Production of Radionuclides

8

Scientific achievement is rooted in the past, is cultivated to full stature by many contemporaries, and… No individual alone is responsible for a single steppingstone along the path of progress. (Ernest O. Lawrence)

8.1 Natural Radioactivity

The phenomenon of spontaneous, continuous, and uncontrollable disintegration of an unstable atomic nucleus accompanied by the emission of radiations (such as α, β^-, and γ) is called natural radioactivity. This spontaneous disintegration of an unstable nucleus of one naturally occurring radioisotope of one element (parent) into an isotope of another element (daughter) continues until a stable nucleus is formed. Isotopes of chemical elements can exist in nature either as stable nuclides, or as radionuclides. Primordial radionuclides (such as ^{238}U, ^{235}U, and ^{232}Th) created before the earth was formed exist in the present time because their half-lives are so long (>100 million years) and that they have not yet completely decayed. Secondary radionuclides (such as ^{226}Ra, ^{227}Ac, ^{227}Th, ^{223}Ra) with shorter half-lives than primordial radionuclides are radiogenic isotopes derived from the decay of primordial radionuclides. These secondary radionuclides are generated in the decay chains of ^{238}U, ^{235}U, and ^{232}Th whereas cosmogenic radionuclides (such as ^{14}C) are present because they are continually being formed in the atmosphere due to cosmic rays. In nature, 34 primordial radionuclides and 61 nonprimordial radionuclides exist as naturally occurring radioisotopes of many elements. All elements heavier than lead (with $Z > 82$) and elements technetium ($Z = 43$) and promethium ($Z = 61$) are all unstable, and exist only as radionuclides.

8.1.1 Decay Chain

The decay chain or radioactive cascade refers to a series of radioactive decays of different radioactive decay products as a sequential series of nuclear transformations until eventually a stable isotope of lead or thallium is reached. Three decay chains of primordial nuclides of uranium and thorium have been observed in nature (Fig. 8.1a–d). The 3 decay chains have a long-lived parent at the top (^{232}Th, ^{238}U, and ^{235}U) and slowly decay by α and β^- emission and ultimately reach a stable isotope of lead. In 1940s, based on the large-scale artificial production of a new radionuclide ^{237}Np, investigators have identified the hitherto extinct fourth decay chain.

In the thorium (4n) series, the radionuclides of interest are ^{224}Ra, ^{212}Pb, and ^{212}Bi. In the neptunium series (4n + 1), the radionuclides of interest are ^{229}Th, ^{225}Ra, ^{225}Ac, and ^{213}Bi. Based on uranium series (4n + 2), the Curies discovered the radioisotopes of two new elements (^{226}Ra, and ^{210}Po). In

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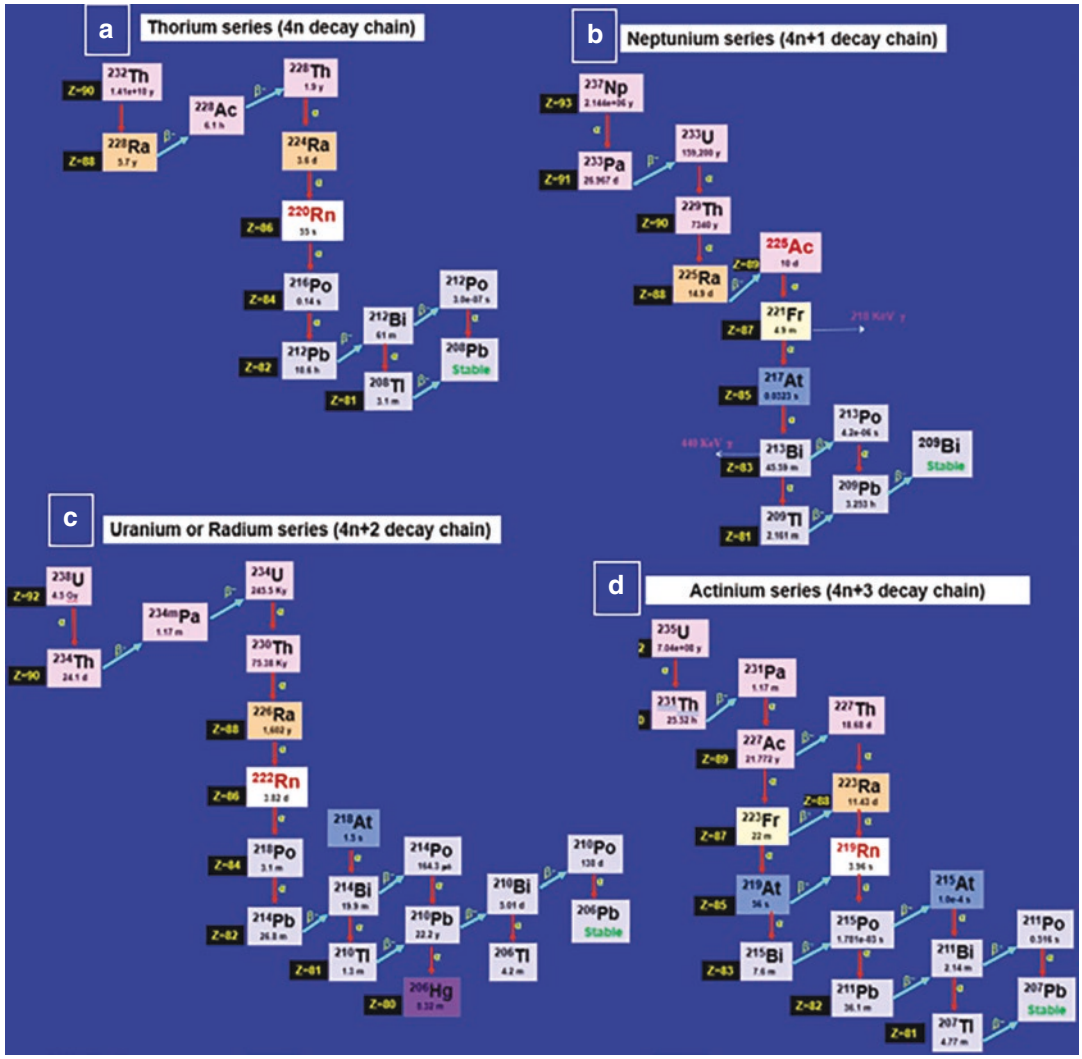

Fig. 8.1 The decay chains of primordial radionuclides ^{232}Th (**a**), ^{238}U (**c**), ^{235}U (**d**), and artificially produced ^{237}Np (**b**). All these four radionuclides ultimately become stable isotopes of lead

the actinium series (4n + 3), ^{227}Th, and ^{223}Ra are of medical interest. While the radionuclides observed in the decay chains are of medical interest, the commercial supply of the α emitting radionuclides for radionuclide therapy is primarily based on the artificial production of radionuclides.

8.2 Nuclear Transformation

The discovery of radioactivity in the late nineteenth century showed that some nuclei spontaneously transform into nuclei with a different number of protons, thereby producing a different element. When scientists realized that these naturally occurring radioactive isotopes decayed by emitting subatomic particles, they realized that—in principle—it should be possible to carry out the reverse reaction, converting a stable nucleus to another more massive nucleus by bombarding it with subatomic particles in a nuclear transmutation reaction. In the last 100 years, more than 3000 radionuclides have been artificially produced in reactors, particle accelerators, cyclotrons, and radionuclide generators.

When two nuclei come close together, a *nuclear reaction* can occur that results in a *nuclear transformation*, which is the conversion of one nuclide to another nuclide. Whereas *nuclear transmutation* is the conversion of one chemical element or an isotope into another chemical element. A transmutation can be achieved either by nuclear reactions (in which an outside particle reacts with a nucleus) or by radioactive decay, where no outside cause is needed. The term *transmutation* dates back to alchemy, when the alchemists in the Middle Ages pursued the philosopher's stone, which was believed to be capable of transforming the base metals (such as lead and bismuth) into gold.

As discussed earlier, radioactive decay by α or β process will result in natural transmutation of radioactive isotopes of one chemical element to a stable or radioactive isotope of another chemical element. The first nuclear transmutation was accomplished by Patrick Blackett and Rutherford following bombardment of natural nitrogen (^{14}N) atoms with α particles (He nuclei) from a radium–carbon source [1]. More specifically, they observed that a nitrogen nucleus was converted into an isotope of oxygen, ^{17}O with the emission of a proton. The process that Rutherford discovered was the disintegration of the stable nucleus and the formation of a stable oxygen isotope. In 1925, using the cloud chamber, Blackett confirmed Rutherford's observation.

$$^{14}_{7}\mathrm{N} + {}^{4}_{2}\mathrm{He} \rightarrow {}^{17}_{8}\mathrm{O} + {}^{1}_{1}\mathrm{H} \tag{8.1}$$

In 1932, when Chadwick bombarded a stable beryllium atom with α particles, the element beryllium was converted into a stable carbon isotope with the emission of a neutron [1].

$$^{9}_{4}\mathrm{Be} + {}^{4}_{2}\mathrm{He} \rightarrow {}^{12}_{6}\mathrm{C} + {}^{1}_{0}n \tag{8.2}$$

In the two nuclear reactions described above, the nuclear transformation involved conversion of a stable isotope of one element into a stable isotope of another element.

8.2.1 Artificial Production of Radioactivity

In 1934, Irene Curie and her husband Frederic Joliot were the first to produce an unstable radioisotope that decayed by positron emission and the first to discover the artificial production of radioisotopes [2].

$$^{27}_{13}\mathrm{Al} + {}^{4}_{2}\mathrm{He} \rightarrow {}^{30}_{15}\mathrm{P} \rightarrow {}^{1}_{0}n \tag{8.3}$$

$$^{30}_{15}\mathrm{P} \rightarrow {}^{30}_{14}\mathrm{Si} + \beta^{+} \tag{8.4}$$

As shown above, the stable Al atom absorbs the helium nucleus and is converted into an unstable ^{30}P radionuclide ($T_{½}$ = 3 min), which in turn is converted into a stable ^{30}Si atom following positron emission. Soon after the discovery of artificial radioactivity, physicists realized that charged protons with higher energies would be better projectiles for nuclear transformation reactions. During 1930s, charged-particle *accelerators* were developed to generate very high-energy subatomic particles, such as protons, deuterons, and α particles.

For almost two decades following Rutherford's pioneering work, α particles from natural radioisotopes such as ^{238}U and ^{234}Th were used as projectiles to induce nuclear reactions. Following the discovery of neutrons by Chadwick in 1932, Fermi realized that a neutron beam could be used as a projectile to induce a nuclear reaction, because neutrons are neutral and not repelled by the stable target nucleus. He also realized that neutron-rich atoms decay by beta emission and that the daughter nuclide with an extra proton is normally an element with an atomic number, $Z + 1$. In 1934, Fermi bombarded ^{238}U with neutrons and reported the discovery of element 93 (transuranic element not found in nature) [1]; however, this turned out to be a false claim. In 1937, a colleague of Fermi, Emilio Segre bombarded the stable ^{98}Mo with neutrons (a reaction known as *neutron activation*) and pro-

duced the element 43, which he called technetium (meaning artificial).

$$^{98}_{42}\mathrm{Mo} + {}^{1}_{0}n \rightarrow {}^{99}_{42}\mathrm{Mo} \xrightarrow{\beta^-} {}^{99m}_{43}\mathrm{Tc} \xrightarrow{IT} {}^{99}_{43}\mathrm{Tc} \quad (8.5)$$

8.2.2 Nuclear Fission

In Germany, Otto Han and Lise Meitner continued the experimental strategy to produce transuramics by bombarding uranium with neutrons. Hahn and Strassmann at the Kaiser Wilhelm institute for chemistry in Berlin bombarded uranium with slow neutrons and discovered that the element barium had been produced. They reported their findings by mail to Meitner in Sweden. Hahn and Strassmann, however, submitted their findings to *Naturwissenschaften* on December 22, 1938, without waiting for Meitner's reply. Meitner and her nephew Frisch theorized, and then proved, that the uranium nucleus had been split with the production of two new nuclides, free neutrons, and liberation of 200 MeV energy. By analogy with the division of biological cells, Frisch named the process "fission" (Fig. 8.2).

Hahn discovered that the nucleus of uranium undergoes fission (later identified as ^{235}U), when struck by a neutron [1]. More specifically, the ^{235}U nucleus absorbs the neutron to form a very highly unstable ^{236}U nucleus, which at once explodes to form two fission fragments (radionuclides) that are neutron rich and decay by beta emission. Meitner and Frisch had correctly interpreted Hahn's results to mean that the nucleus of uranium had split roughly in half. Subsequently in 1939, Niels Bohr had an insight that the fission with low-energy neutrons was due to the U-235 isotope, while at high energies it was mainly due to the far more abundant U-238 isotope.

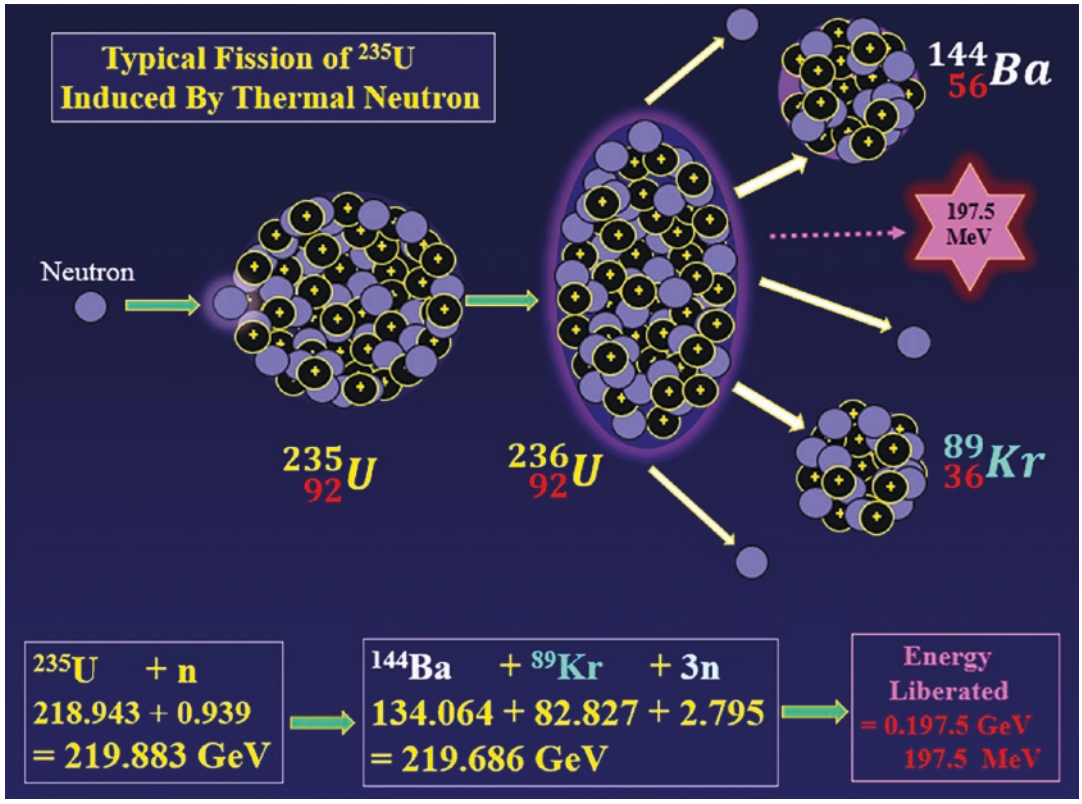

Fig. 8.2 Nuclear Fission of ^{235}U results in the formation of two low atomic number elements (^{144}Ba and ^{89}Kr) with the release of 3 neutrons and a very large amount of energy (MeV)

At the Radiation Laboratory in Berkely, California, physicists finally succeeded in the artificial production of transuramic elements, neptunium ($Z = 93$) and plutonium ($Z = 94$) by bombarding uranium with neutrons. In addition, with the availability of neutrons and high-energy charged particles, hundreds of nuclear reactions have been developed over the years to produce artificial radioisotopes that are either neutron rich or neutron deficient (proton rich). As discussed in the previous chapter, neutron-rich radionuclides decay by β^- or β^-, γ emission, while neutron-deficient radionuclides decay by β^+ or *EC*. Both these decay modes may also involve emission of gamma photons. In addition, positron annihilation will also lead to the emission of high-energy annihilation photons. Some of the early applications of radioisotopes in medicine involved naturally occurring radionuclides. It is the production of artificial radioisotopes, however, that eventually facilitated the development of nuclear medicine with molecular imaging technologies and targeted radionuclide therapies.

8.2.3 Nuclear Reactions

In a nuclear reaction, when the atoms of a stable element (target) are bombarded by a subatomic particle (called projectiles) such as neutron, proton, deuteron, or an α particle, the nucleus of the stable atom absorbs the subatomic particle. The resultant *compound nucleus* is very unstable and excited. The compound nuclei have lifetimes on the order of approximately 10^{-16} s. The compound nucleus may decay in one or more ways, depending on its neutron/proton ratio and excitation energy. It may quickly decompose by emitting some radiation (subatomic particle and/or gamma radiation) to form an unstable product radionuclide.

The general equation for a nuclear reaction can be written as follows:

$$T\left(P,R\right)Y \tag{8.6}$$

where T represents the target nuclide, P is the projectile, the incident or bombarding particle, R represents the radiation (subatomic particle or γ photons) emitted by the compound nucleus, and Y represents the unstable product radionuclide. The P and R in parenthesis, written as (P, R), represent the nuclear reaction. Reactions such as (p, n), (p, α), (d, α), (n, p), and (n, γ) are some of the common nuclear reactions used to produce artificial radioisotopes. In the case of neutron bombardment (e.g., in a reactor), there is no Coulomb repulsion from the positively charged nucleus, and neutrons easily penetrate the nucleus. In the production of radionuclides in a cyclotron, however, the accelerated charged particle must have an energy greater than the electrostatic repulsion between the positive charge of projectile and the positive charge of target nucleus.

8.2.3.1 Excitation Energy and *Q* Value

The total amount of *excitation energy* (U) of the compound nucleus is given by the following equation [3]:

$$U = \frac{M_T}{M_T + M_P} T_P + S_P \tag{8.7}$$

where, M_T = mass of the target nucleus; M_P = mass of the incident particle or the projectile; T_P = kinetic energy of the incident particle; S_P = binding energy of the incident particle in the compound nucleus.

In any nuclear reaction, the total kinetic energy of the products (radiation R and product nucleus Y) may be either greater or less than the total kinetic energy of the reactants (target T and projectile P). The Q *value* is the difference between the energy levels of the reactants and products. Q value can be calculated based on the relationship, $E = mc^2$ and by knowing the rest energies of all the particles involved.

$$Q = \left(M_T + M_P - M_R - M_Y\right)\left(c^2\right) \tag{8.8}$$

If Q is a positive quantity, energy is given off in a nuclear reaction (*exoergic*). If Q is a negative quantity (*endoergic*), kinetic energy (KE) must be supplied to the reacting particles so that the $\mathrm{KE} + Q \geq 0$.

8.2.3.2 Activation Cross Section

For any specific nuclear reaction, the probability that a bombarding particle will interact with, or activate the target nucleus employs the idea of *cross section* (σ), which is expressed as an effective area [4]. It is assumed that each target nucleus presents a certain area, called its cross section, to the incident particle. Therefore, the greater the cross section, the greater the likelihood of reaction. However, the activation cross section depends on the energy of the bombarding particle and the nature of the specific nuclear reaction. It is the effective "target area" presented by the target nucleus; the SI unit for nuclear cross section is m^2. The customary unit, however, is *barn*, where

$$1\text{barn} = 1\text{b} = 10^{-24}\,\text{cm}^2 \text{ or } 10^{-28}\,\text{m}^2 = 100\,\text{fm}^2 \quad (8.9)$$

$$1\text{millibarn}(\text{mb}) = 10^{-3}\,\text{b or } 10^{-27}\,\text{cm}^2 \text{ or } 10^{-31}\,\text{m}^2 \quad (8.10)$$

The cross sections for most nuclear reactions depend on the energy of the incident particle. The nuclear cross sections for thermal neutrons (0.025 eV) with no charge are higher than those for charged particles. The positively charged bombarding particle must have kinetic energy sufficient to overcome the coulomb barrier and the negative Q value (kinetic energy of the products is less than that of the reactants). The higher the atomic number (Z) of the target atom, the higher the kinetic energy (E) of the charged particle needed for a higher nuclear cross section [5]. For many low Z materials, it is possible to use a low-energy accelerator, but for high Z materials, it is necessary to increase the particle energy. A graphical relationship between σ and E for a specific nuclear reaction is known as *excitation function*. The excitation function for ^{18}F production is shown in Fig. 5.3 [6], as an example.

8.2.3.3 Activity

The amount of radioactivity (dps) produced by irradiation of a target material with a charged-particle beam can be described by the following equation [3]:

$$A(dps) = Inx\sigma\left(1 - e^{-\lambda t}\right) \quad (8.11)$$

In the above equation, I is the beam current or the number of bombarding particles per $\text{cm}^{-2}\ \text{s}^{-1}$; n is the number of target nuclei in cm^{-3}; x is the thickness of a target in cm; σ is the nuclear cross section, expressed in cm^2 per nucleus; λ is the decay constant of the product radionuclide; and t is the time of irradiation in seconds.

Saturation Yield

The amount of radioactivity (mCi) produced in a nuclear reaction is generally decay corrected to the end of bombardment (EOB). The saturation yield (mCi/μA) is the theoretical maximum rate of production of a radioisotope for given beam energy conditions and can be calculated using the following equation:

$$\text{Saturation yield}(\text{mCi}/\mu A) = \frac{A_0}{I\left(1 - e^{\lambda t}\right)} \quad (8.12)$$

where A_0 is the activity (mCi) at EOB, I is the beam current, and $1 - e^{-\lambda t}$ is the saturation factor for the radioisotope (Fig. 8.3).

Equation (8.11) is valid only for thin targets where the target beam is not attenuated. With thick targets (in which the energy of bombarding particle is completely absorbed), the particle beam is attenuated, and the target nuclei are bombarded with particles of varying energies. Yields with thick targets, therefore, depend on the energy and stopping power (or specific energy loss) in MeV $\text{cm}^2\ \text{g}^{-1}$ of the bombarding particle.

Specific Activity (SA)

SA is generally, defined as the amount of radioactivity per unit mass of an element, molecule, or compound, which implies that the mass represents the combined mass of radioactive species and the nonradioactive (stable or cold) counterpart. The unit of SA can be expressed as mCi/mg^{-1}, Ci/mmol^{-1}, or GBq μmol^{-1}. When dealing with chemical or molecular reactions, the stan-

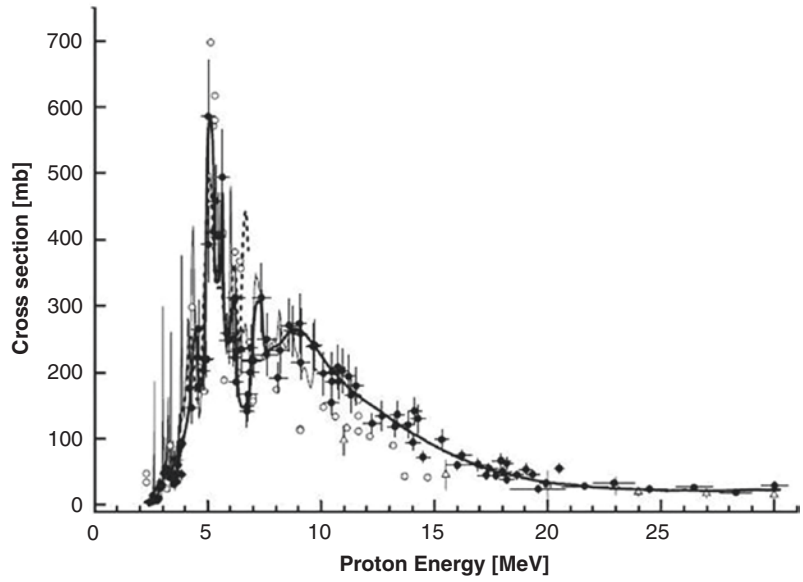

Fig. 8.3 Excitation function of the $^{18}O(p,n)^{18}F$ reaction. Results from several investigators were plotted with the *solid line* representing the data from the Julich group [6]

dard way to express SA is mCi μmol^{-1}. Because 1 mole represents 6.02×10^{23} atoms or molecules (Avogadro's number), one μmol consists of 6.02×10^{17} atoms or molecules.

For example, when ^{11}C radionuclide is produced in a cyclotron as $[^{11}C]CO_2$ gas, ^{11}C carbon atoms are always contaminated with natural carbon (^{12}C) and it is very difficult to obtain pure $[^{11}C]CO_2$ only. Therefore, if the SA of $[^{11}C]CO_2$ produced in a cyclotron target is 1.0 Ci μmol^{-1}, it implies that 1.0 Ci of radioactivity is present in a total mass of 1 μmole of carbon dioxide gas or a total of 6.02×10^{17} molecules (3.4×10^{14} molecules are present as $[^{11}C]CO_2$). That means, for every molecule of $[^{11}C]CO_2$ there are about 1700 molecules of cold, nonradioactive CO_2. The theoretical maximum SA (9220 Ci/μmole) is never really achieved in routine production of positron-emitting radionuclides. However, the SA concept is very important in dealing with PET radiopharmaceuticals, especially in the preparation of radiolabeled receptor-binding radiopharmaceuticals.

Carrier-Free

Carrier-free means that the radioactive species is not contaminated with nonradioactive counterpart, known as *carrier*. In the production of radionuclides in a cyclotron, the target element is converted into a different element (with a higher atomic number). As a result, cyclotron-produced radionuclides are supposed to be *carrier-free* (CF). Practically, however, it is very difficult to eliminate the contamination of natural carbon, fluorine, or trace metals during the synthesis procedure. A more appropriate concept is *no carrier added* (NCA) because the carrier, a stable, nonradioactive species, is not intentionally added. To facilitate chemical and biochemical reactions, a carrier may be added intentionally during radioisotope production. Such preparations should specifically be reported as *carrier added* (CA).

8.3 Production of Radionuclides by Accelerators

A particle accelerator is a machine that accelerates elementary particles, such as protons and electrons, to very high energies and to contain them in well-defined beams. A particle source provides the charged particles that are to be accelerated and then electric fields are used to speed up and increase the energy of a beam of particles. The beam of particles travels inside a vacuum in the metal beam pipe. The vacuum is crucial to maintaining an air and dust-free envi-

ronment for the beam of particles to travel unobstructed. Electro-magnets steer and focus the beam of particles while it travels through the vacuum tube.

There are two basic classes of accelerators: electrostatic and electrodynamic (or electromagnetic) accelerators. Electrostatic accelerators use static electric fields to accelerate particles. The most common types are the Cockcroft-Walton generator and Van de Graaff generator. *Electrodynamic* accelerators, on the other hand, use changing electromagnetic fields (nonresonant magnetic induction, or resonant circuits or cavities excited by oscillating radiofrequency (RF) fields) to accelerate particles. In addition, there are two basic types of particle accelerators: linear accelerators (LINAC) and circular accelerators (cyclotrons). Linear accelerators propel particles along a linear, or straight, beam line. Circular accelerators propel particles around a circular track.

In 1932, two physicists, John Douglas, and Ernest Thomas Walton, working at the Cavendish laboratory in Cambridge performed the first artificial nuclear disintegration in history using an electrostatic particle accelerator (Cockcroft–Walton generator) that generates a high DC voltage and accelerates a proton by passing it through a single DC potential difference between two electrodes. They won the Nobel Prize in 1951 for "Transmutation of atomic nuclei by artificially accelerated atomic particles." The disintegration of lithium into α particles by protons was achieved using a proton beam with <0.77 MeV of energy [1]. Following absorption of the proton, the element lithium atom was converted into beryllium nucleus, which quickly split into two helium nuclei [7].

$$^{7}_{3}\mathrm{Li} + {}^{1}_{1}\mathrm{H} \rightarrow {}^{8}_{4}\mathrm{Be} \rightarrow 2\,{}^{4}_{2}\mathrm{He} \qquad (8.13)$$

It soon became apparent that protons with higher energies were needed to penetrate the repulsive coulomb forces of the nucleus to produce nuclear transformations involving higher Z elements. More specifically, based on the principle of linear acceleration, very high voltage (millions of volts) is necessary to increase the kinetic energy of charged particles.

8.3.1 Linear Particle Accelerator (LINAC)

LINAC accelerates charged subatomic particles or ions to a high speed by subjecting them to a series of oscillating electric potentials along a linear beam line. They were originally invented in 1920s. The design of a LINAC, however, depends on the type of particle that is being accelerated: protons, electrons, or ions.

The radiofrequency (RF) LINAC produces repeated acceleration of ions through relatively small potential differences. Charged particle or ion is injected into an accelerating tube containing number of electrodes. A high-frequency alternating voltage from an oscillator is applied between groups of electrodes. An ion traveling down the tube will be accelerated in the gap between the electrodes if the voltage is in the proper phase. The distance between electrodes increases along the length of the tube so that the particle stays in phase with the voltage.

LINAC (Fig. 8.4) consists of a series of tubes connected to a high-voltage power supply, which can provide alternating polarities to the tubes. At first, the odd-numbered tubes in (1, 3, 5, …) are negatively charged and the even-numbered tubes are positively charged to attract the protons from the H^+ ion source. As the protons enter and pass through tube-1, the polarities of the tubes are reversed. As tube-1 is now positive and tube-2 is negative, protons are attracted to tube-2. This process continues through many tubes, until the velocity and energy of the protons increase.

8.3.1.1 Proton Accelerator

American Physicist Luis Alvarez developed the designs for proton LINAC in 1946. The two largest proton linear accelerators are the LANSCE linac at Los Alamos (800 MeV) and the Spallation Neutron Source Linac at ORNL

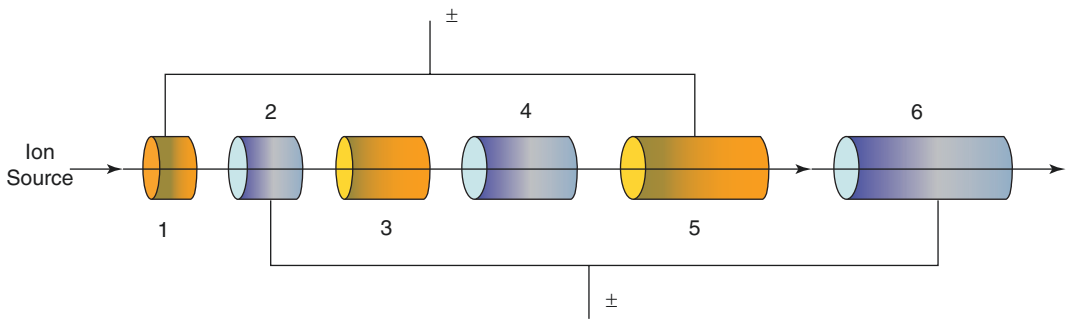

Fig. 8.4 A linear accelerator (LINAC) based on a voltage multiplying circuit designed to accelerate protons along a linear path to achieve higher energies

(1000 MeV). In the United States, the two accelerator installations with significant radionuclide production programs are the Brookhaven Linac Isotope Producer (BLIP) facility at Brookhaven National Laboratory and the Los Alamos National Laboratory Isotope Production facility (LANL-IPF) at the Los Alamos National Laboratory. The BLIP facility consists of a 30 m beam line and can generate 200 MeV protons with 170 μA beam current. The LANF-IPF facility produces radioisotopes at beam currents up to 275 μA using the 100 MeV proton beam generated at the front end of the Los Alamos Neutron Science Center (LANSCE) accelerator. The radioisotopes commonly produced at these two facilities include ^{68}Ge, ^{82}Sr, ^{225}Ac, and ^{67}Cu.

A compact proton-LINAC based radioisotope production, already commercially available, since 2005, is the PULSAR®7 system, by AccSys Technology Inc. It produces a 7 MeV proton beam with 9 mA current for [^{18}F]FDG production [8]. Such low energy has been chosen to reduce the footprint, weight, and cost of the accelerator, allowing, the installation of the accelerator in medical trailers, the only truly mobile PET lab available.

8.3.1.2 Electron Accelerator

The electron linear accelerator (e-LINAC) is an instrument for the acceleration of electrons to high energies by means of guided electromagnetic waves. It may serve as a source of both energetic electrons and X-rays. Although very high energies have been achieved with LINAC to serve the purposes of investigations in nuclear physics, moderate energies (3–30 MeV) are sufficient for external beam radiation therapy. E-LINACs in the 5–10-MeV range are used for irradiation sterilization of medical disposables such as syringes and surgical kits.

The LINAC uses microwave technology to accelerate electrons and then allows these electrons to collide with a heavy metal target (such as tungsten) to produce high-energy bremsstrahlung radiation (X-rays).

When a high-speed projectile electron comes close to the nucleus of the tungsten atom in the target, the positively charged nucleus causes the electron to decelerate and change direction. This deceleration results in a loss of kinetic energy, which is converted into X-rays. Bremsstrahlung X-rays have a spectrum of energies with an average energy proportional to the peak kilovolts used. However, the quantity of bremsstrahlung X-rays is related more to mAs (tube current) than peak kilovolts.

Even though the basic technology has been around for decades, only recently have e-LINACs capable of producing photons with sufficient energy and flux for radioisotope production become available [9, 10]. Photonuclear production of radionuclides using (γ, p) and (γ, n) nuclear reactions provide significant advantages compared to conventional cyclotron-produced methods. Housed in Argonne National Low

Energy Accelerator Facility (LEAF) at the Argonne National Laboratory is a newly upgraded 55 MeV/25-kW e-LINAC, capable of producing a wide range of radioisotopes (^{99}M0, ^{67}Cu, and ^{47}Sc).

8.3.2 Cyclotron

In 1929, Ernest O. Lawrence, an American physicist and inventor at the University of California, Berkeley, conceived the idea of a cyclic accelerator or *cyclotron*. In the presence of a static magnetic field, an ion of specific charge, when introduced at the center of a cyclotron, will accelerate in an expanding spiral path by use of an alternating radiofrequency electric field [11]. In 1939 Lawrence was awarded the Nobel Prize in Physics. The first cyclotron built by Lawrence had a diameter of a few inches and the glass vacuum chamber in which ions were supposed to circulate, could be held in one hand (Fig. 8.5). In 1939, Lawrence's 60-inch cyclotron, with 16 MeV protons was the most powerful accelerator in the world at the time. Glenn T. Seaborg and Edwin M. McMillan used it to discover plutonium, neptunium, and many other transuranic elements and isotopes, for which they received the 1951 Nobel Prize in chemistry.

8.3.2.1 Negative Ion Cyclotron

Traditionally, cyclotrons were designed to accelerate positive ions (H^+, $^2H^+$, and α^{2+}). The first cyclotron designed to accelerate negative ions of hydrogen, or deuterium atoms with two electrons in the *K*-shell (H^- and $^2H^-$) was built in 1966. Since the 1980s, all the medical and commercial cyclotrons are basically negative ion cyclotrons. One of the most important advantages of the negative ion cyclotron is the elimination of a complex *beam extraction system* needed to extract fixed energy positively charged particles. As a result, negative ion cyclotrons provide the opportunity to extract beams with different energies thereby allowing for the simultaneous bombardment of two different targets [12, 13].

The cyclotron (Fig. 8.6) consists of three major components: an electromagnet with a field strength

Fig. 8.5 The first working model of a 4.5 in. cyclotron, which accelerated protons to 80 KeV energy [11]

of 1.5–2.0 tesla, a pair of semicircular hollow copper electrodes, called *dees* located between the poles of the magnet, and an ion source (Penning ion gauge) capable of generating high-intensity negative ions. The entire structure of the cyclotron is kept under high vacuum (up to 10^{-7} torr). Following ionization of the hydrogen gas in an ion source, the ions (protons or deuterons) are injected into the center of the gap between the dees. When a 20–30 MHz radiofrequency alternating potential of 30–100 kV, generated with an oscillator, is applied to the dees, the negative ions will accelerate towards a dee that is at a positive potential. Because the magnetic field is perpendicular to the plane of the dees and particle motion, the negative ions will trace a circular path. Further, because the electrical potential on the dees is alternatively positive and negative, the ions will gain energy at each crossing of the gap between the dees, as they move outward in a spiral path from the center. Lawrence [11] described the basic operational equations as follows:

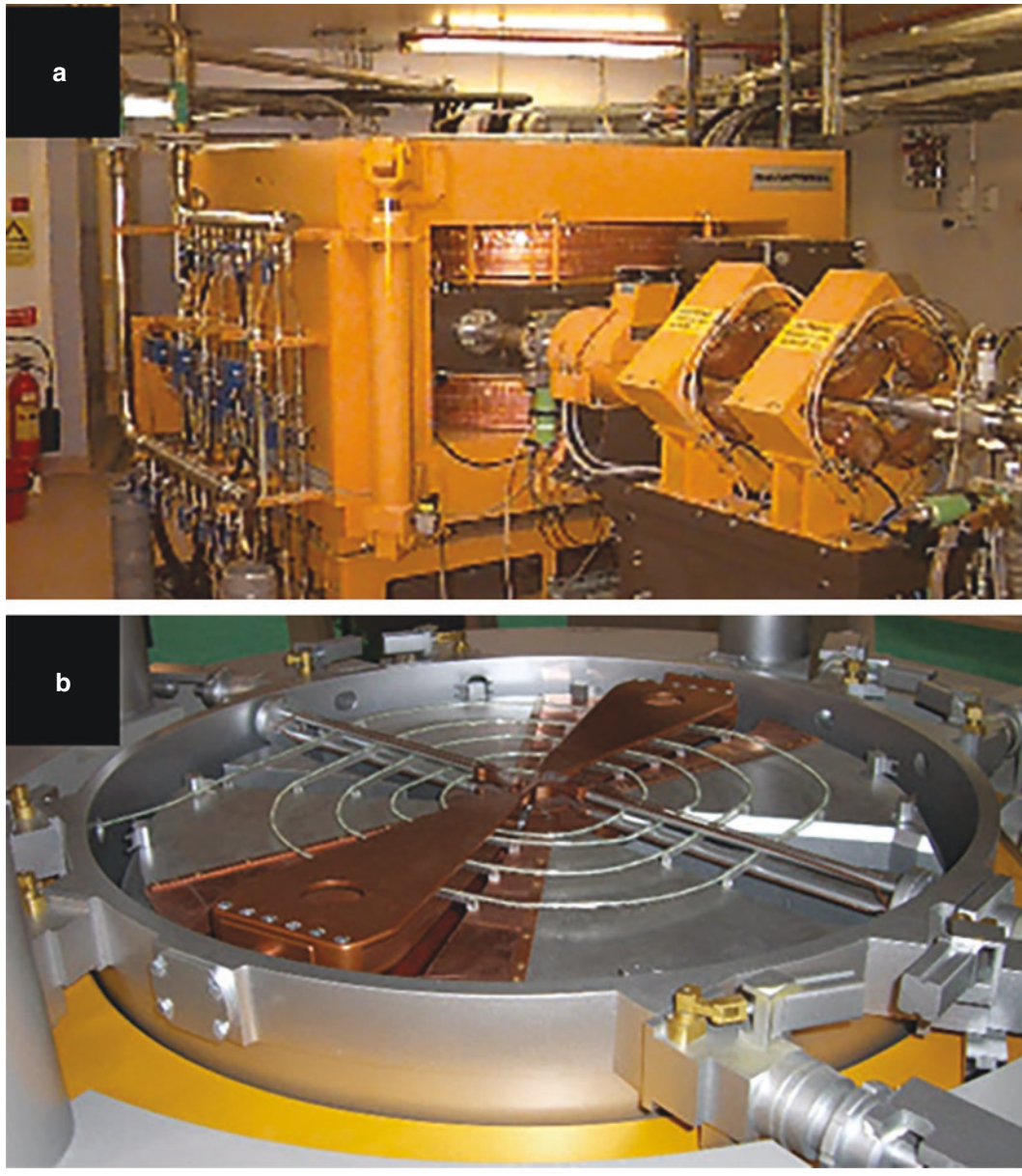

Fig. 8.6 A negative ion cyclotron (EBCO-TR19) with an external beam line (**a**). A model of the vacuum chamber (CTI systems) showing the copper electrodes (dees) in which a negatively charged proton beam making circular orbits (**b**)

Particle Energy

The magnetic force operating on the ion is a centripetal force (Bev), which is exactly balanced by the centrifugal effect (mv^2/r).

$$\text{Bev} = \frac{mv^2}{r} \text{ and } r = \frac{mv}{Be} \tag{8.14}$$

In the above equations, B is the magnetic field strength while m, e, and v represent the mass, charge, and velocity of the ion, respectively. Finally, r represents the radius of the ion's orbit. For a given cyclotron, the maximum kinetic energy that an ion can attain can be estimated if B and r are kept constant.

$$E = \frac{B^2 r^2}{2}\left(\frac{e^2}{m}\right) \tag{8.15}$$

The final energy of the particles is, therefore, dependent on the strength of the magnetic field and the diameter of the accelerating chamber, the dees. Cyclotrons can only accelerate particles to speeds much slower than the speed of light, non-relativistic speeds.

A *synchrocyclotron* is a cyclotron in which the frequency of the driving RF electric field is varied to compensate for relativistic effects as the particles' velocity begins to approach the speed of light. This is in contrast to the classical cyclotron, where the frequency was held constant. An alternative to the synchrocyclotron is the *isochronous cyclotron*, which has a magnetic field that increases with radius, rather than with time. Isochronous cyclotrons (also known as Azimuthally-Varying-Field or AVF Cyclotron) are capable of producing much greater beam current than synchrocyclotrons.

Beam Extraction

Once the desired kinetic energy of the accelerating particles is achieved, the positively charges ions (H^+ and $2H^+$) are extracted from the cyclotron by passing the negative ion beam through an ultra-thin foil of carbon (graphite), which strips the electrons. The positively charged beam will rotate in an opposite direction, which can then be directed to bombard an appropriate target to produce a positron-emitting radioisotope. The typical intensities (beam currents) and the energies of proton and deuteron beams generated in commercial cyclotrons are shown in Table 8.1. The beam current is generally expressed in units of microampere (μA). For example, a 1 μA proton beam current is equal to 6.25×10^{12} protons or deuterons/s.

Types of Cyclotrons

Almost all current available commercial cyclotrons are negative ion machines. Close to 1500 cyclotrons are used in nuclear medicine worldwide, for the production of radionuclides. A wide range of cyclotrons for isotope production have been developed by companies and research centers and may be categorized into 3 types of cyclotrons: (a) Low-energy cyclotrons for PET radioisotope production (<15 MeV, 10–150 μA current). These small-sized medical cyclotrons (SMC) are also referred to as PET cyclotrons. (b) Medium-energy cyclotrons (15–30 MeV, 100–1000 μA) for novel PET nuclides, and SPECT radionuclides. (c) Higher energy cyclotrons (>35 MeV, 500–1000 μA) for the production of therapeutic nuclides and also the parent nuclides for the radionuclide generators. The technical features of several medical cyclotrons are summarized in Table 8.1.

8.3.3 PET Radionuclides

The greatest advantage of PET is the potential to image and study biochemical processes in vivo, without altering or affecting the homeostasis in any way. Low atomic number elements such as carbon, nitrogen, oxygen, and phosphorous are naturally stable. The development of cyclotrons in the 1930s created an opportunity to produce positron-emitting radioisotopes of carbon (^{11}C), nitrogen (^{13}N), and oxygen (^{15}O) and fluorine (^{18}F). Since the 1950s, these four PET radionuclides played a significant role in the development of biochemistry and pharmacology.

The most important nuclear reactions used in the production of positron-emitting radionuclides for imaging and therapy are summarized in Tables 5.2, 5.3, and 5.4. Many reviews have been

Table 8.1 Medical cyclotrons for the production of positron-emitting radionuclides

Company	Cyclotron Model	Particle beam			Number of targets
		Type	Energy MeV	Current μA	
GE	GENtrace™	H^-	7.8		3
GE	MINItrace™ Quilin	H^-	9.6	>50	5
GE	PETtrace™ 800 series	H^-/D^-	16.5 /8.6	60–160	6
Siemens/CTI[a]	Eclipse HP/RDS-111	H^-	11	>120	4 or 8
Siemens	Eclipse RD	H^-	11	>80	2 × 8[b]
IBA	Cyclone 3	D^+	3.6	50	2
IBA	Cyclone 10/5	H^-/D^-	10/5	60/35	8
IBA	Cyclone 11	$H^-/$	11	120	8
IBA	Cyclone 18/9 Cyclone® KIUBE	H^-/D^- H^-	18/9 13–18	80/35 100–300	8 8
IBA	Cyclone-30	H^-/D^-	30/15	400–1200	8
IBA	Cyclone-70	H^-/α^{2-}	70/?	<1500	8
ACSI	TR-14	H^-	14	>100	2 × 4[c]
ACSI	TR-19	H^-/D^-	19/8	300/100	2 × 4[c]
ACSI	TR-24	H^-	24	300	2 × 4[c]
ACSI	TR-30	H^-/D^-	30/15	1500/400	2 × 4[c]
ABT MII	BG-75	H^+	7.5	5	3*
Alcen-PMB	iMiTrace superconducting	H^-	12	50	4
Ionetix	Ion-12sc s-c	H-	12	10	
CIEMAT/Cern	AMIT s-c	H^-	12.5	>25	
PMB-ALCEN	LOTUS s-c	H^-	12	50	4
BEST CSI	Best 15P	H^-	15	400	4
BEST CSI	Best 25P	H^-	15–25	400	4
BEST CSI	Best 35P	H^-	15–35	<1000	4–6
Best CSI	Best 70P	H^-	35–70	<1000	6
Sumitomo	HM12	H^-/D^-	12/6	>120	8
Sumitomo	HM18	H^-/D^-	18/10	>180	8
CIAE	CYCIAE-14	H^-	14	400	8
CIAE	CYCIAE-70	H^-/D^-	70/33	700	8

[a]Self shielding for cyclotrons is standard
[b]Two beam ports, each with an eight-target carousel
[c]Two beam ports, each with a four-target carousel

published on the cyclotron production of positron-emitting radionuclides. The International Atomic Energy Agency (IAEA) published a technical report [14] in 2009 on the physical characteristics and production methods of cyclotron-produced radionuclides.

The target designed for the production of a positron-emitter consists of a target body suitable for the bombardment of a specific target material (gas, liquid, or solid) that undergoes nuclear transformation. Typical gas targets are made up of aluminum, while the liquid targets are made up of aluminum, silver, titanium, and niobium. A generic cyclotron target (Fig. 8.7) consists of a sealed metal tube with a window of thin metal foil at one end to allow the particle beam to pass through and irradiate the target material. In order to dissipate the excess heat generated during irradiation, the target body is generally surrounded by a cooling water jacket, while helium gas is circulated through the foils separating the target material and the vacuum isolation foil through which the beam enters the target (Table 8.2).

8.3.3.1 Oxygen-15

^{15}O decays ($T_{½}$ = 2.04 months) to nitrogen-15, emitting a positron. ^{15}O was one of the first artificial radioisotopes produced by low-energy deu-

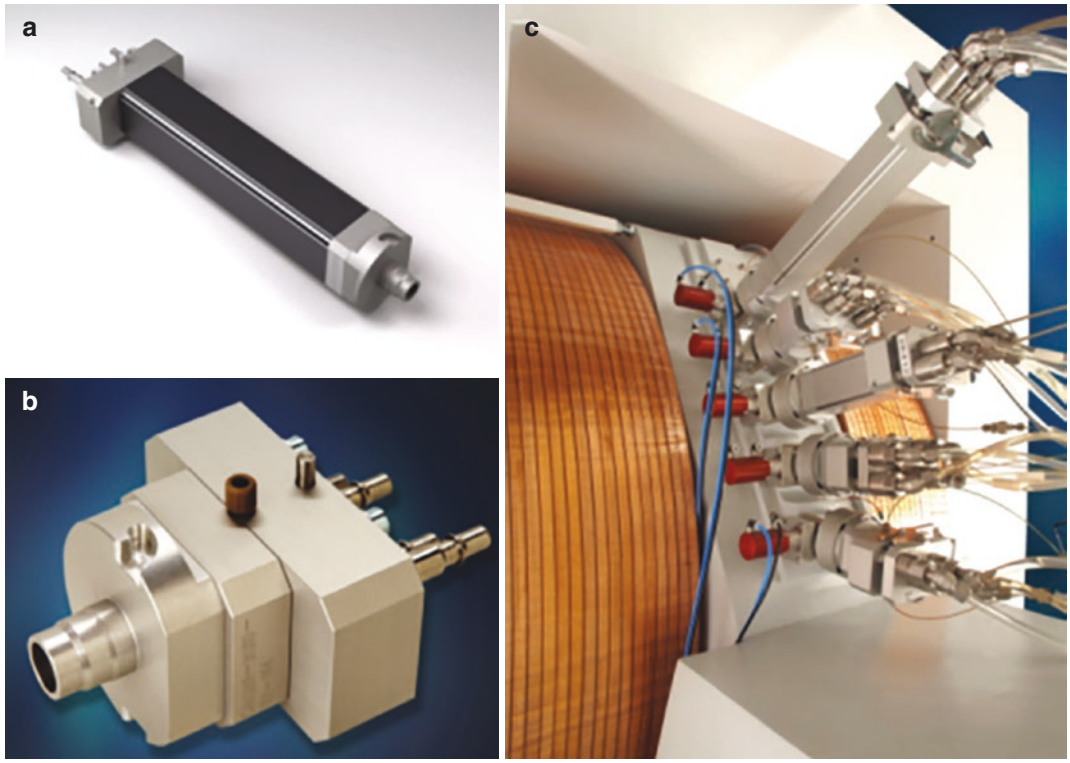

Fig. 8.7 ^{14}N gas target chamber (**a**) for the production of ^{11}C as carbon dioxide and an ^{18}O water target chamber (**b**) for the production of ^{18}F as fluoride. Placement of these targets in the PETtrace (GE) cyclotron (**c**)

terons using a cyclotron [15]. ^{15}O can be produced by different nuclear reactions, including $^{14}N(d,n)^{15}O$, $^{16}O(p,pn)^{15}O$, and $^{15}N(p,n)^{15}O$. For the $^{15}N(p,n)^{15}O$ reaction, low-energy protons (<11 MeV) MeV) or the medium-energy protons (>16.6 MeV) can be used. To use low-energy protons, however, the target must be highly enriched ^{15}N gas [5, 16]. The most common nuclear reaction and most economic method used for the production of ^{15}O is deuteron bombardment of ^{14}N atoms using natural nitrogen containing 0.2–0.5% oxygen as the target gas and the target body is generally made of aluminum. The oxygen-15 ion combines with an oxygen atom to form the stable oxygen gas $[^{15}O]O_2$. To produce ^{15}O as $[^{15}O]CO_2$ gas, the target nitrogen gas is mixed with 2–2.5% carbon dioxide.

To produce $[^{15}O]$water outside the target, a stream of nitrogen gas continuously flows through the target to a hot cell containing a water synthesis module, in which ^{15}O combines with H_2 gas in the presence of palladium–aluminum catalyst at high temperatures (300–400 °C) to produce water vapor, which then bubbles into a saline solution and is drawn into a syringe where it can be applied to the subject. $[^{15}O]$water is used for measuring and quantifying blood flow using PET in the heart, brain, and tumors.

8.3.3.2 Nitrogen-13 and [^{13}N]Ammonia

The first production of ^{13}N was based on bombarding boron atoms with α particles [2]. The most common nuclear reaction for the production of ^{13}N is $^{16}O(p, \alpha)^{13}N$. The natural stable oxygen atoms are bombarded with proton (10–15 MeV) using oxygen gas target or liquid (water) target [5, 17, 18]. When ^{13}N is produced in the target, it reacts with water forming nitrate and nitrite ions. The addition of a reducing agent, such as titanium chloride, to the target water will generate $[^{13}N]NH_3$. With a pressurized target, aqueous ethanol can be used in the

Table 8.2 Cyclotron-produced radionuclides for PET

Radionuclide	$T_{½}$	Decay Mode	Decay %	Energy β^+_{max} (MeV)	Energy γ (MeV)	Production Method Nuclear reaction	Target Material
^{15}O	2.0 min	β^+ EC	99.9 0.1	1.732		$^{14}N(d, n)^{15}O$	N_2 gas
^{13}N	10.0 min	β^+ EC	99.8 0.2	1.199		$^{16}O(p, \alpha)^{13}N$	H_2O
^{11}C	20.4 min	β^+ EC	99.8 0.2	0.960		$^{14}N(p, \alpha)^{11}C$	N_2 + <1% O_2
^{18}F	110 min	β^+ EC	96.9 3.1	0.634		$^{18}O(p, n)^{18}F$ $^{20}Ne(d, \alpha)^{18}F$	$[^{18}O]H_2O$ Ne + 0.2% F_2
^{68}Ga	67.8 min	β^+ EC	88.9 11.1	1.899	1.077 (3%)	$^{68}Zn(p, n)^{68}Ga$	Solid/liquid
^{44}Sc	3.97 h	β^+ EC	94 6	1.474	1.157 (100%)	$^{44}Ca(p, n)^{44}Sc$ $^{45}Sc(p,2n)^{44}Ti \rightarrow ^{44}Sc$	Solid/liquid
^{64}Cu	12.7 h	β^+ β^- EC	17.86 39.00 43.08	0.653	1.346 (0.48%)	$^{64}Ni(p, n)^{64}Cu$	Solid/liquid
^{66}Ga	9.5 h	β^+ EC	56.5 43.5	4.153	1.037 (37%)	$^{66}Zn(p, n)^{66}Ga$	Solid
^{86}Y	14.7 h	β^+ EC	31.9 68.1	1.221	1.077	$^{86}Sr(p, n)^{86}Y$	Solid
^{89}Zr	3.267 days	β^+ EC	22.7 76.2	0.902	0.909 (99%)	$^{89}Y(p, n)^{89}Zr$	Solid/liquid
^{124}I	4.176 days	β^+ EC	22.7 77.3	2.138	0.602 (63%)	$^{124}Te(p, n)^{124}I$ $^{124}Te(d, 2n)^{124}I$	Solid

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target since ethanol acts as a hydroxyl free radical scavenger to improve the production of $[^{11}N]NH_3$.

Because the half-life of ^{13}N is very short (9.97 min), it is very difficult to synthesize ^{13}N-labeled radiotracers for routine clinical PET studies. In the 1970s, $[^{13}N]$ ammonia (NH_3 or NH_4^+ ion) has been shown to be clinically useful as a myocardial perfusion imaging agent. The production of ^{13}N involves the generation of $[^{13}N]NH_3$ gas directly in the target itself.

8.3.3.3 Carbon-11

^{11}C decays 100% by positron decay with a maximum b+ energy of 968 keV. The most common nuclear reaction used to produce ^{11}C is $^{14}N(p, \alpha)^{11}C$. Natural nitrogen gas is bombarded with protons [5, 19, 20]. Because nitrogen gas is relatively inert, it does not interfere with the carbon chemistry and can be easily eliminated. By mixing trace amounts (<1%) of oxygen or hydrogen with the target nitrogen gas, the chemical forms of ^{11}C produced in the target can be either $[^{11}C]CO_2$ or $[^{11}C]CH_4$ (methane). The gas target body is basically made up of an aluminum cylinder (or cone shape) that should be able to handle gas (10–100 cc) at pressures of 300–800 psi. Beam currents of 20–40 μA are typically used. It is very important to prepare or polish the inside of the aluminum target to significantly reduce the contamination of natural carbon. As the natural nitrogen gas is also contaminated with CO_2 gas, it is essential to use extremely high purity (99.99999%) target gases.

Specific activity of ^{11}C is very important to prepare receptor specific C-11 radiotracers. $[^{11}C]CO_2$ can be produced in most cyclotron targets with a SA of 5–20 Ci/μmol at EOB. Even higher SA can be achieved by producing $[^{11}C]CH_4$ directly in the target. The theoretical SA is 9600 Ci/μmol. If possible, all sources of carrier carbon need to be assessed and eliminated.

8.3.3.4 Fluorine-18

Among halogens, ^{18}F ($T_{½}$ = 109.8 months) is the most important radionuclide for PET. Because the atomic radius of fluorine is similar to that of hydrogen, in most molecules, fluorine can be used as pseudo-hydrogen.

There are several nuclear reactions are available to produce F-18. Since fluorine can be introduced into molecules using its nucleophilic and electronegative property, the two common nuclear reactions are $^{18}O(p, n)^{18}F$ and $20Ne(d, \alpha)^{18}F$. Basically, there are two kinds of targets used in a cyclotron to produce two different chemical forms of F-18 radionuclide. A liquid target for the production of ^{18}F as nucleophilic fluoride ion ($^{18}F^-$) and a gas target for the production of ^{18}F as electrophilic fluorine as $[^{18}F]F_2$ gas [21, 22].

The most common nuclear reaction used to produce ^{18}F as fluoride ion is on the basis of proton bombardment of ^{18}O atoms using highly enriched [^{18}O] water as the target material [5, 22]. The coproduction of ^{13}N via the $^{16}O(p, \alpha)^{13}N$ reaction should be taken into account when using ^{18}O of lower enrichment (<90%). A typical target body is made of titanium and niobium to hold 0.3–3.0 mL of target water. Several curies of ^{18}F can easily be made in 1–2 h using 10–19 MeV protons with 20–35 μA beam current. While the theoretical SA of ^{18}F is 1700 Ci/μmol^{-1}, the NCA ^{18}F is generally produced with a SA of <10 Ci/μmol^{-1}.

The most common nuclear reaction to produce [^{18}F] fluorine gas is on the basis of deuteron bombardment of ^{20}Ne atoms using natural neon gas [5]. A passivated nickel target (NiF) is loaded with neon gas containing 0.1% of natural fluorine gas. Following bombardment for 1–2 h with 8–9 MeV deuterons, <1.0 Ci of $[^{18}F]F_2$ is generated with a very low SA of (10–20 mCi/μmol^{-1}). A "double shoot" method was developed to produce [^{18}F]fluorine gas on the basis of proton bombardment of ^{18}O atoms using [^{18}O]oxygen gas loaded into a gas target [23]. After irradiation, ^{18}F species stick to the walls of the target. The ^{18}O target gas is removed from the target, which is then loaded with argon gas mixed with 1% of cold fluorine gas. A second short irradiation for <10 min will generate $[^{18}F]F_2$ gas. This method is very useful to make electrophilic ^{18}F, using cyclotrons generating proton beams only. Since $[^{18}F]F_2$ is always diluted with carrier (cold) fluorine gas, the SA of electrophilic [^{18}F] fluorine is very low and not optimal for synthesizing high SA ^{18}F labeled radiopharmaceuticals.

8.3.3.5 Bromine-75 and Br-76

Both these radionuclides are generally made by proton (17 MeV) bombardment of ^{76}Se atoms using enriched ^{76}Se (96%) Cu_2Se as the target material [5]. Subsequently, ^{76}Br is separated from the solid target by thermal diffusion. The longer half-life (16.2 h) of ^{76}Br is favorable for the synthesis of radiopharmaceuticals and commercialization. However, ^{76}Br has a complex decay scheme and high-energy positrons which may provide an unfavorable radiation dose to the patient.

^{75}Br with a shorter half-life (97 min) may be more optimal for developing PET radiopharmaceuticals. One of the common nuclear reactions is $^{76}Se(p,2n)^{75}Br$, but the energy of proton needed for this reaction is between 18–28 MeV. ^{75}Br is separated from a solid target by dry distillation method and trapped using platinum wool.

These two bromine radioisotopes generally are not used in the development of PET radiopharmaceuticals for imaging studies.

8.3.3.6 Iodine-124

^{124}I ($T_{½}$ = 4.2 days) has often been considered as an impurity in the preparations of ^{123}I. The half-life of ^{123}I is long enough to image the distribution of monoclonal antibodies using PET. However, it also has many gamma emissions (such as 0.602 and 1.691 MeV) and some low-energy beta emissions contributing to the dosimetry.

The best nuclear reaction for the production of ^{124}I is the $^{124}Te(p, n)^{124}I$ reaction on enriched ^{124}Te target [24, 25]. The solid target material consists of a solid solution matrix containing aluminum oxide and enriched ^{124}Te oxide. The separation of iodine from tellurium can be accomplished by distillation of ^{124}I from the tellurium oxide matrix at 750 °C. The iodine is carried away from the target with a sweep of either oxygen or helium

and trapped on a thin pyrex glass tube that is coated with a small amount of sodium hydroxide.

Since the radioiodination of proteins and peptides is relatively easy, ^{124}I has significant potential for the development of radiopharmaceuticals for PET. However, the longer half-life and complicated decay schemes with high-energy positrons may make this radionuclide suboptimal for diagnostic studies, as the radiation dose to the patient can be relatively high.

8.3.3.7 Gallium-66 and Gallium-68

^{66}Ga ($T_{½}$ = 9.4 h) and ^{68}Ga ($T_{½}$ = 67.71 months) are the two gallium PET radionuclides of interest. The short half-life ^{68}Ga emits positrons (β^+, 89%; E_{max} = 1.899 MeV) and has the favorable positron energy for PET imaging studies. While ^{66}Ga has relatively longer half-life, but very high-energy positrons (β^+, 54.7%; E_{max} = 4.1 MeV) and several high-energy gamma photons (0.291–4.806 MeV), it is not ideal for imaging studies.

^{66}Ga can be produced using proton bombardment based on any of these nuclear reactions; ^{66}Zn(p,n)^{66}Ga, ^{67}Zn(p,2n)^{66}Ga, and ^{66}Zn(p,3n)^{66}Ga. Among these ^{66}Zn(p,n)^{66}Ga reaction is the most common method using 7–15 MeV protons (at high beam currents) and enriched ^{66}Zn metal target, electrodeposited on a copper backing plate [5]. Subsequently, ^{66}Ga can be easily separated from zinc by cation-exchange or solvent extraction techniques.

^{68}Ga production method is based on ^{68}Zn(p,n)^{68}Ga nuclear reaction. It is generally necessary to bombard isotopically enriched ^{68}Zn(>98%) since several radioisotopes of gallium with longer half-lives than ^{68}Ga are also coproduced when irradiating natural Zn. However, despite use of isotopically enriched ^{68}Zn, small amounts of ^{66}Ga and ^{67}Ga will occur via ^{68}Zn(p,3n)^{66}Ga and ^{68}Zn(p,2n)^{67}Ga reactions. As shown in Fig. 8.8, the composition of the isotopically enriched ^{68}Zn and the proton energy (~11 MeV) must be selected wisely to balance yield and achieve a purity suitable for human use [26]. For solid targets, ^{68}Ga may be a) electroplated on copper or silver supports, b) used as metal foils, on aluminum support. The irradiation of a ^{68}Zn solution (as zinc nitrate, 1–2 M) in a liquid target (a solution target) also provides a practical and inexpensive alternative to produce clinical quantities of ^{68}Ga.

Purification of ^{68}Ga from the zinc target is generally performed based on solid phase using either cation-exchange resin or hydroxamate resin. For additional purification, anion-exchange resins AG-1X8, TK200 (Trioctylphosphine oxide), UTEVA® (diamyl, amylphosphonate), DGA (tetra-n-octyldiglycolamide) can be used. Finally, ^{68}Ga is supplied as high specific activity, no-carrier-added gallium chloride solution in <0.1 M hydrochloric acid.

8.3.3.8 Copper-64

Copper has several positron-emitting radioisotopes, such as ^{61}Cu, ^{62}Cu, and ^{64}Cu. Because of its longer half-life of 12.7 h and low-energy positrons, ^{64}Cu is more appropriate for developing commercial PET radiopharmaceuticals. It can be produced via the ^{64}Ni(p,n)^{64}Cu nuclear reaction using enriched nickel solid target foils [5]. Subsequently, ^{64}Cu is separated by dissolving the target in an acidic solution, followed by ion-exchange chromatography. Using similar techniques, ^{61}Cu can also be produced via the ^{61}Ni(p,n)^{61}Cu nuclear reaction, using enriched nickel solid target foils.

8.3.3.9 Yttrium-86

^{86}Y ($T_{½}$ = 14.7 h) is a medium half-life radionuclide emitting very high-energy (3.15 MeV) positrons not ideal for high-resolution quantitative PET studies. In addition, it has several high-energy γ emissions. As a trivalent metal, it binds strongly to DOTA-conjugated peptides and antibodies.

It can be produced via the ^{86}Sr(p,n)^{86}Y nuclear reaction using isotopically enriched ^{86}Sr foil or strontium carbonate pellet. The proton reaction can be carried out at relatively low energies (10–15 MeV). Subsequently, ^{86}Y can be separated by dissolving the target in an acidic solution, followed by precipitation and purification by ion-exchange chromatography. The specific activity of the final purified ^{86}Y chloride preparations is 15–30 mCi/mg.

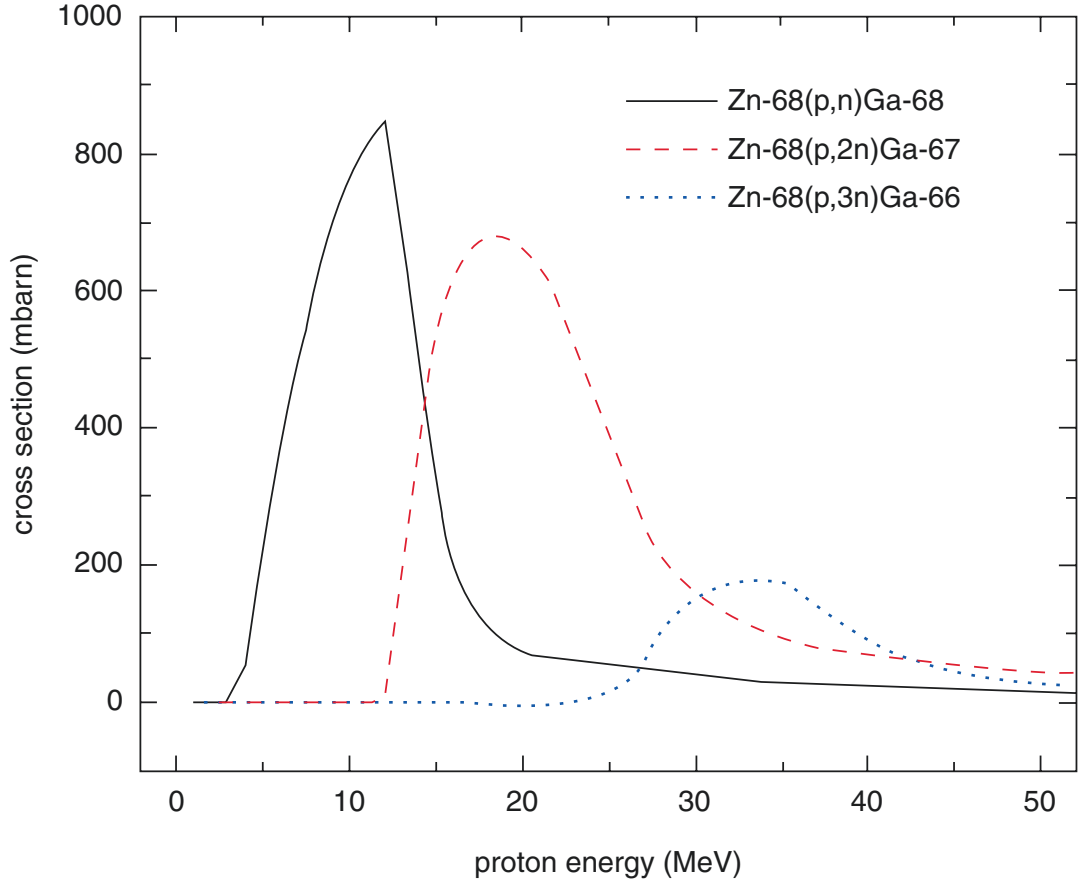

Fig. 8.8 Excitation function for the ^{68}Zn(p,n)^{68}Ga, ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga reactions. Data from (From [26])

8.3.3.10 Zirconium-89

Zr-89 ($T_{½}$ = 3.3 days) is a transition metal and has ideal physical characteristics for immuno-PET imaging studies. The most commonly used nuclear reaction is the ^{89}Y(p,n)^{89}Zr reaction, because a higher yield of ^{89}Zr can be produced from ^{89}Y, which is 100% naturally abundant in the earth's crust [27]. Typically, a proton beam (14–15 MeV) is used to bombard an yttrium foil solid target for 2–3 h with a 65–80 μA beam current. No other radionuclides are produced as impurities. ^{89}Zr can also be produced using ^{89}Y(d,2n)^{89}Zr reaction using 15–20 MeV deuteron energy. In this reaction, an yttrium pellet is used and irradiated with a 16-MeV deuteron beam. ^{89}Zr can be easily purified and separated from the target by ion-exchange chromatography (using hydroxamate resin column) and supplied as ^{89}Zr oxalate.

8.3.3.11 Scandium-44

^{44}Sc is a transition metal with similar chemical properties as gallium. ^{44}Sc with a half-life of 3.97 h is an attractive alternative to ^{68}Ga with only 68 min half-life. It can be produced via the ^{44}Ca(p, n)^{44}Sc nuclear reaction with a proton beam (11–18 MeV at 30-50 μA beam current) using an enriched ^{44}Ca target as $CaCO_3$ or CaO [28, 29]. ^{44}Sc can be easily separated from the target material using DGA extraction resin and concentrated using SCX cation-exchange resin.

8.3.4 SPECT Radionuclides

8.3.4.1 Gallium-67

^{67}Ga ($T_{½}$ = 3.26 days) decays to stable zinc by electron capture with several γ photons of 93.3 keV (37.0%), 184.6 keV (20.4%), and 300.2 keV (16.6%). As a trivalent metal gallium behaves in the body in a similar way to ferric iron. It is a diagnostic imaging agent in the detection and localization of certain neoplasms and inflammatory lesions.

^{67}Ga can be produced by several nuclear reactions using high-energy protons (20–25 MeV). The most common reactions are ^{68}Zn(p,2n)^{67}Ga and ^{66}Zn(d,n)^{67}Ga. The enriched ^{68}Zn may be pressed or electroplated onto a copper plate. Following irradiation, the zinc target is dissolved in concentrated hydrochloric acid (7 N) and ^{67}Ga is extracted into an organic phase using isopropyl ether. Following evaporation of the organic phase, ^{67}Ga is formulated as chloride using dilute HCl (0.1 N). The typical SA of ^{67}Ga is around 1000 mCi/mg (67 mCi/μmol) and radionuclidic purity is about 99.4%. The ion-exchange method involves dissolving the zinc target in concentrated HCL and separating the ^{68}Ga using Dowex 50 W-X8 resin (Table 8.3).

8.3.4.2 Indium-111

^{111}In ($T_{½}$ = 2.83 days) decays to stable cadmium by electron capture with two γ photons of 171.3 keV (90.2%), and 245.4 keV (94%). ^{111}In is a very important radionuclide for imaging studies in nuclear medicine and several radiopharmaceuticals were developed in the last 4 decades.

^{111}In can be produced by proton bombardment of natural ^{111}Cd or enriched ^{112}Cd using either ^{111}Cd(p,n)^{111}In reaction or ^{112}Cd(p, 2n)^{111}In reaction. Following irradiation, the cadmium target is dissolved in mineral acid and the acidity is kept at 1 N using HCl.

^{111}In is separated from the target using anion-exchange resin and HCl (1 N). The high SA, no-carrier-added ^{111}In has a radionuclidic purity of ≥99.9%.

8.3.4.3 Thallium-201

^{201}Tl ($T_{½}$ = 73.06 h) decays to stable mercury atom by electron capture with several γ photons of low abundance; 135 keV (2.65%), and 167 keV (10%). The low-energy X-rays (70–80 KeV) from the mercury atom are used for SPECT studies to assess myocardial blood flow.

The most common nuclear reaction used to produce ^{201}Tl is the ^{203}Tl(p, 3n)^{201}Pb→^{201}Tl reaction using high-energy protons (25–35 MeV) on enriched ^{203}Tl target. After irradiation, ^{201}Pb is separated from the target ^{203}Tl. Subsequently, ^{201}Pb is allowed to decay for several days to generate the daughter ^{201}Tl, which then is separated and purified from lead.

8.3.4.4 Iodine-123

^{123}I can be produced directly in a cyclotron using ^{124}Te(p,2n) reaction. The most common methods,

Table 8.3 Cyclotron-produced Radionuclides for SPECT

Radio nuclide	$T_{½}$	Decay		Energy		Production method	Target
		Mode	%	γ (KeV)	%	Nuclear reaction	
^{123}I	13.22 h	EC	100	159	83.6	^{123}Te(d, 2n)^{123}I ^{124}Xe(p,2n)^{123}Cs→ ^{123}Xe→$_{β-}$ ^{123}I	Solid/Gas
^{67}Ga	3.262 days	EC	100	93 185 300	38.6 28.4 16.6	^{68}Zn (p,2n) ^{67}Ga ^{66}Zn (d,n) ^{67}Ga	Solid
^{111}In	2.805 days	EC	86	171 245	90.7 94.1	^{112}Cd (p, 2n) ^{111}In ^{111}Cd (p, n) ^{111}In	Solid
^{201}Tl	3.042 days	EC	100	69–82 (X-ray) 167	75 10	^{203}Tl(p, 3n)^{201}Pb→$_{β-}$ ^{201}Tl	Solid

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however, use indirect methods based on the following nuclear reactions:

$$^{127}\mathrm{I}\left(p,5n\right)^{123}\mathrm{Xe}\rightarrow{}^{123}\mathrm{I} \quad (8.16)$$

$$^{124}\mathrm{Xe}\left(p,2n\right)^{123}\mathrm{Cs}\rightarrow{}^{123}\mathrm{Xe}\rightarrow{}^{123}\mathrm{I} \quad (8.17)$$

$$^{124}\mathrm{Xe}\left(p,pn\right)^{123}\mathrm{Xe}\rightarrow{}^{123}\mathrm{I} \quad (8.18)$$

The high SA, NCA ^{123}I is supplied as sodium iodide in a 0.1 N NaOH solution with a radionuclidic purity >99.8%.

8.3.5 Therapy Radionuclides

8.3.5.1 Astatine-211

Astatine (Greek *astatos*, meaning "unstable") is the rarest naturally occurring element in the earth's crust, and continuously produced, as a result of the decay of radioactive thorium and uranium ores. Astatine element belongs to the halogen family and was first discovered in 1940 at the University of California, Berkeley, where it was produced by α particle bombardment of natural bismuth, ^{209}Bi [30]. All of astatine's isotopes are short-lived; the most stable is ^{210}At, with a half-life of 8.1 h. Since it decays to ^{210}Po (an α-particle emitter with a half-life of 138 days), it is not suitable for medical purposes. ^{211}At decays with a half-life of 7.2 h and emits two α particles through a split decay pathway with energies of 5.87 and 7.45 MeV (Fig. 8.9). One path is to ^{207}Bi by α particle emission followed by electron capture to ^{207}Pb, and the other is by electron capture to ^{211}Po followed by emission to ^{207}Pb. An advantage of this decay path is that ^{211}Po emits 77–92 keV characteristic X-rays which can be used for imaging.

A more practical and direct method of producing ^{211}At is by cyclotrons utilizing the nuclear reaction ^{209}Bi(α,2n)^{211}At. The excitation function for the ^{209}Bi(α, 2n)^{211}At reaction indicates that the maximum production yield can be obtained using an α-beam of 31–35 MeV. However, the typical energy of 28 MeV is used to avoid or minimize the production of unwanted ^{210}At contaminants. The efficiency of cyclotron production of ^{211}At is related to the helium ion source, the a-beam energy, the current of the beam, and the cooling of the target. These parameters need to be optimized, taking into account the described physical properties of bismuth and astatine. Currently, ^{211}At is routinely produced in the United States (Seattle, Bethesda, and Durham) and Denmark (Copenhagen).

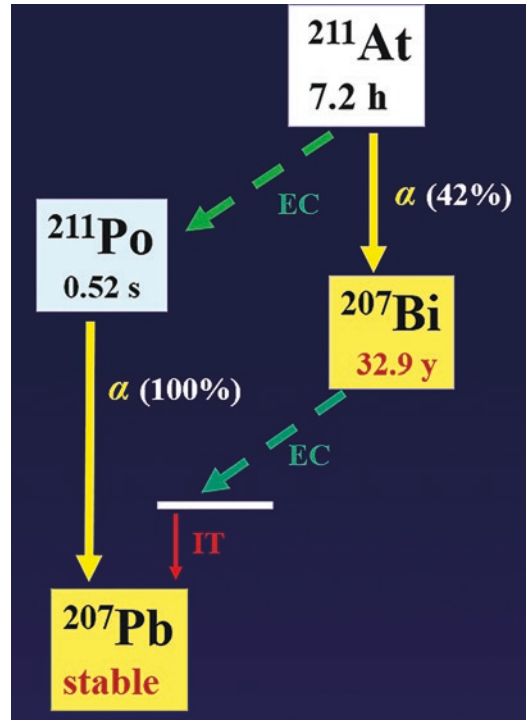

Fig. 8.9 Decay scheme of astatine-211 (^{211}At)

Alternative methods for producing ^{211}At involve accelerator production of ^{211}Rn ($T_{½}$ = 14.6 h), which can be obtained by proton spallation of uranium or thorium targets or by irradiation of natural bismuth with lithium-7 atoms [30]. ^{211}Rn/^{211}At generators may facilitate easier distribution due to the relatively longer half-life of ^{211}Rn. However, only 27.4% of ^{211}Rn decays to ^{211}At while 72.6 decays to ^{211}Po (Table 8.4).

8.3.5.2 Actinium-225

^{225}Ac ($T_{½}$ = 10 days) is a pure α emitter, and is an isotope of radioactive actinium element, ^{227}Ac

Table 8.4 Cyclotron-produced radionuclides for therapy

Radio nuclide	$T_{½}$	Decay		Energy		Production method	Target
		Mode	%	MeV	γ (KeV)	Nuclear reaction	
^{67}Cu	2.576 days	β^-	100	E_{max} = 0.562	184.6 (48.7%)	^{70}Zn (p, α) ^{67}Cu ^{68}Zn (p, 2p) ^{67}Cu ^{68}Zn (γ, p) ^{67}Cu	Solid
^{211}At	7.2 h	α	41.8	5.867 α	77–92 X-rays	^{209}Bi (α, 2n) ^{211}At	Solid
^{225}Ac	10 days	α	100	5.830 α		^{226}Ra(p,2n)^{225}Ac	Solid

National Nuclear Data Center (NNDC): NuDat 3.0 @NuDat 3 (bnl.gov)

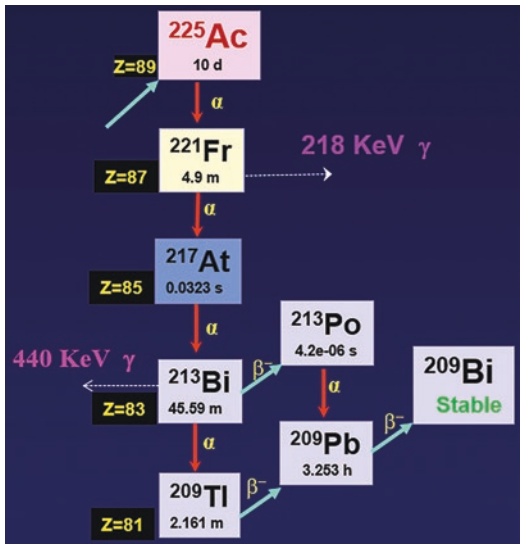

Fig. 8.10 Decay scheme of actinium-225 (^{225}Ac). Before Ac-225 reaches stable bismuth isotope, several radionuclides are generated as decay product, which decay either by alpha or beta emission

($T_{½}$ = 21.7 years), originally was discovered in 1989, in the pitchblende ore by a French chemist Andre-Louis Debierne. The name actinium originates from the ancient Greek *aktis, or aktinos* meaning beam or ray. Ac-225 does not exist in nature but was discovered in 1947 as part of the radioactive neptunium decay series (Fig. 8.1b) by the American and Canadian physicists. At present, Ac-225 is available for clinical use from the radioactive decay of ^{229}T and ^{225}Ra (refer to Thorium "cow" generator). The decay of ^{225}Ac generates 5 α particles and 3 β^- particles (Fig. 8.10).

^{225}Ac can be produced using accelerators and reactors based on several nuclear reactions as shown in Fig. 8.11. The potential of using low-energy cyclotrons (<20 MeV) based on ^{226}Ra(p, 2n)^{225}Ac nuclear reaction was first reported in 2005 [31]. This reaction has a high (710 mb) cross section peak at 16.8 MeV. Another advantage of this approach is that it would not coproduce long-lived ^{227}Ac contaminants. However, some ^{226}Ac ($T_{½}$ = 29.4 h) and ^{224}Ac ($T_{½}$ = 2.9 h) may be coproduced as impurities. It was estimated that a 20 MeV proton beam (with 500 μA current) incident on a ^{226}Ra target (~1 g) could produce a theoretical maximum of TBq (108 Ci) of ^{225}A per month [32]. Another estimate reported that a 24 h proton irradiation (16 MeV at 100 μA) of a 50 mg ^{226}Ra target may produce approximately, 5 GBq of ^{225}Ac. A major challenge, however, with this cyclotron method is related to the preparation and handling of targets containing milligram amounts of ^{226}Ra ($T_{½}$ = 1600 years), and management of its gaseous decay product ^{222}Rn ($T_{½}$ = 3.8 days).

Large-scale production of ^{225}Ac has been investigated based on the spallation of ^{232}Th targets with highly energetic protons (>70 MeV) [33–35]. The nuclear reaction ^{232}Th(p, x)^{225}Ac was studied at different proton energies and beam currents (Table 8.11). The feasibility of this spallation method based on ^{232}Th target has been demonstrated at the Institute for Nuclear Research, Russian Academy of Sciences, in Troitsk, Russia, and at Los Alamos National Laboratory in the United States [36]. In recent years, the routine production of ^{225}Ac has been successfully established within the United States, Department of Energy Tri-Lab (ORNL, BNL, LANL) effort. The spallation of thorium produces number of isotopes other than ^{225}Ac (such as radium isotopes). The separation and

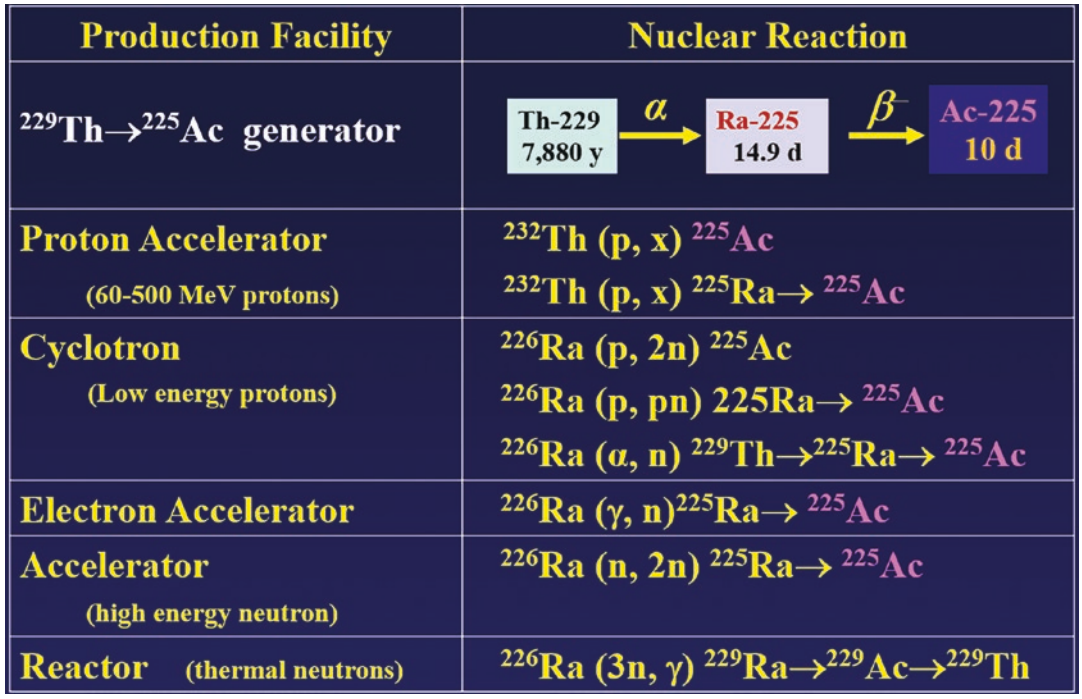

Fig. 8.11 Different nuclear reactions used to produce Ac-225 based on accelerator, cyclotron, and reactor facility

Table 8.5 Accelerator production of ^{225}Ac: The effect of beam energy and current

	Proton beam		Monthly production	
Accelerator facility	MeV	μA	GBq	Ci
iThemba LABS, South Africa	66	250	127.7	3.450
Los Alamos National Laboratory, USA	100	250	444.0	12.0
INR	160	120	1002	27.08
Arrownax	70	2x370	462.1	12.49
Brookhaven National Laboratory, USA	200	173	2675.84	72.32
TRIUMF, Canada	500	120	11,266.5	304.05

Maximum Ac-225 produced at ORNL based on Th-229 generator is about 1.0 Ci/year
Table modified from [32]
National Nuclear Data Center (NNDC): NuDat 3.0 @NuDat 3 (bnl.gov)

purification of ^{225}Ac are a very complicated process. However, large quantities of ^{225}Ac (2–11 TBq/month) can be produced compared to the current method of Ac-225 production using Th-229 generator. The main limitation of the process, however, is the coproduction of long-lived ^{227}Ac ($T_{½}$ = 21.8 years) at levels of 0.1–0.2% activity (at EOB) (Table 8.5).

8.4 Production of Radionuclides in a Nuclear Reactor

8.4.1 Nuclear Fission

Nuclear fission is a nuclear reaction or a nuclear transmutation process in which the nucleus of an

atom splits into two or more smaller lighter nuclei or isotopes of several elements. In addition, a large amount of energy is released. In high mass number isotopes, spontaneous fission may occur. A slow-moving neutron is absorbed by a ^{235}U nucleus, turning it briefly into an excited ^{236}U, which, in turn, splits into fast-moving lighter elements (fission products) and releases 2 or 3 free neutrons and high-energy prompt γ rays (Fig. 8.2). For heavy nuclides, fission is an exothermic radiation which can release large amounts of energy both as electromagnetic radiation and as kinetic energy of the fragments. The isotopes of heavy elements that can sustain a fission chain reaction are called nuclear fuels and are said to be *fissile*. The most common nuclear fuels are ^{235}U, ^{233}U, and ^{239}Pu. These fuels break apart into a bimodal range of chemical elements (fission products) with atomic numbers (A) centering near 95 ± 15 and 135 ± 15. (Fig. 8.12).

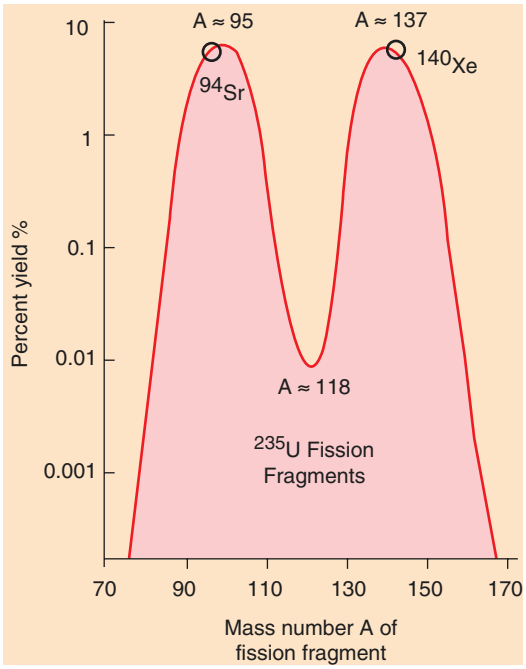

Fig. 8.12 Fissionable nuclides (such as ^{235}U and ^{238}Pu) break apart into a bimodal range of chemical elements (fission products) with atomic numbers (A) centering near 95 ± 15 and 135 ± 15. The most common fission products produced in a reactor are ^{131}I and ^{99}Mo

Shortly after the discovery of nuclear fission, scientists realized that, because fission leads to the release of additional neutrons, in a given mass of uranium fuel, known as the critical mass, a self-sustaining sequence of additional fissions can lead to a *chain reaction*, induced by at least one fission neutron. Such a reaction, in which the *multiplication factor* (MF) is ≥1, is called a *critical* reaction. However, if too few neutrons cause fissions, the reaction is *sub-critical* (MF <1) and will stop. If the frequency of fissions increases at a faster rate (MF >1), the "run-away" reaction can be *supercritical* and may lead to a nuclear explosion. In 1942, Fermi was able to demonstrate that by carefully controlling the availability of neutrons, a sustained chain reaction (MF = 1) can be maintained. The *nuclear reactor* operates based on the principle of *controlled chain reaction*.

Compared to ^{238}U, the cross section for induced fission reaction with slow or *thermal neutrons* (0.25 eV) is much higher for ^{235}U. Because the natural uranium contains only 0.7% of ^{235}U isotope, *enriched uranium* containing >3% of ^{235}U, is typically used as the fuel in a reactor core. In a nuclear reactor (Fig. 8.13), the fuel cells containing enriched uranium (as UF_6 or UO_2) pellets are surrounded by a *moderator*, graphite, or heavy water, to slow down the energetic fission neutrons. *Control rods* (cadmium and boron) capable of absorbing neutrons, but not undergoing any nuclear reaction, are used to sustain the chain reaction. Following the absorption of a neutron, the natural ^{238}U decays by emitting a beta particle to become ^{239}Np, which in turn emits a beta particle to become ^{239}Pu. These reactions are the basis of a *breeder reactor*, in which uranium produces more fuel in the form of ^{239}Pu.

8.4.2 Radionuclides Produced by Fission

The research reactors used for radioisotope production could be either a) swimming pool type

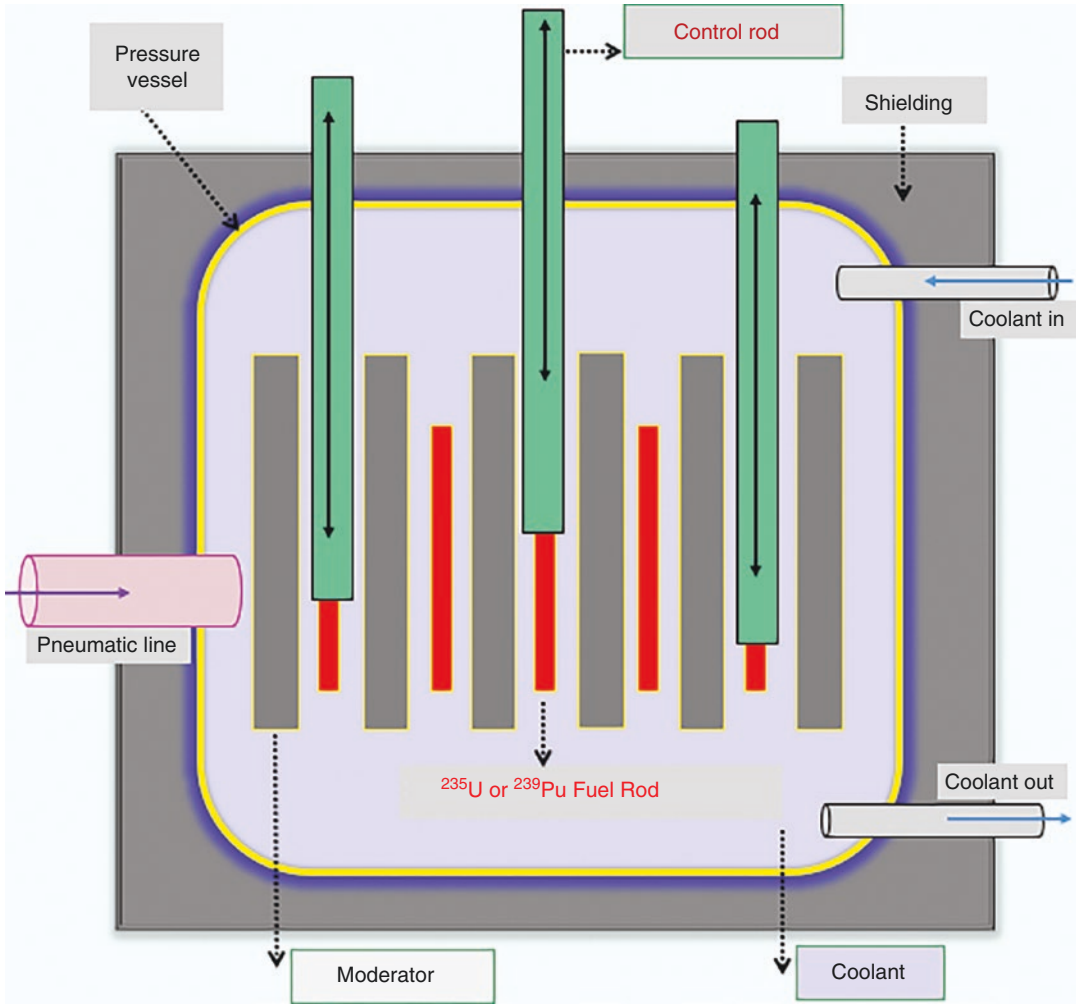

Fig. 8.13 Nuclear reactor facility animation showing reactor core with ^{235}U or ^{239}Pu radionuclides and the control rods containing boron or cadmium capable of absorbing fission neutrons

reactors with enriched uranium and light water as the moderator or b) cooled tank type reactors with natural uranium and heavy water as the moderator. When the reactor is in operation, the nuclear reaction (n, f) produces many neutron-rich fission fragments (Z = 28–65), which decay by β^- emission. Radionuclides, such as ^{99}Mo, ^{131}I, ^{90}Sr, ^{89}Sr, and ^{137}Cs, accumulate in the fuel rods to produce enormous activity (thousands of GBq). All the fission fragments can be chemically separated and purified to yield no-carrier-added, high SA radionuclides.

8.4.3 Radionuclides Produced by Neutron Activation

A nuclear reaction in which a neutron is captured or absorbed by the nucleus of a stable atom, leading to a nuclear transformation, is called *neutron activation*. The most common nuclear reactions are (n, γ) (n, p), (n, 2 n), and (n, α), in which the atomic mass or atomic number of the target nucleus may change.

The neutrons released during the fission reaction have a wide range of energies, from a few

KeV to 10 MeV. The average energy is approximately 2 MeV, which decreases substantially as a result of collisions with other atoms in the core and the moderator. The average energy of thermal neutrons at room temperature is about 0.038 eV. Neutrons between 0.01 and 0.1 MeV are known as slow or resonance neutrons, while neutrons with >0.1 MeV are known as fast neutrons. In general, the cross section (σ) for thermal neutrons in neutron activation reactions is very high, compared to that of higher energy neutrons.

In a (n,γ) reaction, the target nucleus with a mass number A captures a neutron to become an unstable, excited radioisotope of the target nucleus, with a mass number $A + 1$. The excited nucleus immediately emits a γ-photon, and the product radionuclide will eventually decay by beta emission to reach a ground state. Because the product nuclide is an isotope of the target element, the product cannot be separated and purified to avoid the contamination of the carrier. As a result, radioisotopes produced using (n, γ) reaction are generally very low in SA. However, it is possible to produce carrier-free, high SA nuclides in a reactor using (n, p) reactions. Important therapeutic radionuclides produced by fission and by neutron activation are summarized in Table 8.6.

8.4.4 Beta Emitting Radionuclides for Therapy

8.4.4.1 Phosphorous-32

Georg de Hevesy (Nobel Laureate and the inventor of the tracer principle) in 1935 was the first investigator to use ^{32}P in biological research. ^{32}P ($T_{½}$ = 14.268 days) decays into ^{32}S by β^- (E_{max} = 1.709 MeV) particle emission. ^{32}P has been available for the treatment of myeloproliferative neoplasms for over 80 years. It was first used in 1938 by John H. Lawrence to treat polycythemia and chronic leukemia. ^{32}P can be produced in a reactor by neutron activation using either $^{31}P(n, \gamma)^{32}P$ or $^{32}S(n, p)^{32}P$ nuclear reaction and supplied as orthophosphoric acid in water with a specific activity of 8–9 Ci (314–337 TBq)/mMole. In a (n, p) reaction, the target and the product are two different elements. As a result, it

Table 8.6 Reactor produced radionuclides for therapy

	$T_{½}$	Decay		β^- E_{max}	γ- Energy		Production method
Radio nuclide	Days	Mode	%	MeV	KeV	%	Nuclear reaction
^{89}Sr	50.53	β^-	100	1.501	910	1	^{88}Sr (n, γ) ^{89}Sr ^{89}Y (n, p) ^{89}Sr
^{32}P	14.268	β^-	100	1.710	–	–	^{31}P (n, γ) ^{32}P ^{32}S (n, p) ^{32}P
^{169}Er	9.392	β^-	100	0.351	–	–	$^{168}Er(n, \gamma)$ ^{169}Er
^{131}I	8.025	β^-, γ	100	0.606	364.5	81.5	^{235}U n, fission)^{131}I $^{130}Te(n, \gamma)^{131}Te \rightarrow_{\beta-} {}^{131}I$
^{177}Lu	6.6443	β^-, γ	100	0.497	113 208.4	6.6 10.4	$^{176}Lu(n, \gamma)^{177}Lu$ ^{176}Yb ((n, γ)$^{177}Yb \rightarrow_{\beta-} {}^{177}Lu$
^{186}Re	3.7186	β^-, *EC*	92.5	1.070	137.2	9.5	$^{185}Re(n, \gamma)^{186}Re$
^{198}Au	2.694	β^-, γ	100	0.961	411.8	95.6	$^{197}Au(n, \gamma)^{198}Au$
^{98}Y	2.67	β^-	100	2.28	–	–	$^{235}U(n, \text{fission})^{90}Sr \rightarrow_{\beta-} {}^{90}Y$
^{67}Cu	2.576	β^-, γ	100	0.561	184.6	48.7	^{67}Zn (n, p) ^{67}Cu
^{153}Sm	1.9375	β^-, γ	100	0.807	103.2	29	$^{152}Sm(n, \gamma)^{153}Sm$
^{166}Ho	1.120	β^-, γ	100	1.854	80.6	6.56	^{165}Ho (n, γ) ^{166}Ho
^{188}Re	0.708	β^-, γ	100	2.120	155	15.5	$^{187}W(n, \gamma)^{188}W \rightarrow_{\beta-} {}^{188}Re$
^{117m}Sn	13.76	*IT*	100	0.152 *(CE)*	159		$^{116}Sn(n, \gamma)^{117m}Sn$

National Nuclear Data Center (NNDC): NuDat 3.0 @NuDat 3 (bnl.gov)

is very easy to separate the product from the target, chemically.

8.4.4.2 Iodine-131

^{131}I is an important radioisotope of iodine discovered by Glenn Seaborg and John Livingood in 1938 at the University of California, Berkeley. ^{131}I decays with a half-life of 8.02 days with β^- (E_{max} = 606 KeV) and γ (364 KeV) emissions. ^{131}I is a major fission product of ^{235}U and ^{239}Pu comprising nearly 2.8336% of the total products of fission (by weight). In comparison, the long-lived ^{129}I fission product is only 0.9%. However, extracting the iodine from spent nuclear fuel would require expensive and time-consuming reprocessing in a sophisticated facility. Also, extracting only approximately 3% of the fuel would produce a large amount of nuclear waste. Radionuclidic purity of fission produced ^{131}I is not less than 99.9% of the total radioactivity. The specific activity is approximately 130 Ci/mg or 4.81TBq/mg.

As described earlier, ^{131}I can be produced by the fission of enriched ^{235}U based on (n, f) nuclear reaction. However, a more practical method of ^{131}I production is based on (n, γ) reaction in a research reactor using ^{130}Te target. Natural tellurium is easily available and is a mixture of several stable isotopes. ^{130}Te is approximately 30% of natural Te element. Certain (n, γ) reactions produce a short-lived radioisotope of the target element, which decays by beta emission to another unstable radioactive nuclide with longer half-life compared to that of the intermediate. As shown below, both the ground state ^{131}Te and metastable ^{131m}Te decay to^{131}I.

$$^{130}\mathrm{Te}\left(\mathrm{n},\gamma\right)^{131}\mathrm{Te}_{(25\mathrm{m})\rightarrow\beta^-}{}^{131}\mathrm{I} \qquad (8.19)$$

$$^{130}\mathrm{Te}\left(\mathrm{n},\gamma\right)^{131}\mathrm{Te}_{(25\mathrm{m})\rightarrow\beta^-}{}^{131}\mathrm{I} \qquad (8.20)$$

Following neutron irradiation, ^{131}I is extracted from the natural tellurium target generally by the dry distillation method. The process involves heating the irradiated sample to release the ^{131}I and ^{131}I in a sodium hydroxide solution (pH 8–10). The specific activity (~TBq/mg) is generally less than that of fission produced ^{131}I (4–5 TBq/mg).

8.4.4.3 Yttrium-90

^{90}Y ($T_{½}$ = 64.1 h) is one of the important radionuclides for TRT. It is a pure β^- emitter with very high-energy (E_{max} = 2.28 MeV) and no γ emissions. Selective internal radiation therapy (SIRT) with ^{90}Y-labeled microspheres has become a widely employed brachytherapy for the treatment of primary and metastatic hepatic malignancies.

It can be produced in a reactor by neutron irradiation of stable yttrium-89 via ^{89}Y(n, γ)^{90}Y reaction. Exposing a 1 cm cube (approximately 5 g), natural yttrium target to 10^{14} n/cm^2/s flux would create Y-90 at a rate of 1.1 Ci/hr. To make high specific activity ^{90}Y, e-LINAC is used to generate a neutron beam (12.1 MeV) and directing the neutron beam onto the zirconium target (^{90}Zr) to isotopically convert some of the atoms to ^{90}Y via ^{90}Zr(n, p)^{90}Y. However, the most common method of producing high specific activity ^{90}Y is the nuclear decay of parent isotope ^{90}Sr ($T_{½}$ = 29 years), which is a fission product of uranium. The theoretical specific activity is 20 GBq(540 mCi)/μg of Yttrium-90.

8.4.4.4 Lutetium-177

Lutetium is a transition metal and the last member of lanthanide series. ^{177}Lu ($T_{½}$ = 6.734 days) is a low-energy β^- emitter (E_{max} = 0.498 MeV) with suitable γ photons (113 and 208 KeV) suitable for SPECT imaging studies. ^{177}Lu-DOTATATE (Lutathera®) is the first therapeutic ^{177}Lu peptide radiopharmaceutical approved by FDA for TRT of patients with neuroendocrine tumors (NETs). Several ^{177}Lu labeled peptides and antibodies are in Phase II-III clinical trials for TRT.

In a nuclear reactor, ^{177}Lu can be produced by direct neutron activation using enriched ^{176}Lu or through the indirect route by activation of ^{176}Yb followed by β^- decay to ^{177}Lu (Fig. 8.14). For both methods, the amount of ^{177}Lu produced, however, depends on the neutron energy, neutron flux, and the irradiation time [37, 38]. The direct production route also results in formation of a small amount of long-lived metastable ^{177m}Lu in activity (<0.02%). The specific activity depends on the ^{176}Lu enrichment and one can obtain 20–40 Ci/mg with >80% enriched ^{176}Lu targets.

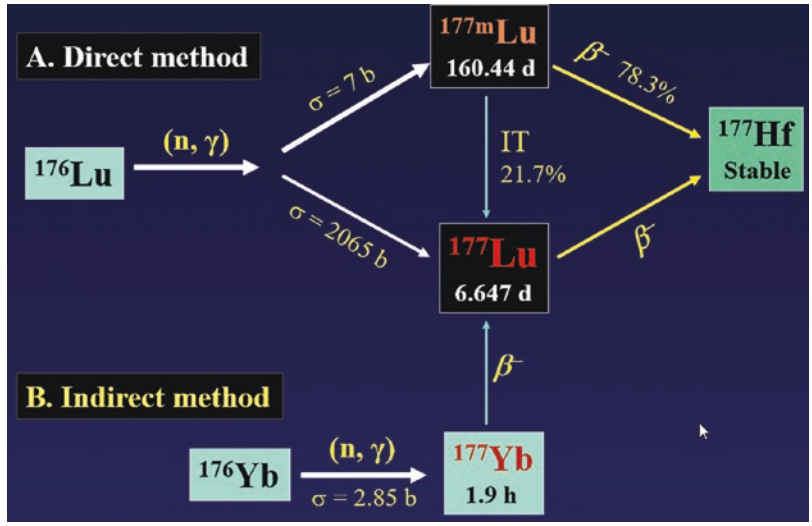

Fig. 8.14 Nuclear Reactions commonly used to produce Lu-177

The major advantage of the indirect method with ^{176}Yb target followed by the decay of ^{177}Yb provides no-carrier-added (NCA) ^{177}Lu which is then separated by suitable radiochemical processes. In addition, the indirect method does not produce any ^{177m}Lu radionuclide impurity. With enriched ^{176}Yb targets, it is possible to achieve very high specific activity approaching the theoretical specific activity of 110 Ci (4.07 TBq)/mg [37] (Fig. 8.14).

8.4.4.5 Copper-67

^{67}Cu, a transition metal ($T_{½}$ = 2.58 days), decays by β^- emission (E_{max} = 0.562 MeV) and provides several γ photons (91, 93, 184 KeV) for SPECT. Despite the potential for both imaging and therapy, the use of ^{67}Cu for therapy has been hampered for decades by its limited supply and low specific activity. The production of ^{67}Cu has been tested both in reactors and in cyclotrons on a variety of nuclear reactions such as ^{67}Zn(n,p)^{67}Cu, ^{68}Zn(p, 2p)^{67}Cu, and ^{70}Zn(p, α)^{67}Cu. The ^{68}Zn(p,2p)^{67}Cu route of production (using 70 MeV proton) appears to be the most attractive method. However, large quantities of ^{64}Cu($T_{½}$ = 12.7 h) and ^{67}Ga ($T_{½}$ = 78.3 h) are the major radionuclidic impurities. The specific activity is <20 Ci/mg [39].

A major breakthrough in the production of high specific activity ^{67}Cu is based on the photonuclear activation, using highly enriched (98.9%) ^{68}Zn targets. For the ^{68}Zn(γ,p)^{67}Cu reaction high-energy γ rays can be produced by bremsstrahlung conversion of electrons from e-LINAC [39, 40]. The specific activity of ^{67}Cu so produced has reached over 5.55 GBq/μg (150 mCi/μg). Due to this breakthrough in ^{67}Cu production, no-carrier-added ^{67}Cu has been made available in large scales at the US-DOE National Isotope Development Center.

8.4.4.6 Scandium-47

^{47}Sc with a half-life of 3.35 days and low-energy β^- particles (E_{max} = 441 keV) is ideal for therapy. In addition, the emission of 159 KeV γ photons is ideal for SPECT imaging studies. Also, ^{43}Sc ($T_{½}$ = 3.89 h, $E_{\beta+avg}$ = 476 keV, I = 88.1%) and ^{44}Sc($T_{½}$ = 3.97 h, $E_{\beta+avg}$ = 632 keV, I = 94.3%) have been proposed for PET imaging studies.

^{47}Sc can be produced by two different neutron induced reactions: ^{46}Ca(n, γ)^{47}Ca→^{47}Sc or ^{47}Ti(n, p). The (n, γ) reaction is induced by thermal neutrons, while the (n, p) reaction requires fast neutrons (>1 MeV). Enriched ^{46}Ca as $CaCO_3$ is generally used for thermal neutron activation reaction. The chemical separation of Sc from Ca was performed using DGA resin and SCX cation-exchange cartridges.

^{47}Sc can be produced with higher specific activities via the ^{48}Ti(γ, p)^{47}Sc using the photonuclear reaction by irradiation of a natural titanium target foil stack using bremsstrahlung

radiation generated by impinging 22 MeV electrons onto a 0.762-mm-thick tungsten radiator [41, 42]). Target foils dissolved in 2.0 M H_2SO_4. ^{47}Sc ions can be separated from natural titanium using AG-MP 50 cation-exchange resin. The recovered ^{47}Sc is purified using CHELEX 100 ion-exchange resin.

8.4.4.7 Strontium-89

^{89}Sr ($T_{½}$ = 50.53 days) is an alkaline earth metal and undergoes β^- decay (E_{max} = 1.495 MeV) into ^{89}Y with no gamma emissions. ^{89}Sr chloride (Metastron™) is used for bone pain palliation. ^{89}Sr is a anthropogenic radionuclide that is produced as a result of nuclear fission at thermal neutron fission yields of 4.69 ± 0.06% [43].

^{89}Sr can also be produced by neutron activation using $^{88}Sr(n, \gamma)^{89}Sr$ using $SrCO_3$ as the target with neutrons having a thermal neutron spectrum. A highly enriched target ^{88}Sr (>99%) is used to eliminate strontium-85 impurity. This is a convenient production method and takes place in a normal research reactor. ^{89}Sr can also be produced via $^{89}Y(n, p)^{89}Sr$ nuclear reaction using fast neutrons and yttrium oxide pellets.

8.4.4.8 Strontium-90

^{90}Sr ($T_{½}$ = 28.8 years) undergoes β^- decay (E_{max} = 0.546 MeV) into ^{90}Y. ^{90}Sr is produced as a result of nuclear fission at thermal neutron fission yields of 5.73 ± 0.13% [43]. The approximate specific activity of ^{90}Sr is about 140 mCi/mg. $^{90}Sr \rightarrow {}^{90}Y$ generator provides significant amounts of ^{90}Y for radionuclide therapy studies.

8.4.4.9 Samarium-153

^{153}Sm($T_{½}$ = 1.93 days) is a transition metal and one of the elements in the lanthanide series. It decays by β^- emission (E_{max} = 0.810 MeV) to europium-153, with useful γ emissions (103 KeV). ^{153}Sm-EDTMP or Lexidronam (Quadramet®) is clinically used for bone pain palliation.

^{53}Sm is produced by neutron activation of both natural Sm_2O_3 and 98% enriched $^{152}Sm_2O_3$ targets via $^{152}Sm(n, \gamma)^{153}Sm$ nuclear reaction [44]. Specific activity achieved at EOB is 14.8–16.8 GBq (400–450 mCi)/mg oxide. The specific activity of enriched ^{152}Sm targets can be up to 1200 mCi/mg.

8.4.4.10 Holmium-166

^{166}Ho($T_{½}$ = 26.763 h) is a transition metal and one of the elements in the lanthanide series. It decays by β^- emission (E_{max} = 1.854 MeV)) to erbium-166, with useful γ emissions (81 KeV) for SPECT. Several clinical applications for therapy are under investigation [45].

^{166}Ho is most frequently produced via the $^{165}Ho(n, \gamma)^{166}Ho$ nuclear reaction [44]. Because $^{165}H0$ has a natural abundance of 100% and a cross section of 64 b, it can be produced with a high purity. However, ^{166m}Ho ($T_{½}$ = 1200 years), a beta emitter may be produced as a radionuclidic impurity. The specific activity is NLT 75 mCi/mg.

^{166}Ho can also be produced by an indirect method via the $^{164,165}Dy(2n, \gamma)^{166}Dy_{\rightarrow}{}^{166}Ho$ nuclear reaction. The cross section of ^{164}Dy is extremely high (2650 b). The second neutron irradiation of the unstable ^{165}Dy is necessary to result in ^{166}Dy, which decays by beta emission to carrier-free ^{166}Ho. A $^{166}Dy_{\rightarrow}{}^{166}Ho$ generator can provide on-site supply of high specific activity ^{166}Ho for targeted therapy.

8.4.4.11 Rhenium-186, Re-188

^{186}Re ($T_{½}$ = 3.718 days) is a transition metal and decays by β^- emission (E_{max} = 1.07 MeV) with useful γ photons (137 KeV) for SPECT. The primary production of ^{186}Re in a reactor is via ^{185}Re (n, γ) nuclear reaction using enriched ^{185}Re target (>94%). The typical specific activity is 1.84 Ci/mg [46].

High specific activity ^{186}Re can be produced through cyclotron irradiation of enriched tungsten-186 target via the $^{186}W(d, 2n)^{186}Re$ nuclear reaction [47]. The target thickness and beam currents are critical to achieve high specific activity. Specific activity of 80 Ci/mg was obtained using a graphite-encased ^{186}W target and 18.7 MeV deuteron bombardment for 2 h, at a beam current of 27 μA [48].

^{188}Re ($T_{½}$ = 16.9 h) also decays by β^- emission (E_{max} = 2.12 MeV) with useful γ photons (155 KeV) for SPECT. ^{188}Re as no-carrier-added

nuclide can be produced in high specific activity from the $^{188}W \rightarrow ^{188}Re$ generator system.

Rhenium and technetium elements exhibit similar chemical properties and preparation and targeting of $^{186/188}Re$ radiopharmaceuticals for therapy is similar to imaging agents prepared with ^{99m}Tc, the most commonly used diagnostic radionuclide.

8.4.4.12 Tin-117 m

^{117m}Sn ($T_{½}$ = 13.6 days) is a post-transition metal that decays by isomeric transition and emits low and mono-energetic conversion electrons (0.127, 0.129, and 0.152 MeV). It also emits γ photons (159 KeV) suitable for SPECT. Bone marrow toxicity of this radionuclide is low because of its short range (~3 mm) electrons. It is a novel radionuclide with low-energy electrons for radionuclide therapy applications including rheumatoid arthritis and bone pain palliation,

^{117m}Sn can be produced in large quantities as a low specific activity (up to 21 mCi/mg) product in reactors via the $^{116}Sn(n, \gamma)^{117m}Sn$ or $^{117}Sn(n, n'\gamma)^{117m}Sn$ reactions. A carrier-free, high specific activity (up to 20 Ci/mg) isotope can be manufactured with >50 MeV cyclotrons employing either stable antimony target $^{nat}Sb(p, x)^{117m}Sn$ or $^{116}Cd(\alpha, 3n)$ nuclear reactions [49, 50].

8.4.4.13 Molybdenum-99

Technetium-99 m ($T_{½}$ = 6 h), the most widely used radioisotope in nuclear medicine, is produced via the decay of its parent radionuclide, ^{99}Mo ($T_{½}$ = 65.94 h), which decays by β^- (E_{max} = 1.214 MeV) and γ (181, 740, and 778 KeV) emissions. Mo-99 is produced by the fission of ^{235}U in the highly enriched uranium (HEU)-bearing targets by irradiating them with thermal neutrons. ^{99}Mo is a major fission product of ^{235}U comprising nearly 6.1% of the total products of fission (by weight). The amount of ^{99}Mo produced in a target is a function of irradiation time, the thermal neutron fission cross section for ^{235}U, the thermal neutron flux on the target, the mass of U-235 in the target, and the half-life of Mo-99 (IAEA TR). For typical reactor thermal neutron fluxes on the order of 10^{14} neutrons per square centimeter per second, irradiation times of about 5 to 7 days are required to achieve near maximum ^{99}Mo production in the targets No-carrier-added ^{99}Mo is supplied as molybdate in 0.2 N NaOH solution with a radionuclidic purity of NLT 95%. Several radionuclidic impurities (^{103}Ru, ^{131}I, and ^{132}Te) may be present in the final product.

^{99}Mo can also be produced in a reactor using neutron activation via $^{98}Mo(n, \gamma)^{99}Mo$ nuclear reaction. However, the specific activity of ^{99}Mo is very low since the target ^{98}Mo cannot be separated from ^{99}Mo by chemical separation methods since they both are isotopes of the same element.

There are alternative routes for generating ^{99}Mo that do not require a fissionable target, such as high or low enriched uranium (i.e., HEU or LEU) [51]. Cyclotron production of ^{99}Mo is based on proton bombardment of $^{100}Mo(p, 2n)^{99}Mo$ nuclear reaction, while photonuclear activation using e-LINAC is based on $^{100}Mo(\gamma, n)^{99}Mo$ reaction using enriched ^{100}Mo target. Photons for this reaction are provided from the electron deceleration radiation. This technology uses high-energy X-rays produced by a 30–35 meV, 100 kW electron beam to irradiate a ^{100}Mo target [52].

8.4.4.14 Tungsten-188

^{188}W ($T_{½}$ = 69.78 days) is a transition metal and decays 100% by β^- emission to ^{188}Re which also decays by β^- *emission to stable* ^{188}Os. ^{188}W is primarily used as a parent for the $^{188}W_{\rightarrow}{}^{188}Re$ generator system. ^{188}W is produced in a reactor by double neutron capture of enriched ^{186}W (>90%) targets by the double neutron capture pathway (IAEA.) via the nuclear reactions, $^{186}W(n, \gamma)^{187}W(n,\gamma)^{188}W$. High neutron flux ($>8–10 \times 10^{14}$/cm^2/s) reactor is essential to produce high specific activities.

^{188}W is produced at the US-DOE High Flux Isotope Reactor at Oak Ridge National Laboratory and is offered as sodium tungstate in NaOH solution or loaded on a $^{188}W_{\rightarrow}{}^{188}Re$ generator.

8.4.5 Alpha Emitting Radionuclides for Therapy

8.4.5.1 Radium-223

^{223}Ra ($T_{½}$ = 11.4 days), historically known as actinium-X, was discovered in 1905 by T. Godlewski, a Polish chemist. ^{223}Ra dichloride (RaC_2) is an alpha particle-emitting radiotherapy drug (known as Alpharadin or Xofigo®) that mimics calcium and forms complexes with hydroxyapatite at areas of increased bone turnover. In 2013, it was the first α- particle-emitting radiopharmaceutical approved by FDA for therapy as a treatment for metastatic bone cancer in patients with castration-resistant prostate cancer (CRPC).

Although ^{223}Ra is naturally formed in trace amounts by the decay of ^{235}U, it is generally made artificially in a reactor, by neutron activation of ^{226}Ra to produce ^{227}Ra, which decays to ^{227}Ac, which in turn decays via ^{227}Th to ^{223}Ra. This decay path makes it convenient to prepare ^{223}Ra by "milking" it from an ^{227}Ac→^{223}Ra generator. The six-stage decay of ^{223}Ra to stable ^{207}Pb occurs via short-lived daughters (Fig. 8.15) and is accompanied predominantly by the emission of 5 alpha particles (5–7.5 MeV). There are also beta and gamma emissions with different energies and emission probabilities.

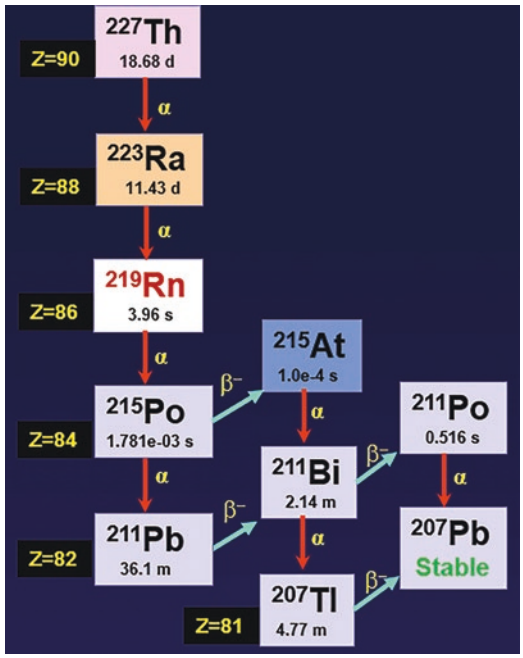

Fig. 8.15 ^{223}Ra (the daughter of ^{227}Th) decay scheme shows emission of several α and β^- particles before it reaches stable ^{207}Pb

8.4.5.2 Actinium-225

As ^{225}Ac does not occur in any appreciable quantities in nature, it must be synthesized in specialized nuclear reactors. The majority of ^{225}Ac results from the alpha decay of parent nuclide, ^{229}Th. It is also possible to breed ^{225}Ac by neutron activation from ^{226}Ra via the ^{226}Ra(p,2n)^{225}Ac nuclear reaction. The potential to populate ^{225}Ac using a ^{226}Ra target was first demonstrated in 2005, the production and handling of ^{226}Ra, however, are difficult because of the respective cost of extraction and hazards of decay products such as ^{222}Rn gas [32]. For the current methods of ^{225}Ac production, refer to Fig. 8.11.

8.5 Radionuclide Generators

Certain radionuclides may be generated by longer-lived parent radionuclide. The parent radionuclide can be made in a reactor or in a cyclotron. Both parent and daughter radionuclide pair may exist either in a transient or in a secular equilibrium when the parent is a longer-lived radionuclide than the daughter. If the parent and daughter nuclides are two different elements, they can be separated chemically, and the radioactivity of the daughter can be of high SA. Such a parent–daughter (mother–daughter) radionuclide pair is ideal to build a generator system to produce the daughter radionuclide, when needed [53, 54]. The *radionuclide generator* is a device used to separate the daughter radionuclide from the parent radionuclide. Various types of physicochemical separation methods, such as distillation or liquid/liquid extraction may be used. A chromatographic method based on an inorganic or resin adsorbent material, however, is the most practical method for routine clinical utility. Several important radionuclide generator systems (Table 8.7) are available commercially to produce radionuclides of clinical interest.

Table 8.7 Radionuclide generator systems for imaging and therapy

Parent				Daughter				
Nuclide	$T_{½}$	Decay	Parent produced by	Nuclide	$T_{½}$	Decay	E_{mean} MeV	Particles/decay
^{99}Mo	2.75 days	β^-	^{235}U-fission	^{99m}Tc	6.0 h	*IT*	0.140γ	–
^{82}Sr	25.34 days	*EC*	Accelerator	^{82}Rb	75 s	β^+	1.480	–
^{62}Zn	9.19 h	EC	Cyclotron	^{62}Cu	9.7 months	β^+	1.319	–
^{68}Ge	271 days	*EC*	Accelerator	^{68}Ga	67.7 months	β^+	0.829	–
^{90}Sr	28.8 years	β^-	Fission product	^{90}Y	2.67 days	β^-	0.932	–
^{188}W	69.8 days	β^-	Reactor	^{188}Re	17.0 h	β^-	0.763	–
^{228}Th	1.9125 years	α	Decay chain	^{212}Pb	10.64	β^-	0.101	$1\beta^-$
^{224}Ra	3.632 days	α	Decay chain	^{212}Bi	60.1 months	β^-, α	7.8	1α, $1\beta^-$
^{225}Ac	10.0 days	α	Decay chain/ accelerator	^{213}Bi	45.6 months	β^-, α	8.32	2α, $3\beta^-$
^{211}Rn	14.6 h	EC, α	Cyclotron	^{211}At	7.214 h	α	6.78	2α, $2EC$
^{227}Ac	21.772 years	β^-, α	Decay chain	^{223}Ra	11.43 days	α	6.59	5α, $4\beta^-$
^{229}Th	7932 years	α	Decay chain	^{225}Ac	10.0 days	α	6.87	5α, $3\beta^-$
^{227}Ac	21.772 years	β^-, α	Decay chain	^{227}Th	18.697 days	α	6.46	7α, $4\beta^-$

8.5.1 Generators for SPECT/PET Imaging

8.5.1.1 $^{99}Mo_{\rightarrow}$ ^{99m}Tc Generator

The ^{99m}Tc generator was first developed in 1960s at the Brookhaven National Laboratories in New York [55]. As discussed earlier, ^{99}Mo is one of the fission products of ^{235}U fission, known as "fission moly" and is produced in very high SA compared to ^{99}Mo which is produced by neutron activation. Most commercial generators are made with fission produced ^{99}Mo. The generator is made on the basis of a solid column method, in which 5–10 g of preheated alumina (Al_2O_3) is loaded in a plastic or glass column. The ^{99}Mo activity (2–32 Ci) in the form of molybdate ion is adsorbed on the column. The column is thoroughly washed to remove undesirable contaminants. The amount of ^{99}Mo activity on the column along with the date and time of calibration, for each generator, is provided. Commercial generators are sterilized and well shielded with lead or depleted uranium.

After the generator has been washed and calibrated, at time T_0, there is no ^{99m}Tc activity on the column. As $^{99}Mo(T_{½} = 66$ h) decays, ^{99m}Tc activity ($T_{½} = 6$ h) is produced and builds up in the column as a function of time, as shown in Fig. 8.16. Unlike molybdenum, technetium does not bind to alumina but, is immediately converted into ^{99m}Tc-pertechnetate ion ($^{99m}TcO4^-$), which is the most stable chemical form of technetium with an oxidation state of +7. Typically, >75% of ^{99m}Tc-activity can be eluted with 3–10 mL of physiological saline solution. The equations to estimate the amount of ^{99m}Tc activity in a generator have been previously shown (Eqs. (4.21) and (4.23)).

Small amounts of ^{99}Mo activity may occasionally *breakthrough* (leakage or partial elution) the column into the ^{99m}Tc-pertechnetate solution. The maximum ^{99}Mo contamination allowed is 0.15 μCi/mCi^{-1} or 0.15 KBq MBq^{-1} of ^{99m}Tc-pertechnetate solution at the time of elution. Each ^{99m}Tc dose to a patient, however, should not contain >5 μCi of ^{99}Mo activity. As a chemical impurity, Al ion concentration should be <10–20 μg mL^{-1} of eluant.

Both, ^{99}Mo (13%) and ^{99m}Tc decay producing the long-lived ^{99}Tc, which in turn decays slowly by beta emission, to the stable ^{99}Ru. Since ^{99m}Tc and ^{99}Tc are isomers and chemically the same

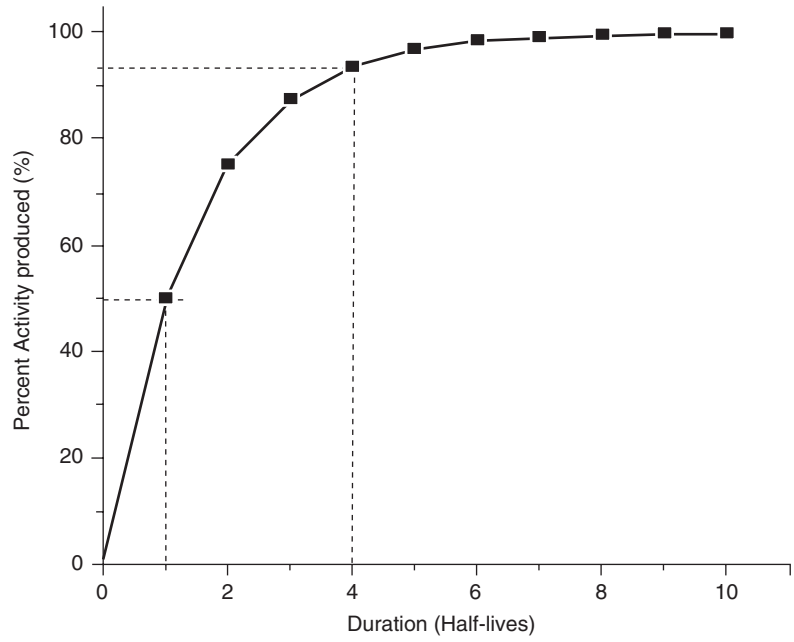

Fig. 8.16 In a radionuclide generator, the build-up of daughter activity is a function of time (half-life): Approximately 90% of the expected daughter activity will build up in the generator after 4 half-lives of daughter radionuclide. 50% of the expected activity will build up only after 1 half-life of the daughter

element, ^{99}Tc may act as a carrier in the preparation of ^{99m}Tc radiotracers. If the generator is eluted once a day (every 24 h), the number of ^{99m}Tc atoms is 27% of the total Tc atoms. If the generator is eluted after 4 days, for example, the number of ^{99m}Tc atoms is only 5% of the total Tc atoms.

8.5.1.2 ^{82}Sr→ ^{82}Rb Generator (Cardiogen®)

^{82}Rb chloride was the first PET radiopharmaceutical approved by the FDA in 1989 for assessment of regional myocardial perfusion. Cardiogen® was first manufactured and supplied by Bracco Diagnostics. Rb-82 generator (RUBY-FILL™, is supplied by Jubilant DraxImage Inc). The parent ^{82}Sr ($T_{½}$ = 25.6 days) is a neutron-deficient radionuclide that decays by electron capture and is produced using a high-energy cyclotron [56]. ^{82}Sr (90–150 mCi) is loaded on a stannic oxide column and the daughter ^{82}Rb ($T_{½}$ = 75 s) is eluted from the column with a sterile saline solution using an infusion pump calibrated to administer a specific unit dose to a patient.

8.5.1.3 ^{68}Ge→ ^{68}Ga Generator

In many PET facilities, ^{68}Ga is routinely used for transmission scans (for attenuation correction of PET data) using a ^{68}Ge rod source (5–10 mCi). The parent ^{68}Ge is a long-lived ($T_{½}$ = 271 days) neutron-deficient radionuclide, generally produced by a high-energy cyclotron based on spallation reaction [3]. The ^{68}Ga generator was developed, in 1960s for brain imaging studies [57] and, subsequently, improved [58].

Following several modifications in the chromatographic column technology, ^{68}Ga is currently produced using several ^{68}Ge/^{68}Ga generator systems in the clinical and research environments. For example, titanium dioxide-based IGG100 (Eckert & Ziegler), Galli EO (IRE Elit), Obninsk (Cyclotron Co.Ltd.), tin dioxide-based iThemba (iThemba Labs), and do-decyl gallate-modified silica-based ITG (ITG). These commercial generators are supplied with 10–100 mCi capacity, have very low ^{68}Ge-breakthrough, very low metal/chemical impurities, and are eluted with <0.1 M HCl.

8.5.1.4 ^{62}Zn→ ^{62}Cu Generator

Several ^{62}Cu radiotracers are under development and clinical evaluation for assessing perfusion and hypoxia. ^{62}Zn ($T_{½}$ = 9.13 h) is a neutron-deficient radionuclide produced by the proton irradiation of a copper disc or copper electroplated alloy on the basis of the nuclear reaction ^{63}Cu(p,2n)^{62}Zn using 26–21 MeV protons [3]. ^{62}Zn is separated from the target copper using an anion-exchange column. Subsequently, an acidic solution of ^{62}Zn can be loaded onto an anion-exchange column and the daughter ^{62}Cu ($T_{½}$ = 9.76 min) can be eluted from the generator for the preparation of radiotracers [59–61].

8.5.2 Generators for Radionuclide Therapy

8.5.2.1 ^{90}Sr→^{90}Y0 Generator

The ^{90}Sr parent radionuclide is very long-lived ($T_{½}$: 28.8 years) and the generators theoretically have a very long lifetime. However, ^{90}Sr may induce substantial radiation degradation of the column matrix. Several methods were developed to produce the generator system [62]. One of the designs (developed in Italy) consisted of two cation-exchange columns connected in series. The first column (cross-linked cation-exchange resin) contained the adsorbed ^{90}Sr, while the second served as a safety column to trap any possible leakage of ^{90}Sr from the first column, and the ^{90}Y is eluted with acetate buffer solution. The pH and molarity of the acetate solution are optimized to efficiently elute the ^{90}Y in low volumes and to avoid the breakthrough of ^{90}Sr. The maximum permissible levels are extremely low and set up to 74 kBq (2 μCi) to prevent excessive body burden. Several ^{90}Y labeled peptides and antibodies have been developed for therapy [46].

8.5.2.2 ^{188}W→^{188}Re Generator

Alumina-based chromatographic generator systems, similar to those available for ^{99m}Tc, are prepared for obtaining ^{188}Re as ReO_4^-. Active acidic aluminum oxide is used to prepare the columns. Tungsten-188 (185 GBq/g) as sodium tungstate 0.26 M sodium hydroxide solution is used to load

on the column after adjusting the pH to 2–3. The column is washed with 100 mL of 0.9% NaCl solution (normal saline) and, after allowing growth of the ^{188}Re, eluted with 10 mL of saline. However, $^{188}ReO_4^-$ eluent from the generator is not suitable for the direct formulation of radiopharmaceuticals. Concentration of the generator eluent solution is essential to radioactive concentration sufficient for radiopharmaceutical formulation [63]. The generator system is commercially available from several manufacturers.

8.5.2.3 ^{227}Ac→ ^{227}Th→ ^{223}Ra Generator

^{223}Ra ($T_{½}$ = 11.4 days) belongs to the alkaline earth family and is generated naturally from the decay of ^{235}U. However, for practical reasons, ^{223}Ra is artificially produced through a generator from ^{227}Ac parent ($T_{½}$ = 21.8 years), which also is produced artificially in a reactor starting from ^{226}Ra. A natural source of ^{227}Ac, originating from the decay chain of ^{235}U, is also available in limited quantities. The decay scheme (Fig. 8.15) of ^{227}Th shows the daughter ^{223}Ra and all the decay products from Ra-223.

The generator method is based on using 2-mL cartridges of UTEVA and DGA resins. The source material containing the mixture of ^{227}Ac, ^{227}Th, and ^{223}Ra isotopes in 4 M nitric acid is loaded onto the cartridges. Thorium is retained by UTEVA resin, while actinium is retained by DGA resin. Radium is not retained by these two cartridges. Currently, the clinical and commercial production of $^{223}RaCl_2$ (Bayer Health Care Pharmaceuticals) involves ^{227}Ac and ^{227}Th isolation from a ^{231}Pa source (3.28×10^4 years) [64].

8.5.2.4 ^{229}Th→^{225}Ac Generator (Thorium Cow)

Actinium-225 is a pure α emitter with a half-live of 10 days. ^{225}Ac is mainly produced by isolation from ^{229}Th ($T_{½}$ = 7340 years), which is a decay product of uranium-233 ($T_{½}$ = 165,000 years). ^{233}U is a fissile isotope of uranium and was artificially produced by neutron irradiation of natural thorium. Between 1995 and 2005, ^{229}Th generated by the decay of ^{233}U (Fig. 5.11) was extracted and stored at Oak Ridge National Laboratory (ORNL). This ^{229}Th now exists at ORNL (~5.55 GBq (150 mCi), or ~704 mg) and another (1.7 (46 mCi), or 215 mg) at the Institute for Transuranium Elements (ITU, Karlsruhe, Germany). A third ^{229}Th source (5.55 GBq (150 mCi), 704 mg) obtained from Russia ^{233}U stockpiles exists at the Leipunskii Institute for Physics and Power Engineering (IPPE, Obninsk, Russia). These three sources provide the ^{229}Th (parent) needed to make the ^{225}Ac generator and provide approximately 26.6 GBq (720 mCi) at ORNL and 13.1 GBq (350 mCi) at ITU) of ^{225}Ac annually.

ORNL is a major producer of ^{225}Ac based on Th-229 generator. The chemical separation process consists of anion-exchange separation using hydrochloric and nitric acids followed by cation-exchange separation for the final purification. Gamma spectroscopy is used for quality control analysis of the final product before shipping, and mass spectroscopy data are used to evaluate chemical purity.

8.5.2.5 ^{225}Ac→ ^{213}Bi Generator

The use of radioisotopes to trace flow of molecules through the body was first proposed by George Charles de Hevesy in 1913. He saw the practical use in 1927 when ^{214}Bi was used as a tracer to study the velocity of blood.

Bismuth-213 is a hybrid α/β^- emitter with a half-life of 45.6 min. It is generated as a decay product of ^{225}Ac (Fig. 8.10). In addition, the decay of ^{213}Bi is accompanied by a 440 keV γ photon emission. The generator requires purified ^{225}Ac and uses an organic anion-exchange system (AG-MP 50 resin) capable of isolating ^{213}Bi from a HCl solution of ^{225}Ac. The anion resin is then washed and stripped of the Bi product using a sodium acetate buffer [65]. A commercial Ac-225/Bi-213 Generator is currently supplied by iTM, Germany.

8.5.2.6 ^{228}Th→^{224}Ra→ ^{212}Pb→ ^{212}Bi Generator

Bismuth-212 is a hybrid α/β^- emitter with a half-life of 60.6 min and is generated from the decay of ^{228}Th, ^{224}Ra, and ^{212}Pb (Fig. 8.17). The major disadvantage of ^{212}Bi is the high-energy (2.6 MeV) γ emission of ^{208}Tl, one of the decay products of ^{212}Bi.

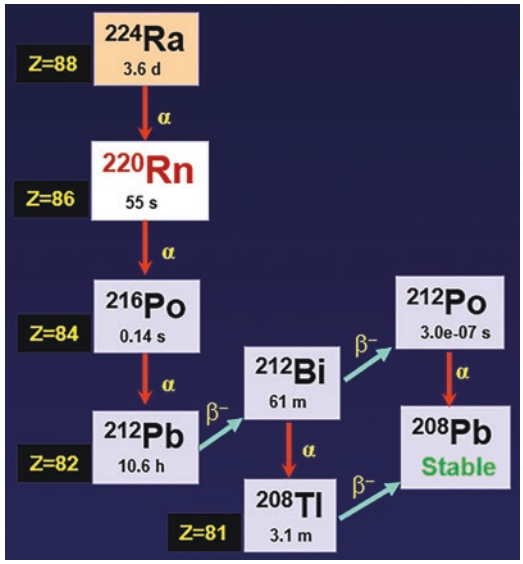

Fig. 8.17 Ra-224 decay scheme. ^{224}Ra (parent radionuclide) generator is used to produce ^{212}Pb and/or ^{212}Bi nuclides

The original ^{228}Th→^{212}Bi generator used a Na_2TiO_3 column to bind both ^{228}Th and its immediate daughter radionuclide ^{224}Ra. The generator was operated by eluting ^{220}Rn with water into a reservoir, waiting a few minutes for the radon gas to decay to ^{212}Pb, followed by passing that solution through an organic cation-exchanger to absorb the ^{212}Pb. This generator based on ^{228}Th experienced problems with radiolytic damage in the resin with consequent diminished yield and was also a serious radiation safety problem.

To avoid problems originating from ^{228}Th-based generators, another generator based on ^{224}Ra ($T_{½}$ = 3.7 days) was designed [66, 67]. ^{224}Ra is separated from ^{228}Th by absorbing ^{228}Th as the nitrate complex onto an anion-exchanger, while ^{224}Ra elutes through the column. The ^{224}Ra is then absorbed on to the macroporous organic cation ion-exchange resin (AG-MP 50) which then serves as the source for either a ^{212}Bi or ^{212}Pb. ^{212}Bi can selectively be eluted from the generator with low acid concentrations of HI (0.05–0.2 M). At higher acid concentrations, a mixture of both ^{212}Pb and ^{212}Bi can be eluted. Alternatively, ^{212}Pb can be first eluted with 2 M HCl. The ^{212}Pb eluate is then diluted to 0.1 M HCl and loaded onto a small AG-50 × 4 resin and the ^{212}Bi eluted from the resin with 0.2 M hydroiodic acid. ^{224}Ra→^{212}Pb→^{212}Bi generator is available for distribution from the NIDC of the US Department of Energy.

8.5.2.7 ^{227}Ac→ ^{227}Th→ ^{223}Ra Generator

^{227}Th belongs to the actinium series and has a physical half-live of 18.72 days. The decay chain of ^{227}Th generates 6 α particles with an average energy of 6.02 MeV. ^{227}Th can be produced by natural decay of ^{227}Ac ($T_{½}$ = 21.8 years), which can be produced in a reactor by neutron irradiation based on nuclear reaction, ^{226}Ra (n, γ)^{227}Ra. ^{227}Ra ($T_{½}$ = 42 min), which in turn decays by β^- disintegration to provide the desired ^{227}Th. The long half-life of ^{227}Th allows for transportation and preparation of the radiopharmaceuticals.

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