging of neuroendocrine tumors using PET/CT (*right*) compared to ^{111}In-octreoscan SPECT (middle) and ^{18}F-FDG PET (*left*) (Courtesy of H. Bihl, Stuttgart)



research continues to develop new ^{68}Ga radiopharmaceuticals. For recent reviews cf. Fani et al. (2008), Rösch and Riss (2010).

Another interesting and potentially important application of ^{68}Ga is the use of ^{68}Ga liquid-filled angioplasty balloons for the inhibition of arterial restenosis following coronary angioplasty (Stoll et al. 2001). This technique with a high-energy positron emitter is similar to the techniques demonstrated using balloons filled with ^{188}Re and other medium and high-energy β emitters (Knapp et al. 2001).

^{82}Sr ($T_{½}$ = 25.6 d)/^{82}Rb ($T_{½}$ = 1.273 min). The ^{82}Rb positron emitter was recognized as a potential PET nuclide due to its analogy to the physiological monovalent potassium cation, which is transported across the cell membrane via the sodium-potassium ATP ion exchange pathway. ^{82}Rb is partially extracted by the myocardium during a single capillary pass. The development of this generator has taken place over the past 25 years and has been intensively discussed in numerous reviews (Waters and Coursey 1987; Vereschchagin et al. 1993). Production routes for ^{82}Sr include ^{85}Rb(p,4n) (Horiguchi et al. 1980; Kastleiner et al. 2002), ^{82}Kr(^{3}He,3n) (Tárkányi et al. 1988, 1990), and proton-induced spallation processes on Rb, Mo, or Y targets (Erdal et al. 1975; Grütter 1982; Grant et al. 1982). The most common production route is the Mo(p,spall) process (Horlock et al. 1981; Thomas and Barness 1984). The requirement for 600–800 MeV protons, however, limits the production capacities of the generator. As ^{82}Rb is injected intravenously directly from the generator, ^{82}Rb must be obtained from the generator in a sterile pyrogen-free physiological medium. Synthetic resins such as BioRex-70 (Yano and Anger 1968; Yano et al. 1977) and Chelex (Grant et al. 1977; Krizek et al. 1977; Grant et al. 1978) and inorganic ion exchangers such as ZrO_2 (Brihaye et al. 1981) and Al_2O_3 (Neirinckx et al. 1982) were developed, with ^{82}Rb eluted with 2% NaCl solutions. Other systems utilize α-SnO_2 (Neirinckx et al., 1982), with ^{82}Rb eluted with physiological NaCl solution used either for bolus (Gennaro et al. 1984) or continuous infusion (Brihaye et al. 1987). Commercial generators with up to 3.7 GBq (100 mCi) are available. Corresponding to the flow rate, ^{82}Rb yields range from 10–40%, while the ^{82}Sr breakthrough is in the order of 10^{-6}% per mL (Brihaye et al. 1987).

The automated elution system (Gennaro et al. 1984; Knapp and Butler 1984) provides ^{82}Rb for direct intravenous bolus injection, with an average dose of about 1.9 GBq (~50 mCi) for cardiac PET and sequential rest versus stress studies, is used to identify normal versus abnormal myocardium in patients with suspected myocardial infraction, as well as for the assessment of coronary blood flow, degree of stenosis, viability assessment, and to monitor recovery and maintenance. The generator is routinely used in clinical practice (e.g., Williams et al. 1994; Alvarez-Diez et al. 1999). ^{82}Rb infusion systems for quantitative perfusion imaging were developed (Epstein et al. 2004; Klein et al. 2007).

With commercial generators available, there is a continuous effort to improve its performance concerning PET protocols. A two-dimensional vs. three-dimensional scanning was compared (Votaw and White 2001) and wavelet-based noise reduction (Lin et al. 2001) could assess myocardial flow in humans in regions smaller than 1 cm^3 to the accuracy of that achieved with $H_2{}^{15}O$. The use of rubidium-82 for PET evaluation of myocardial perfusion has witnessed continued growth and typical studies involve gated PET for myocardial imaging (Anagnostopoulos et al. 2008; Bateman et al. 2006; Brown et al. 2008; Chander et al. 2008; Chow et al. 2005; Dorbala et al. 2007, 2009; Dorbaia et al. 2009; Eisner and Patterson 2007; El Fakhri et al. 2005; Gibbons and Chareonthaitawee 2009; Javadi et al. 2008; Knesaurek et al. 2003, 2007, 2009; Lertsburapa et al. 2008; Lodge et al. 2005; Lortie et al. 2007; Manabe et al. 2009; Nye et al. 2007; Schuster et al. 2008; Shi et al. 2007; Slomka et al. 2008;

Yoshinaga et al. 2006; Tang et al. 2009; Rahmim et al., 2008; Smith 2008; Schleipman et al. 2006; Parkash et al. 2004; Rosman et al. 2005; Tang et al. 2009).

40.3 Generator-Produced Photon Emitters

40.3.1 Overview

Although the use of ultra short-lived generator-derived radionuclides for first-pass radionuclide angiography (FPRNA) for evaluation of ventricular function (wall motion) is not currently widely practiced, the development and use of generator systems for evaluation of pulmonary ventilation and cardiac function was a major research area in the 1970s and 1980s (see, e.g., Paras and Thiessen (1985)). High count-rate imaging systems and advanced computer technology are required for data acquisition, storage, and analysis. High levels of activity are required for FPRNA, but the short half-lives permit rapid, repeat studies, since the vascular recirculation time is longer than the radionuclide physical half-life. The short radionuclide physical half-lives also ensure greatly reduced radiation burden to both personnel and patients. Generators that provide ultra short-lived daughter radionuclides ($T_{½} < 1$–2 min) for FPRNA include the ^{195m}Hg/^{195m}Au ($T_{½} = 30.5$ s) and ^{191}Os/^{191m}Ir ($T_{½} = 4.94$ s) systems. More recently, the ^{178}W/^{178m}Ta ($T_{½} = 9.31$ min) generator has been introduced. For pulmonary ventilation studies and evaluation of the right ventricular chamber, the ^{81}Rb/^{81m}Kr generator is commercially available and approved for human use in Europe.

Several other generator systems have been developed providing photon-emitting daughter nuclides, but did not receive adequate medical attention. Others were proposed for basic radiochemical and radiopharmaceutical studies rather than for a direct application of the daughter nuclide in nuclear medicine.

^{77}Br ($T_{½} = 2.377$ d)/^{77m}Se ($T_{½} = 17.4$ s). ^{77m}Se decays by isomeric transition with the emission of 162 keV photons in 50% abundance and appeared ideal for radionuclide angiocardiography and to study the effects of exercise and pharmaceuticals on hemodynamics (Lambrecht et al. 1977; Norton et al. 1978; Madhusudhan et al. 1979).

^{109}Cd ($T_{½} = 1.267$ a)/^{109m}Ag ($T_{½} = 39.6$ s). This generator was suggested for FPRNA, although the 88 keV photon emission of ^{109m}Ag shows a rather low abundance of 3.73% of the ^{109}Cd decay (Steinkruger et al., 1986). While Bartos and Bilewicz (1995) used crystalline antimony acid as absorbent yielding increasing ^{109}Cd breakthrough, Mansur et al. (1995) used cation exchange chromatography, but needed a scavenger column to reduce the ^{109}Cd breakthrough of 10^{-4}%.

^{113}Sn ($T_{½} = 115.09$ d)/^{113m}In ($T_{½} = 1.658$ h). Because of its long shelf life, the ^{113}Sn/^{113m}In generator has been proposed for labeling and evaluation of various radiopharmaceuticals with the 392 keV photon-emitting ^{113m}In as an analogue of ^{111}In (Liu et al. 1989). ^{113}Sn production (Qaim and Döhler 1984) and generators were described (Seidl and Lieser 1973; Rao et al. 1976, 1977; Camin 1977; Al-Janabi and Al-Hashini 1979; Lin et al. 1982).

^{115}Cd ($T_{½} = 2.228$ d)/^{115m}In ($T_{½} = 4.486$ h). This generator has been considered as an alternative to the ^{113}Sn/^{113m}In system. Parent radionuclide production and generator design (Ramamoorthy and Mani 1976; Bhattacharya and Basu, 1979; Erhardt et al. 1981; Yagi et al. 1982) were investigated.

Several radiolanthanides such as ^{140}Ba/^{140}La (Sakar and Bhattacharya, 1979; Das and Bhattacharya 1982), ^{144}Ce/^{144}Pr (Skraba et al. 1978), and ^{172}Hf/^{172}Lu (Daniels et al. 1978, 1987;

Grant et al. 1981, 1985; Thomas 1983; Lebedev et al. 1984; Organessiant et al. 1992; Das et al. 1996; Kueppers, 1999; Novgorodov et al. 2002) are available via generator systems as surrogates for various "medical" radiolanthanides. Some other metallic nuclides are available via generator systems as surrogates for ^{89,90}Sr or ^{90}Nb, for example: ^{87}Y/^{87m}Sr (Jannsen et al., 1986) and ^{97}Zr/^{97}Nb (Bhattacharya and Basu 1979; Das et al. 1993).

40.3.2 Key Examples of Generator-Produced Photon Emitters with Proven Medical Applications

^{81}Rb ($T_{½}$ = 4.58 h)/^{81m}Kr ($T_{½}$ = 13 s). This generator was introduced in the late 1960s (Yano and Anger 1968; Jones and Clark 1969; Jones et al. 1970; Yano et al. 1970; Colombetti et al. 1974) and was soon made available on a routine scale for clinical use (Clark et al. 1976; Ruth et al. 1980; Finn et al. 1982; Guillaume et al. 1983) for continuous inhalation or infusion studies on regional pulmonary ventilation and perfusion. The short half-life of ^{81m}Kr and continuous administration enables imaging at high count rates, which results in low patient radiation dose. The common method of production of ^{81}Rb is the ^{82}Kr(p,2n) route on isotopically enriched ^{82}Kr gas targets (Ruth et al. 1980; Acerbi et al. 1981; Kovács et al. 1991; Steyn et al. 1991; Uhlir et al. 1996). ^{81}Rb is typically adsorbed on cation exchange resins such as AG 50W-X8 or BioRad AG MP50. Alternatively, $ZrPO_4$ has been used as the generator support (Clark et al. 1976; Ruth et al. 1980). ^{81m}Kr is isolated by either purging the generator with air or oxygen (gas generator, for ventilation studies), or by eluting with normal saline or 5% glucose (solution generator, for perfusion studies). A typical generator consists of a small glass column (4 mm I.D.) filled with resin to the height of 15–20 mm (about 200 mg of resin) and washed with distilled water. A moveable shield with infrared air pump assembly is also available for easy handling. One recent study (Rizzo-Padoni et al., 2001) has reported that the use of the commercial Kryptoscan® generator for localization of pulmonary emboli is cost effective and that the cost varied based on the number of patients evaluated with each generator. Bubble type generators were proposed for parallel gas and solution separation (Jannsen et al. 1990, 1992). An online mass separator facility was used to separate ^{81}Rb following Nb(p,spall) processes at E_p = 600 MeV with a 2-min collection period providing 0.84 GBq of the parent nuclide. Subsequently, a generator was constructed as Mylar foils implanted with 2×10^{13} atoms of ^{81}Rb (Hanser et al. 1986; Beyer et al. 1991). Although krypton-81m is not widely used currently, some investigators still believe this is an excellent approach for the evaluation of pulmonary perfusion and one recent study described its unique role for lung ventilation scanning in critically ill children on long-term mechanical ventilation (Sundariya et al. 2007).

^{99}Mo ($T_{½}$ = 2.7477 d)/^{99m}Tc ($T_{½}$ = 6.006 h). This handbook describes in detail the reactor production of ^{99}Mo (Chap. 1), the radiochemistry of this man-made element and the state-of-the-art of ^{99m}Tc-radiopharmaceutical chemistry (Chap. 6). Because of the shortage of fission-produced ^{99}Mo resulting from the undetermined length of the recent NRU reactor shutdown in Canada and the long maintenance outages of other reactors in Europe, the continued availability of ^{99}Mo worldwide for fabrication of the widely used ^{99}Mo/^{99m}Tc generators is a major topic of discussion. Several strategies are being discussed to move forward with alternatives to traditional research reactor fission production of ^{99}Mo by irradiation of uranium-235 targets. These strategies include the traditional current fission of ^{235}U targets in research reactors, the use of the *Aqueous Homogeneous Reactor (AHR)* technology originally demonstrated by Enrico Fermi, and the use of high energy accelerators for the ^{238}U(n,f) ^{99}Mo

and $^{100}Mo(\gamma,n)\ ^{99}Mo$ routes. The AHR technology involves operation of a system where the aqueous ^{235}U salt solution (nitrate or sulfate), which is continuously fissioned, and recycled to remove the ^{99}Mo and off-line separation of other fission products. The advantages of such a system are the low operating temperature, more controlled safety envelope, and compact design, which does not require any specialized/sophisticated cooling or control systems. The expected time is 4–5 years until the new production facility would operate. The regulatory and licensing issues are under discussion and have to be addressed, but such AHR units would presumably not be subject to the complex safety and operational issues that are encountered by traditional research reactors. It is not yet clear which ^{99}Mo production strategy would overcome the recurring severe supply shortages of ^{99}Mo.

The $^{99}Mo/^{99m}Tc$ generator has been described in previous reviews (Boyd 1982; Boyd et al. 1982, 1986). Technetium-99m continues to be the most widely used diagnostic radionuclide in nuclear medicine, and ^{99m}Tc-labeled tissue-specific radiopharmaceuticals are available for diagnostic studies of essentially all major organs, and represent an estimated 90% of all diagnostic procedures. The widely used chromatographic-type $^{99}Mo/^{99m}Tc$ generator system provides sodium pertechnetate ($Na^{99m}TcO_4$) by elution with saline and uses very high specific activity no-carrier-added ^{99}Mo, produced by the $^{235}U(n,fission)^{99}Mo$ process, which is adsorbed on aluminum oxide. In addition to the chromatographic-type generators, "batch" preparation of ^{99m}Tc involves solvent extraction (Evans et al. 1982), for instance with methyl ethyl ketone, or sublimation of the low specific activity ^{99}Mo, which can be reactor produced by neutron activation of enriched ^{98}Mo. The latter approach may become more attractive in the future as radioactive waste disposal issues become more crucial.

Two options using low specific activity ^{99}Mo produced by the $^{98}Mo(n,\gamma)^{99}Mo$ for generator fabrication involve the "gel-type" generator or post-elution concentration strategies. The "gel-type" generator approach (Boyd 1982) involves preparation of a molybdenum–zirconium gel. Even if the "gel-type" generator system is used, the specific concentration of the ^{99m}Tc may be too low for practical use. A useful alternative involves post-elution concentration of ^{99m}Tc on an anion-exchange column in tandem with the Al_2O_3 generator column, similar to that developed for the $^{188}W/^{188}Re$ generator (Knapp et al. 1998a; Guhlke et al. 2000; Sarkar et al. 2001). Although the chromatographic alumina generator is generally considered impractical for use with low specific activity ^{99}Mo because of the significantly larger amounts of alumina adsorbent that are required, the post-elution concentration of the initial low specific volume ^{99m}Tc provides sufficiently high specific volume activity solutions for labeling.

^{178}W ($T_{½}$ = 21.5 d)/^{178m}Ta ($T_{½}$ = 9.31 min). ^{178m}Ta decays with the emission of X-rays with energies of 55 keV (K_α, 67.4%) and 64 keV (K_β, 17.7%). The relatively long-lived parent ^{178}W can be produced with the $^{181}Ta(p,4n)^{178}W$ reaction with yields of 2 MBq μA^{-1} h^{-1} at 40 → 32 MeV proton energy (Neirinckx et al. 1978, 1979; Holman et al. 1978). Neirinckx et al. (1981) evaluated AGI-X8 as the support, and concluded that the generator can operate satisfactorily when eluted with 0.1–0.15 M HCl containing 0.1% H_2O_2. The ^{178}W breakthrough initially was 10^{-3}%, increasing, however, after 100 elutions. The current generator uses a Dowex AG 1-X8 anion exchange column (Lacy et al. 1988a). Elution with 0.03 M HCl provides reproducible ^{178m}Ta yields with consistently low ^{178}W parent breakthrough.

Preliminary studies explored preparation of ^{178m}Ta-labeled myocardial perfusion agents (Holman et al. 1979; Layne et al. 1991) and also applications for lung and liver imaging (Neirinckx et al. 1979). High resolution and statistical quality FPRNA studies of ventricular performance were demonstrated in a group of 38 patients in comparison with the traditional ^{99m}Tc methods (Lacy et al. 1991). Verani et al. (1992a) demonstrated the usefulness of this

system for evaluation of systolic and diastolic left ventricular function in 46 patients undergoing coronary balloon angioplasty. Verani et al. (1992b) reported evaluation of right ventricular performance in 46 patients. The $^{178}W/^{178m}Ta$ generator in combination with a portable multiwire proportional counter gamma camera (MWGC) has recently been shown to be an excellent source of ^{178m}Ta for the evaluation of ventricular performance (Lacy et al. 2001). These studies clearly demonstrate that the $^{178}W/^{178m}Ta$ generator is the only current system providing a short-lived daughter for the evaluation of FPRNA. In spite of the fact that first-pass ventriculography with ultra-short lived radioisotopes is not currently widely practiced, a recent study described the advantages for the assessment of left ventricular function during upright treadmill exercise using a multiwire gamma camera (Heo et al. 2005).

^{191}Os ($T_{½}$ = 15.4 d)/^{191m}Ir ($T_{½}$ = 4.94 s). The ^{191}Os is produced via the $^{190}Os(n,\gamma)$ reaction. Radiochemical separations of the generator system were based on ion exchange chromatography (Yano and Anger 1968; Campell and Nelson 1956; Hnatowich 1977; Hnatowich et al. 1977). More recent systems used absorption of $K_2/^{191}OsO_2Cl_4$ or $K_2/^{191}OsO_2(OH)_2Cl_2$ on AGMP-1 anion exchange resin. A second column was required to guaranty radionuclidic purities with a breakthrough of $<10^{-2}$% ^{191}Os, while the overall separation yield of ^{191m}Ir remained relatively low (<10%) (Cheng et al. 1980, 1982). More than 100 patients received injections of ^{191m}Ir in isotonic saline Na_2HPO_4 buffers. Another system used Os(VI) bound to silica gel impregnated with tridodecylmethylammonium chloride (SG-TDMAC) (Issacher et al. 1989; Hellmann et al. 1989) and provided ^{191m}Ir in 21–33% yield by elution with acidic (HCl) saline at pH 1 with the final eluate buffered with 1 M succinate solution to pH 9. An activated carbon "scavenger" column was used in tandem with the SG-TDMAC column to remove ^{191}Os parent breakthrough before the eluant is rapidly buffered. Another generator system was also developed for angiocardiography in children which utilized a potassium Os (VI)oxalate species adsorbed on AGMP-1 anion exchange resin (Packard et al. 1986, 1987), which did not require a "scavenger" column. Elution with pH 1 0.9% saline solution provided ^{191m}Ir in good yields (10% per mL) with low ^{191}Os parent breakthrough (3×10^{-4}%). The use of $^{191}Os(IV)$ species bound on heat-activated carbon eluted with 0.9% saline at pH 2 containing 0.025% KI was also developed and represented an excellent generator system, providing the daughter nuclide in 16–18% yields with correspondingly low ^{191}Os parent breakthrough ($2–3 \times 10^{-4}$% per bolus). For patient studies, the low-pH bolus was neutralized with 0.13 M TRIS, followed by rapid intravenous administration of the neutralized bolus with physiological saline (Franken et al. 1989, 1991), using a microprocessor-controlled automated elution/injection system.

^{191m}Ir was proposed for the evaluation of heart disease and blood flow for various organs (Yano and Anger 1968; Treves et al. 1976, 1980; Thiesson et al. 1983). This first generator provided ^{191m}Ir for intravenous administration (Yano et al. 1968) and another system was used for quantification of cardiac shunts in children (Treves et al. 1976, 1980) and evaluation of ventricular function in adults (Heller et al. 1986). Studies by Franken et al. (1989, 1991) described rapid sequential multiple view FPRNA for the evaluation of left ventricular ejection fraction and regional wall motion studies in over 600 patients. More recent studies have described the use of ^{191m}Ir in rabbits via dynamic studies (Kariemo et al. 1994) for renal radionuclide angiograms and continuous infusion for the rapid renal single-photon emission tomographic evaluation of renal blood flow (Treves et al. 1999).

^{195m}Hg ($T_{½}$ = 1.73 d)/^{195m}Au ($T_{½}$ = 30.5 s). Like ^{191m}Ir, the short-lived ^{195m}Au was of interest for first-pass radionuclide angiography (Thiesson and Paras 1983). The parent nuclide

is produced via the ^{197}Au(p,3n) reaction at 34 → 26 MeV proton energies with relatively high thick target yields of 170 MBq μA^{-1} h^{-1} (Birattari and Bonardi 1982; Panek et al. 1985; Guillaume and Brihaye 1986). The ^{195m}Hg was separated either by solvent extraction (Bett et al. 1981, 1983) or by distillation (Guillaume and Brihaye 1986). Dithiocellulose adsorbents were used showing 1–2% breakthrough of ^{195m}Hg and 10–20% elution yield of ^{195m}Au using 10 mM NaCN solution (Bett et al. 1983), while silica gel coated with ZnS showed better retention of the parent nuclide and higher elution yield of 28–30% using $Na_2S_2O_3/NaNO_3$ solutions (Panek et al. 1984, 1985). For bolus injections, ^{195}Hg was loaded onto a Chelex 100 column, while ^{195m}Au was eluted with 5% glucose solutions with about 20% yield in mainly ionic form; the ^{195}Hg breakthrough being about 10^{-3}% (Garcia et al. 1981; Brihaye et al. 1982). Some limitations concern the formation of ^{195}Au by isomeric transition of ^{195m}Au, resulting in an increasing absorbed radiation dose. Nevertheless, both cardiac metabolism and function studies have been performed comparing ^{195m}Au with ^{201}Tl (Mena 1985) and [^{123}I]IPPA (Wagner et al. 1990).

40.4 Generator-Produced Particle Emitters for Therapy

40.4.1 Overview

During the last decade there has been a tremendous increase in the development and use of new therapeutic radiopharmaceuticals radiolabeled with radionuclides, which are available from radionuclide generator systems. The availability of generator-derived therapeutic radionuclides is necessary for the development and testing and commercialization of agents with potential for endoradiotherapy (ERT). Just as availability of ^{99m}Tc from the ^{99}Mo/^{99m}Tc has played such a key role in the development of a wide variety of ^{99m}Tc-labeled radiopharmaceuticals, the availability of generator-derived radionuclides has stimulated the development of an increasing spectrum of therapeutic tracers. It is important to note that in most cases, increased need for and further development of generators, which provide therapeutic radionuclides has been driven by the success in the development of the targeting agents or vectors.

Generator-derived therapeutic radionuclides have a number of characteristic decay processes, and can emit β particles, Auger electrons, low-energy photons, and α particles. Since many therapeutic radionuclides are characterized by β decay, they are often directly produced in a nuclear reactor, since neutron capture by the target nuclide forms a radioactive or unstable product that decays by β emission. Key examples of therapeutic radionuclides obtained from reactor-produced parent radionuclides include ^{166}Ho – from the ^{166}Dy/^{166}Ho generator, and ^{188}Re – from the ^{188}W/^{188}Re generator.

Another important source of generator parent radionuclides is recovery of generator parent radionuclides that are produced during nuclear fission. Strontium-90 is the parent for the ^{90}Sr/^{90}Y generator system and is isolated from fission products. The recent approval by the US Food and Drug Administration (FDA) on February 19, 2002, for "Zevalin" (Ibritumomab tiuxetan) – a ^{90}Y-labeled murine anti CD20 antibody – for the treatment of patients with low grade, follicular, or transformed non-Hodgkin's lymphoma, represents the first antibody radiolabeled with a therapeutic, generator-derived radionuclide, and would be expected to represent the first of many new therapeutic radiopharmaceuticals for oncologic applications.

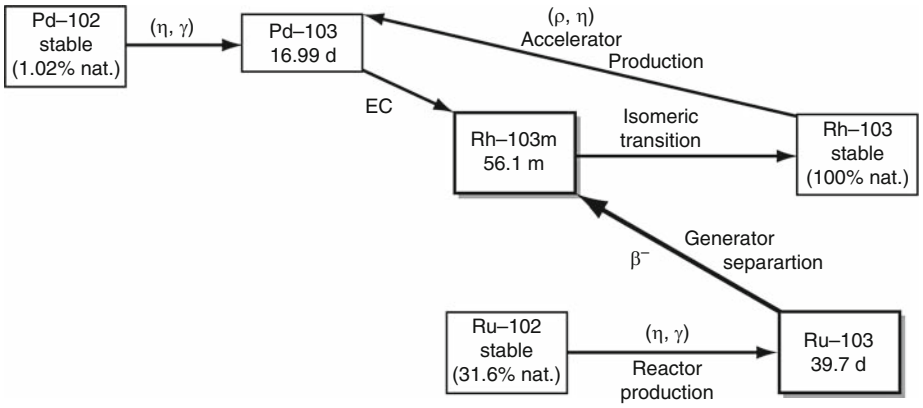
A third source for radionuclide generator systems is the recovery of radioactive parents from "extinct" radioactive decay processes, such as ^{229}Th, which is recovered from ^{233}U decay products. The ^{229}Th represents a convenient, long-lived ($T_{½}$ = 7,340 years) source from which ^{225}Ac is recovered, which is the parent of the ^{225}Ac/^{213}Bi generator system.

The α-emitter ^{211}At has great potential for labeling compounds of potential interest in cell biology and endoradiotherapy. Although it is produced mainly via the direct ^{209}Bi(α,2n) route, it can be produced through the decay of 14.6 h ^{211}Rn (Vachtel et al. 1976; Visser et al. 1979; Mirzadeh and Lambrecht 1980).

^{103}Ru ($T_{½}$ = 39.25 h)/^{103m}Rh ($T_{½}$ = 56.12 min). Rhodium-103m is a key example of an Auger-emitting candidate, which can be obtained from decay of reactor-produced ^{103}Ru. Interest for use of ^{103m}Rh in radioimmunotherapy and other strategies for targeted therapy results from its attractive decay properties (see *Table 40.1*) and potential availability from a ^{103}Ru/^{103m}Rh generator system for targeted radiotherapy (Bernhard et al. 2001). The 40 keV isomeric decay energy is totally converted in the electronic shells of the stable ^{103}Rh daughter with no measurable γ-rays and results in a "shower" of low-energy electrons and X-rays. Daily elution of equilibrium levels of ^{103m}Rh is possible from the ^{103}Ru/^{103m}Rh generator. Rhodium-103m is expected to exhibit high cytotoxicity resulting from its decay by highly converted isomeric transition and emission of Auger electrons. Availability of a ^{103}Ru/^{103m}Rh generator system would offer an opportunity to provide carrier-free ^{103m}Rh on a routine basis for the assessment of its potential for Auger therapy. Either fission- or reactor-produced ^{103}Ru could be used for the generator system. Although the 3% fission yield of ^{103}Ru from ^{235}U is quite high, fission products are not routinely available. The availability of lower specific-activity ^{103}Ru from reactor irradiation of enriched ^{102}Ru production with sufficient specific activity in many research reactors on an international basis would be expected to be reliable routine source of ^{103}Ru for fabrication of the ^{103}Ru/^{103m}Rh generator system. Rhodium-103m can also be obtained by the decay of ^{103}Pd (*Fig. 40.5*), and the use of the ^{103}Pd/^{103m}Rh in vivo generator has been proposed (Van Rooyen et al. 2008), which may suggest that a ^{103}Pd/^{103m}Rh generator for routine availability of ^{103m}Rh may be feasible. Development of a chromatographic-type ^{103}Ru/^{103m}Rh generator would be expected to provide ^{103m}Rh from

Fig. 40.5

Availability of ^{103m}Rh from reactor-produced long-lived ^{103}Ru and from decay of ^{103}Pd



separation of Rh from Ru compared to Rh from Pd. In addition, the very low 1.02% natural abundance of ^{102}Pd, coupled with the high costs of enrichment for reactor production of ^{103}Pd, the high costs of accelerator-production of ^{103}Pd from ^{103}Ru(p,n) and the shorter physical half-life of ^{103}Pd compared to ^{103}Ru are other issues.

The separation of Rh from Ru had been described some years ago by solvent extraction techniques (Chiu et al. 1978; Epperson et al. 1976), and these methods with carbon tetrachloride extraction for RuO_4 from Ru/Rh mixtures in HCl have served as the basis for the more recent interest in the availability of ^{103m}Rh. A recent solvent-extraction type ^{103}Ru/^{103m}Rh generator, which is based on the earlier extraction work of Epperson et al. (1976) and Chiu et al. (1978), has recently been reassessed (Bartos et al. 2007, 2009; Skarnemark et al. 2009). Recent studies have used both fission- and reactor-produced Ru for these studies (Bartos et al. 2009). The use of batch liquid extraction/post processing of Rh from Ru by liquid extraction technology to routinely provide ^{103m}Rh may be impractical and could be expected to be primarily centered at a central processing site and not accessible in most research centers. Use of a chromatographic-type generator would be expected to be much more practical and accessible on a routine institutional basis to provide the ^{103m}Rh Auger emitter for widespread research use.

40.4.2 Key Examples of Generator-Derived Therapeutic Radionuclides with Proven Medical Applications

^{90}Sr ($T_{½}$ = 28.6 a)/^{90}Y ($T_{½}$ = 64.1 h). Yttrium-90 decays with the emission of a high-energy β particle (E_{max} = 2.3 MeV) and is of broad interest for therapy of solid tumors where deep penetration of radiation is important for cross-fire (cf. Chaps. 45 and 46 of this Volume). Although various forms of the ^{90}Sr/^{90}Y generators have been available for a number of years, broad interest in clinical therapeutic applications of ^{90}Y was stimulated by the development of methods of radiation synovectomy of large synovial joints, and more recently, the development of bifunctional chelating groups that strongly bind the Y^{3+} cation, since the skeletal localization of free trivalent yttrium species would result in significant marrow suppression. The availability of DOTA and the CHX-substituted DTPA chelates provides an opportunity to use ^{90}Y in a predictably safe manner. The availability of the chelates in consort with vectors having very specific cellular targeting, such as the DOTATOC octreotide agent, which binds with high specificity to the somatostatin receptors, provided important agents for the treatment of a wide variety of tumors. Because of the safety issues associated with the use and handling of ^{90}Y and ^{90}Sr, these high-level generators are typically installed in a centralized processing area for preparation of the no-carrier-added ^{90}Y by batch solvent extraction techniques and distribution of the highly purified ^{90}Y product. One method (Bray and Wester, 1996) involves freshly purified HDEHP extraction of ^{90}Y from a nitric acid solution of the purified ^{90}Sr/^{90}Y mixture. The final ^{90}Y/^{90}Sr activity ratio of the purified ^{90}Y is $<10^{-7}$ with a concentration of metal impurities of <10 ppm per Ci ^{90}Y. A generator system has also been described for the separation of ^{90}Y from ^{90}Sr and involves the use of strongly acidic Dowex exchange resin (Chinol and Hnatowich, 1987).

A comparison of solvent extraction, ion exchange, and other radiochemical separation techniques applied to this generator was made by Chuang and Lo (1988). Ion exchange based generators utilize various organic cation exchange resins, but also inorganic compounds, with a particular focus on high radiation resistance (Hsieh et al. 1991; Bielewicz, 1995; Chinol et al. 1996;

Bläuenstein et al. 1996). Because of the limited availability, significant costs of high purity ^{90}Sr and the potential dangers in handling ^{90}Sr, installation of this generator in a hospital-based nuclear pharmacy or a central radiopharmacy is unusual, and high purity ^{90}Y is generally obtained from a central processing approved GMP facility providing both research-grade and sterile, pyrogen-free ^{90}Y for human studies.

^{166}Dy ($T_{½}$ = 3.4 d)/^{166}Ho ($T_{½}$ = 1.117 d). Although ^{166}Ho can be produced with a specific activity of only 8–9 Ci mg^{-1} (~300 GBq mg^{-1}) ^{165}Ho by the ^{165}Ho(n,γ)^{166}Ho reaction even at saturation in a high thermal flux of 2.5 × 10^{15} n cm^{-2} s^{-1}, no-carrier-added ^{166}Ho with a theoretical specific activity of about 700 Ci mg^{-1} (~ 26 TBq mg^{-1}) is obtained by decay of ^{166}Dy. The ^{166}Dy is reactor produced by the ^{164}Dy(n,γ)^{165}Dy(n,γ)^{166}Dy reaction series. Separation of ^{166}Ho from ^{166}Dy has traditionally been a challenge. Although not a true generator system – since the ^{166}Dy parent is also recovered and requires column reloading for subsequent ^{166}Ho/^{166}Dy separations following adequate ^{166}Ho in-growth – a method has been described for successful ^{166}Ho/^{166}Dy separation, which uses an HPLC reversed phase ion-exchange chromatographic method utilizing Dowex AG 50WX12 or Aminex A5 cation exchangers by elution with α-hydroxy-isobutyric acid (α-HIB) of 0.085 M at pH 4.3. This approach provides a Dy/Ho separation factor of approximately 10^{3}, with subsequent purification of the ^{166}Ho^{3+} by cation-exchange column chromatography after acid decomposition of the Ho-α-HIB complex (Dadachova et al. 1995a, b). More recently, an apparently simple and efficient method has described separation on the Eichrome Ln resin by elution with dilute nitric acid (Ketring et al. 2002).

Although ^{166}Ho has attractive radionuclidic properties as a lanthanide for various vector labeling and therapeutic strategies, it has not yet been widely used. Examples are studies of protein labeling with the CHX-B-DTPA ligand system (Dadachova et al. 1997). Animal studies demonstrated that no translocation of the ^{166}Ho daughter radionuclide occurred when the [^{166}Ho]DTPA complex was administered to rats (Smith et al. 1995). The results of these studies may suggest that the ^{166}Dy/^{166}Ho system may have some promise as an in vivo generator. Clinical applications that have been recently reported include radiation synovectomy with ^{166}Ho-ferric hydroxide (Ofluoglu et al. 2002), the use of [^{166}Ho]DTPA liquid-filled balloons for the inhibition of restenosis following coronary angioplasty (Hong et al. 2002), and use of [^{166}Ho]DOTMP for myeloablative therapy of multiple myeloma (Rajendran et al. 2002). If the availability of no-carrier-added ^{166}Ho becomes a reality, use of this generator system may be a source for these and other applications.

^{188}W ($T_{½}$ = 69 d)/^{188}Re ($T_{½}$ = 16.9 h). Rhenium-188 is currently of broad interest for the development of a wide variety of new therapeutic approaches for applications in nuclear medicine, oncology, and even interventional cardiology, because of the benefits, advantages, and significantly reduced expense of using ^{188}Re in comparison to many other therapeutic radionuclides (Knapp et al. 1997, 1998a, b). There are currently a large number of physician-sponsored clinical protocols in progress. Tungsten-188 is reactor produced by double neutron capture of enriched ^{186}W by the ^{186}W(n,γ)^{187}W(n,γ)^{188}We route. Since the production yield is a function of the square of the thermal neutron flux, even at high thermal neutron flux (>2 × 10^{15} n cm^{-2} s^{-1}) ^{188}W is produced with only modest specific activity of 4–5 Ci g^{-1} (~180 GBq g^{-1}) per cycle (Knapp et al. 1994). This is due to the modest neutron capture cross sections and burnup of the ^{188}W product (Mirzadeh et al. 1997). Although the first prototype ^{188}W/^{188}Re generators were described as early as 1966 using zirconium oxide (Lewis and Eldridge, 1966) and with aluminum oxide in 1972 (Mikheev et al. 1972), in spite of the excellent radionuclidic properties of ^{188}Re, there was no practical use of this therapeutic

radionuclide until nearly 25 years later, when appropriate carrier molecules and targeting agents became available (Knapp et al. 1997, 1998a, b).

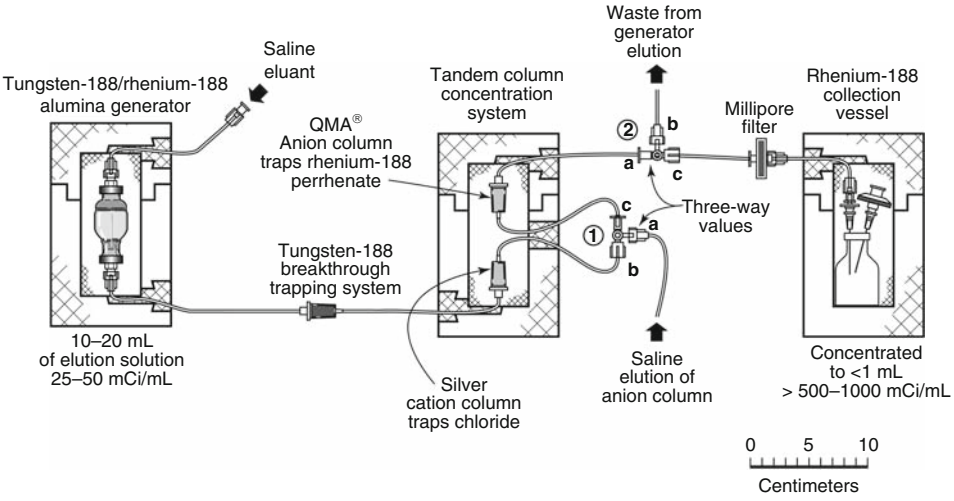
The $^{188}W/^{188}Re$ generator systems today are mainly based on separation chemistry similar to that used for the $^{99}Mo/^{99m}Tc$ generator, which includes the adsorption of tungstic acid in the alumina-based generator (Mikheev et al. 1972; Callahan et al. 1989; Knapp et al. 1994) (*Fig. 40.6*). In addition to the adsorption column chromatographic separation on alumina, zirconium oxide (Dadachova et al. 1994) and gel-type generators (Erhardt et al., 1992) have been reported. For batch separation of ^{188}Re a thermochromatographic technique was described (Novgorodov et al. 2000).

The adsorption type generator is most practical, since it is easy to prepare, has long-term stability with high ^{188}Re yields and consistently low ^{188}W breakthrough. The availability of effective and inexpensive post-elution tandem column-based concentration systems (Guhlke et al. 2000; Knapp et al. 1997, 1998a) provides a useful method for ^{188}Re concentration to very high specific volumes (<1 mL total volume).

There are presently a large number of physician-sponsored clinical trials in progress using the Oak Ridge National Laboratory (ORNL) alumina-based $^{188}W/^{188}Re$ generator system. ^{188}Re-labeled HEDP (Palmedo et al. 2000; Savio, et al. 2001) and DMSA (Blower et al. 2000) have proven to be effective agents for the palliative relief of bone pain from skeletal metastases in patients with prostatic carcinoma, and may represent a more cost-effective alternative to

Fig. 40.6

Scheme of the $^{188}W/^{188}Re$ generator. Post-elution concentration after saline elution of the alumina-based $^{188}W/^{188}Re$ generator system conveniently provides high specific volume ^{188}Re perrhenate solutions. The generator is eluted with physiological saline (for instance, 25–50 mL) at a flow-rate of 1–2 mL min^{-1} through the disposable, one time use tandem cation/anion exchange system, with stopcocks (SC) 1 and 2 in the following positions: SC 1, position b–c and SC 2, position a–b. After generator elution, the ^{188}Re perrhenate trapped on the QMA anion column is then eluted with a small volume (1–2 mL) of saline with SC 1, in position a–c and SC 2, in position a–c



other radionuclides used for this application. In addition, the use of liquid-filled angioplasty balloons for the inhibition of hyperplastic restenosis after coronary balloon angioplasty using ^{188}Re-perrhenate (Hoeher et al. 2000; Kotzerke et al. 2000; Makkar et al. 2000; Schuelen et al. 2001; Kropp et al. 2002), ^{188}Re-MAG3 (Weinberger and Knapp 1999; Weinberger et al. 1999; Park et al. 2001) and [^{188}Re]DTPA (Hong et al. 2002) are in progress, and the use of the ^{188}Re-labeled anti-CD66 has also been reported (Nowak et al. 2001). The use of the ^{188}Re-labeled anti-CD66 antibody (anti-NCA95) has been found to be a useful new method for marrow ablation using combinational preconditioning in leukemia patients (Bunjes et al. 2000; Reske et al. 2001; Buchman et al. 2002). The use of the ^{188}W/^{188}Re generator in developing regions has been demonstrated to be of particular usefulness because of its cost-effectiveness, and multicenter trials supported by the International Atomic Energy Agency are in progress for restenosis therapy with ^{188}Re-perrhenate and for the treatment of liver cancer (Sundram et al. 2002) with ^{188}Re-labeled lipiodol analogues (Jeong et al. 2001a, b). A ^{188}Re-labeled antibody has been used for treatment of bladder cancer (Murray et al. 2001) and use of the ^{188}Re-labeled P2045 sstr-targeting peptide for the treatment of lung cancer has also been reported (Bugai et al. 2002) and is now in clinical trials in the USA.

Several new generator prototypes for the separation of nca ^{188}Re from ^{188}W have been recently described, which use a new high-capacity adsorbent consisting of synthetic alumina functionalized with sulfate moieties prepared from a sol-gel process (Lee et al. 2009). This material is reported to have a tungsten loading capacity of >450 mg/g, allowing preparation of a 3 Ci generator using only 1 g of adsorbent, which is a much higher loading capacity than reported for acid-washed alumina. Elution with 5 mL of saline at 1 mL/min results in ^{188}Re yields of 70–90%. In this manner, a 1 Ci generator can provide ^{188}Re solutions with a specific volume of >200 mCi/mL saline. In addition, a simple electrochemical separation technique has been reported using platinum electrodes immersed in ^{188}W/^{188}Re equilibrium mixture by applying a constant 7 V potential difference at 80°C for 60 min. The ^{188}Re is stripped as perrhenic acid from the platinum cathode with warm 0.1 N HCl (Chakravarty et al. 2009). Decay-corrected ^{188}Re yields of >70% have been reported in preliminary studies using 30 mCi of ^{188}W. There are several examples of recent clinical applications with ^{188}Re which include use of the ORNL ^{188}W/^{188}Re generator for preparation of the HDD agent for liver cancer therapy (Jeong and Knapp 2008). Results of the recent multicenter clinical trial with this agent coordinated through the IAEA have demonstrated the efficacy of ^{188}Re-labeled HDD/Lipiodol for the transarterial palliative treatment in patients with non-resectable/non-transplantable liver tumors (Padhy et al. 2008). Further assessment of the initial use of ^{188}Re liquid-filled angioplasty balloons for the inhibition of hyperplasia following PCTA of the coronaries has now been demonstrated for the peripheral arteries (Wohlgemuth et al. 2008).

^{225}Ac ($T_{½}$ = 10 d)/^{213}Bi ($T_{½}$ = 45.6 min). Because of the very high linear energy transfer (LET) in the 50–90 μm range, α particles are very suitable for therapy of microscopic or subclinical disease, such as for the treatment of micrometastatic disease (cf. Chap. 46 of this Volume). The attachment of α emitters to cellular-targeted carrier molecules such as antibodies or peptides is the most common approach. For this reason, interest in the ^{225}Ac/^{213}Bi generator system has rapidly increased in the last few years. The ^{225}Ac is generally obtained as a decay product of ^{229}Th, which is extracted as a radioactive decay product of the ^{233}U, a member of the "extinct" ^{237}Np decay chain (see Fig. 5.5 in Chap. 5, Vol. 1). Production has also been proposed via accelerators, as an example, by the ^{226}Ra(p,2n)^{225}Ac reaction. The ^{229}Th can be obtained from processing of the ^{233}U stockpile, which had originally been produced in a proposed molten salt breeder reactor program at ORNL. From a complex series of

ion-exchange and extraction chromatographic steps for recycling of ^{229}Th(IV), the Ra(II) decay product is separated at optimal timing, and the ^{225}Ac then separated. A variety of chromatographic-type ^{225}Ac/^{213}Bi generators have been described (Geerlings et al. 1993; Lambrecht et al. 1997; Wu et al. 1997; Boll et al. 1997; Mirzadeh 1998; Hassfjell and Brechbiel 2001).

At ORNL, the ^{225}Ac in 1 M HNO_3 solution is provided to investigators with generator components for on-site generator loading, to minimize the effects of radiolysis. This solution is loaded onto a small AG 50W-X4 strong cation exchange resin with elution of the ^{213}Bi daughter with 0.15 M HI solution. Several other ^{225}Ac/^{213}Bi generator systems have also been described. One example (Geerlings et al. 1993) used two successive Dowex 50W-X8 cation exchange columns, with initial separation of ^{225}Ac from $^{224/225}$Ra with subsequent separation of the desired ^{213}Bi from the ^{225}Ac formed from radon decay. Wu et al. (1997) reported a generator using the inorganic AC-Resin ion exchanger. The ^{213}Bi was eluted with 1 M HCl in a continuous elution mode, diluted to 0.2 M HCl and then loaded on a second small AGMP-50 cation exchange resin and eluted with 0.1 M HI. A similar column is being used (McDevitt et al. 1999a) where ^{213}Bi is being applied for the clinical treatment of acute myeloid leukemia (AML) under physician-sponsored protocols (McDevitt et al. 1999b; Sgoruos et al. 1999; Jurciv et al. 2002). Another variation proposed by Bray et al. (1999) passes a ^{225}Ac solution through a disc containing a thin film of the Anex (3M Company) strong anion-exchange resin that binds the ^{213}Bi, which is subsequently eluted with pH 5.5 solution of 0.05 M NaOAc.

As discussed later in the in vivo generator section, in addition to its utilization in a generator system to provide ^{213}Bi for α-targeted therapy, interest is increasing in using the ^{225}Ac parent for targeted therapy, because of the emission of four α particles and the long half-life (Chang et al. 2008; Miederer et al. 2008; Sofou et al. 2007; Antczak et al. 2006). The current major clinical application of bismuth-213 is for treatment of myelogenous leukemia and use of actinium-225 is gaining interest for α therapy because of the longer physical half-life (McDivitt et al. 2001).

^{224}Ra ($T_{½}$ = 3.66 d)/^{212}Pb ($T_{½}$ = 10.64 h)/^{212}Bi ($T_{½}$ = 1.01 h). Bismuth-212 has been of interest for some time and is available from decay of ^{212}Pb. The traditional generator involves loading a cation exchange resin with ^{224}Ra with subsequent elution of the ^{212}Bi with HCl or HI (Atcher et al. 1988), which requires replacement of the generator every 3–6 days. More recently, a generator based on gaseous ^{222}Ra emanating from thin films of ^{228}Th barium stearate has been described (Hassfjell and Brechbiel 2001), which involves collecting the gaseous ^{224}Ra in a trap containing an organic solvent such as methanol or hexane or a methanol/hexane mixture, at temperatures lower than –72°C. The ^{212}Pb decay product can be obtained in about 70% yield and this system has the advantage of an indefinite shelf life of the long-lived ^{228}Th ($T_{½}$ = 1.913 a) source.

^{227}Ac ($T_{½}$ = 21.77 d)/^{223}Ra ($T_{½}$ = 11.43 d). Because of availability from decay of ^{227}Ac, localization of ionic radium in growing bone and the high LET, radium-223 has emerged as a promising new candidate for routine use for palliative treatment of bone pain from tumor metastases to the skeleton (Bruland et al. 2008; Nilsson et al. 2005, 2007). Radium-223 can be conveniently repeatedly obtained from separation from the ^{227}Ac parent. The ^{227}Ac is obtained from decay of ^{235}U and decays to ^{227}Ac through ^{227}Th, or can be reactor produced by neutron irradiation of ^{226}Ra (Larsen et al. 2007) or from α irradiation of protactinium-231 targets. The availability of beryllium/actinium neutron sources often used for well logging can provide a ready source of ^{227}Ac. The purified ^{227}Ac/^{227}Th, purified by traditional ion exchange methods, can be adsorbed on 1 M HCl preconditioned *P,P′*-di(2-ethylhexyl)

methanediphosphonic acid/silica (Dipex-2) extraction resin (Hendricksen et al. 2001). The ^{223}Ra then eluted with 1 M HCl or HNO_3. Further purification of the ^{223}Ra is accomplished using a small AG 50W-X12 cation resin by elution with 1 M nitric acid. Although there are no practical complexing/chelating agents for ionic radium, the targeting of Ra^{2+} to metabolically active bone, allows the simple administration of radium chloride. In this manner, the generator can be eluted, the ^{223}Ra eluant evaporated, then dissolved in saline/sodium citrate buffer, and dispensed by sterile filtration. It is then ready for administration precluding any complex radiolabeling and purification procedures normally encountered for radiopharmaceutical administration.

40.5 In Vivo Generators

40.5.1 Concept

A relatively recent and potentially useful approach is based on the concept of an in vivo generator (Mausner et al. 1989). The concept involves labeling of various molecular carriers (complexes, peptides, mcAb, mcAb-fragments, etc.) with intermediate half-life generator parents, which after accumulation in the desired tissue generate much shorter half-life daughter radionuclides (*Table 40.3*). These in vivo generated daughter radionuclides can act either as imaging agent (if decaying via single-photon or positron emission) or as therapeutic agent (if decaying via α, β^-, or Auger electron emission). In particular, for therapy, since the daughter will be in equilibrium in vivo with the parent, formation of the particle-emitting daughter will add in situ a significant radiation dose. This concept of targeting the parent radionuclide will

Table 40.3
Potential parent/daughter pairs for the in vivo generator concept

Generator system	Parent		Daughter			Application
	$T_{½}$	decay	$T_{½}$	Emission (%)	$E_{β/α}$ (MeV)	
^{66}Ni/^{66}Cu	2.275 d	β^-	5.10 min	γ, β^-	1.076	ERT
^{112}Pd/^{112}Ag	21.04 h	β^-	3.14 h	γ, Auger-e, β^-	1.380	ERT
^{134}Ce/^{134}La	3.16 d	EC	6.45 min	γ, Auger-e, β^+ (63%)	0.756	PET
^{140}Nd/^{140}Pr	3.37 d	EC	3.39 min	γ, Auger-e, β^+ (51%)	0.544	ERT, PET
^{166}Dy/^{166}Ho	3.400 d	β^-	1.117 d	γ, Auger-e, β^-	0.711	ERT
^{212}Pb/^{212}Bi	10.64 h	β^-	1.01 h	γ, Auger-e, α (64%), β^- (36%)	2.170 0.492	ERT
^{213}Bi/^{209}Pb	45.6 min	β^-, α	3.253 h	β^-	0.198	ERT
^{225}Ac/chain	10.6 d	α	Various	α	Various	ERT
^{227}Th/^{223}Ra	18.7 d	α	11.4 d	α	Various	ERT

assist to focus the therapeutic efficacy to the tumor cells, which is of particular importance, since the potential usefulness of radiotherapy is often limited by the irradiation of radiation-sensitive non-target tissues. The in vivo generator is thus a potential alternative to minimize exposure.

However, the concept implies that the chemical binding of the daughter nuclide is analogous to the parent one and the daughter radionuclide is thus not released from the original position. If not, i.e., if released from the targeted tracer due to various factors, which are well known from hot atom chemistry processes, the decay product will be bound in the near surrounding environment of the parent due to other chemical or biochemical binding (such as intracellular trapping effects) or is released from the target site.

40.5.2 Examples of In Vivo Generators

Several generator pairs could potentially be utilized as in vivo systems, presuming the parent nuclide offers the adequate chemical properties for synthesis of labeled compounds and a half-life adequate to the biochemical/physiological process the labeled compound is involved. In this context, stable labeling with ^{66}Ni and ^{112}Pd, for instance, is not yet established, whereas there are reliable bifunctional chelators available to bind trivalent parent nuclides such as ^{134}Ce, ^{140}Nd, ^{166}Ho, and ^{213}Bi. The most intensively studied pair as in vivo generator is ^{166}Ho/^{166}Dy (Ma et al. 1993; Mirzadeh et al. 1994; Smith et al. 1995). After intravenous injection of [^{166}Dy] DTPA and accumulation of the parent nuclide in bone, no translocation of the daughter ^{166}Ho was observed subsequent to the β^- decay of ^{166}Dy.

Issues related to the possible in vivo use of the ^{103}Pd ($T_{½}$ = 16.99 d)/^{103m}Rh ($T_{½}$ = 56.1 min) generator have also recently been discussed on a theoretical basis (Suzcs et al. 2009; Van Rooyen et al. 2008).

Interest in the use of the in vivo generator concept for tumor therapy has reemerged with increased focus on ^{225}Ac ($T_{½}$ = 10 days), which decays to the ^{213}Bi ($T_{½}$ = 45 min) daughter. Although the dose rate is much lower, the integrated delivered radiation dose is much higher for administered levels of radioactivity. The use of complexed ^{225}Ac as an in vivo generator has also been evaluated by McDevitt et al. (2001), where it is described as a "nano generator." Other studies with ^{225}Ac have demonstrated that select carboxylate-derived calixarene agents have an ionophore cavity capable of highly selective complexation of Ac^{3+} in weak acid and neutral solution. Successful functionalization of these molecules may provide other candidate chelate approaches for use of ^{225}Ac for the in vivo generator approach.

The ongoing clinical application of ^{213}Bi-radiotherapeuticals themselves may already be considered as a version of an in vivo generator, as the various nuclides of the decay chains

$$^{213}\mathrm{Bi}\left\{\begin{array}{l}\xrightarrow{\alpha}{}^{209}\mathrm{Tl}\xrightarrow[[2.20\,\mathrm{min}]]{\beta^-}\\ \xrightarrow{\beta^-}{}^{213}\mathrm{Po}\xrightarrow[[4.2\mu\mathrm{s}]]{\alpha}\end{array}\right\}{}^{209}\mathrm{Pb}\xrightarrow[3.253\mathrm{h}]{\beta^-}{}^{209}\mathrm{Bi(stable)} \qquad (40.12)$$

probably stay in the vicinity of the parent nuclide cellular environment and do significantly contribute to an enhanced radiation dose in the target tissue.

However, as investigated for the ^{140}Nd/^{140}Pr generator system, the daughter (^{140}Pr) may quantitatively be released from initial (^{140}Nd-DOTA) complexes in, e.g., (^{140}Nd)-DOTA-octreotide compounds despite the very high thermodynamic and kinetic stability of the

trivalent lanthanide with the macrocyclic chelator (Zhernosekov et al. 2007b). This dramatic effect – different to the ^{166}Ho/^{166}Dy system – is explained by the difference in the radioactive decay. The electron capture ^{140}Nd → ^{140}Pr, namely, ruptures the initial chemical bonds of the mother radionuclide and releases a daughter atom in situ, which is not able to form complexes with DOTA-like compounds at room temperature. Thus, nuclide pairs connected by EC and ligands involved with kinetically determined complex formation characteristics are not useful as in vivo generators.

In addition, in vivo generators have been discussed in the context of radiation therapy seeds and of diagnostic tests with ultra-short-lived daughters (Lambrecht et al. 1997).

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