Therapeutic Radionuclides Decay with Particle Emission for Therapeutic Applications

2

2.1 Introduction

Unsealed radioactive sources are administered by certified medical staff, and the use of ^{131}I-iodide for ablation of thyroid tissue and surgical remnants is the classic example in endocrinology. While application of sealed radioactive sources such as ^{192}Ir in radiation oncology generally involves the use of afterloading devices, for instance, unsealed radioactive sources for the selective delivery of radiation to target tissues or organs without significantly affecting normal tissues are known as radionuclide therapy and are practiced by nuclear medicine specialists. This promising treatment option has been available for more than 70 years but had been for many years confined for radiation therapy of limited diseases, with the treatment of thyroid cancer the most prominent example.

Over the last 40–50 years, rapid and widespread interest in radionuclide therapy has been the driving force behind extensive research focused on the design, development, testing, and clinical evaluation of many novel radiopharmaceuticals. Production of radionuclides which are required for radionuclide therapy (Chaps. 5, 6, 7, and 8) is the first step in the development of therapeutic radiopharmaceuticals and also the most crucial aspect for the success as well as sustainable growth of radionuclide therapy. Development of production and processing technologies has been an area of intense research since there are a variety of therapeutic radionuclides which differ based on their physical half-lives, type of particle emission (β^-, σ, Auger), particle emission energy, specific activity, and chemistry (Ehrhardt et al. 1998; Karenlin and Toporov 1998; IAEA 2012; Mausner et al. 1988; Neves et al. 2005; Qaim 2012; Ruth et al. 1989; Troutner 1987; Volkert et al. 1991; Yeong et al. 2014; Zhuikov 2014). While the production of therapeutic radionuclides requires a thorough understanding of the nuclear reactions and decay schemes, development and implementation of processing methods require knowledge of the appropriate aqueous solution chemistry. This chapter discusses the key aspects related to the production of important therapeutic radionuclides, embracing current and possible future needs in the rapidly advancing field of radionuclide therapy. While both research reactors and accelerators are the principal technologies which offer the possibility for sustainable production of a wide range of radionuclides, there are several issues and challenges that must be considered in order to fully realize their potential (Ehrhardt et al. 1998; IAEA 2012; Mausner et al. 1988; Neves et al. 2005; Qaim 2012; Ruth et al. 1989; Troutner 1987; Volkert et al. 1991; Yeong et al. 2014; Zhuikov 2014). Depending on both the demands and applications, efficient production of therapeutic radionuclides plays a key role for current opportunities in technology development and to fulfill future research needs for radionuclides of emerging interest that appear promising for radionuclide therapy.

F.F. (Russ) Knapp, A. Dash, *Radiopharmaceuticals for Therapy*, DOI 10.1007/978-81-322-2607-9_2

Radionuclide therapy utilizes unsealed radioactive sources designed to deliver therapeutic doses of ionizing radiation to specific disease sites and is an attractive treatment option either for curative intent or for disease control and palliation (Chatal and Hoefnagel 1999; Joensuu and Tenhunen 1999). This methodology combines the advantages of target selectivity similar to that of brachytherapy or external beam radiotherapy and at the same time is systemically similar to chemotherapy. Systemic administration strategies offer the prospect of treating disseminated metastatic tumors (McDougall 2000; Volkert and Hoffman 1999). The basic principle primarily underlines the administration of a radiopharmaceutical for selective accumulation at the diseased tissue either to ablate or damage cells through the emission of energetic β^--particles, α-particles, or Auger electrons (e^-) (Britton 1997; Heeg and Jurisson 1999; McEwan 1997; Serafini 1994). The targeting feature of radionuclide therapy is achieved either by the intrinsic targeting properties of some radionuclides or by conjugating the radionuclide to specific carrier molecules. Therapeutic radiopharmaceuticals generally consist of two entities, which include the radionuclide, which is the radiation source, and a targeting moiety that determines tissue localization. In light of the explicit need to deliver sufficient cytotoxic radiation to the target cells while not causing unmanageable side effects, it is imperative that the radiopharmaceutical accumulates selectively in the diseased tissue, clears rapidly from the blood and other normal organs, and has rapid transit through the excretory organs, in order to minimize radiation damage to normal tissues.

Over the years, radionuclide therapy has undergone rapid and continual evolutionary cycles, relying on empirically prepared radiopharmaceuticals and presently progressing to the use of intelligent design of specific agents for targeted therapy. As the development of therapeutic radiopharmaceuticals has progressed, the use of the metallic radionuclides as well as novel target-specific pathways is now a hallmark (Spencer et al. 1987; Hoefnagel 1991; Stöcklin et al. 1995; O'Donoghue et al. 1995; Ercan and Caglar 2000; Srivastava 1996a, b; Mausner and Srivastava 1993; Srivastava and Dadachova 2001; Cuaron et al. 2009; Tolmachev et al. 2004; Unak et al. 2002; Stanciu 2012; Srivastava and Dadachova 2001; Das and Pillai 2013). A number of metallic radionuclides have been combined with key targeting macromolecules, which include whole antibodies, antibody fragments, small peptides, peptidomimetics, or nonpeptide receptor ligands, and have been studied for their potential use in tumor therapy. The use of metallic radionuclides is attractive and offers the convenience of designing a broad spectrum of exotic radiopharmaceuticals by modifying the coordination environment which surrounds the metal. These advances have thus led to considerable fascinating research and innovative strategies for treating disseminated human malignancies and various other disorders.

In principle, to achieve desired therapeutic effects, the radionuclide chosen should exhibit the necessary physical, chemical, and biological properties. A wide range of radionuclides based on their physical half-lives, energy of particle emission, type of particle emission and specific activity, etc., are available which can be used for the treatment, control, and palliation of many disseminated diseases. Although a summary is not provided here, subsequent chapters provide detailed information describing the properties of key therapeutic radioisotopes of current interest (see Chaps. 3, 4, 5, and 6). The chronology includes selection of a radionuclide with apparent optimal properties for a specific application with subsequent development of methods for routine production, processing, and purification.

A variety of therapeutic radionuclides are now regularly commercially produced as well as at many nuclear science research centers, utilizing research reactors and accelerators. In view of the tremendous prospects associated with the production of therapeutic radionuclide, a number of excellent review articles have been published (Cutler et al. 2013; Ruth et al. 1989, Volkert et al. 1991; Ehrhardt et al. 1998; Karenlin and Toporov 1998; IAEA 2012; Knapp et al. 1998; Mausner et al. 1988; Qaim 2012; Neves et al. 2002, 2005; Qaim and Coenen 2005; Karelin et al. 2000; Troutner 1987; Yeong et al. 2014; Zhuikov 2014). The rate at which interest and production methods are developing for a variety of radionuclides appears to be increasing. In order to sustain and broaden the scope and promote further

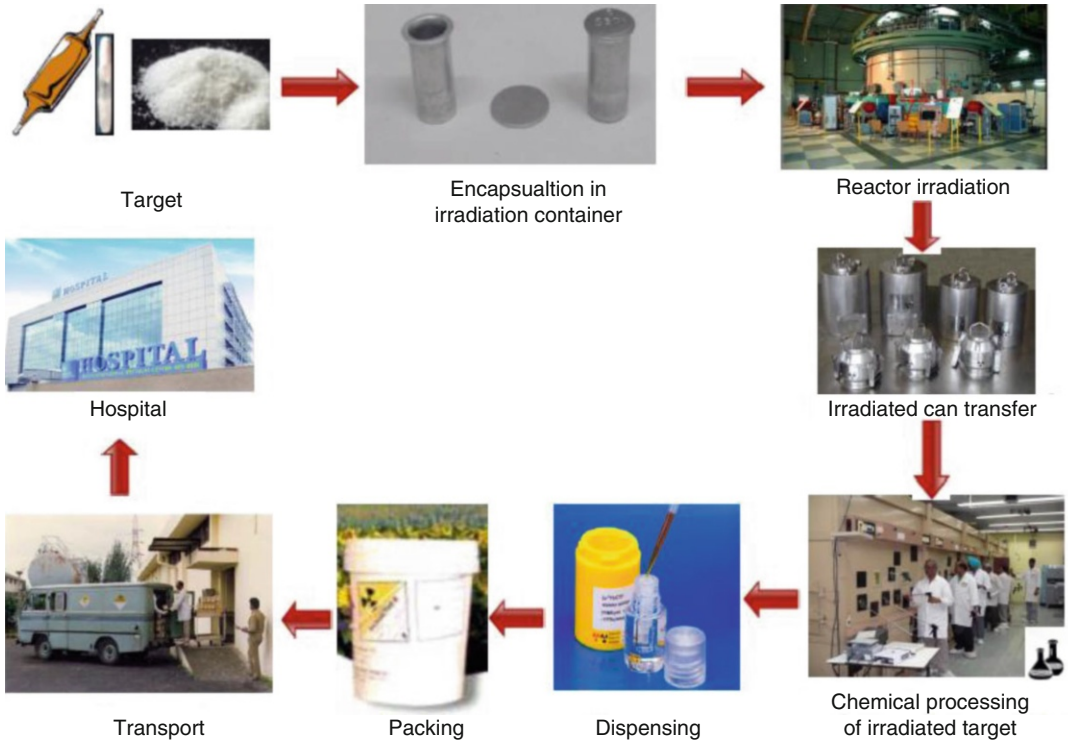

Fig. 2.1 Various steps of the therapeutic radionuclide production cycle

development of radionuclide therapy, radionuclide production and processing strategies need a vision for sustained future growth. Taking account of the progress made in therapeutic radionuclide production, it is timely to provide up-to-date information for current and expected activities in this field. The goal of this chapter is to present a comprehensive overview of production technologies and separation methodologies for several radionuclides of current interest and for those which have considerable potential for future applications in radionuclide therapy.

2.2 Criteria for Selection of Therapeutic Radionuclides

The success of radionuclide therapy in the nuclear medicine arena is dependent on the selection of appropriate radionuclides (Volkert and Hoffman 1999; Srivastava 1996a; Volkert et al. 1991). Although numerous radionuclides have potential applications in radionuclide therapy, only a very few possess favorable nuclear, physical, and biological characteristics which would identify them as practical for clinical use. The ultimate choice is based on several factors described in the following sections.

2.2.1 Particle Emission

Radionuclides which are suitable for radionuclide therapy owing to their high linear energy transfer (LET) to deliver localized cytotoxic ionizing radiation include those which decay by beta-particle emission (β^-), alpha-particle emission (α), and radionuclides that decay by electron capture (EC) and internal conversion (IC), leading to the emission of Auger and Coster–Kronig (C–K) electrons. The choice of a particular radionuclide is strongly dependent on the LET value and tissue range of emissions. Each type of particle emitted by the radionuclide has a different range, effective distance (see Fig. 2.1, Chap. 12), and relative biological effectiveness (RBE). The size of the tumor or the tissue mass to be

Table 2.1 General characteristics of therapeutic radionuclides

Decay	Particles (#)[a]	$E_{(min)}$–$E_{(max)}$	Range	LET (KeV/μm)
α^{++}-particle	He nuclei (1)	5–9 MeV[b]	40–100 μm	~80
β^{-}-particle	Energetic electrons (1)	50–2300 keV[c]	0.05–12 mm	~0.2
EC/IC	Nonenergetic electrons (5–30)	eV–keV[b]	2–500 nm	~4–26

[a]Number of particles emitted per decaying atom
[b]Monoenergetic
[c]Average (>1 % intensity); continuous distribution of energy

treated should be matched with the appropriate effective radiation range. Radionuclides emitting beta particles are effective for large tumors owing to their large millimeter range and cross fire. Since the range of α–particles is confined to 50–100 μm, they are effective for small tumors and micrometastases. Radionuclides that emit Auger and C–K electrons are effective for only single cells when they across the cell membrane. Nuclear targeting to induce irreversible DNA damage is the goal for Auger therapy, although the established efficacy of some radiopharmaceuticals labeled with Auger emitters such as ^{111}In-octreotate, which do not reach the cell nucleus, has not yet been elucidated (Table 2.1).

2.2.2 Tissue Treatment Morphology

The nature of the particle emission required largely depends on the size of the tumor or tissue treatment site, tissue distribution pharmacokinetics of the tracer, and other factors which are important to maximize therapeutic effectiveness.

2.2.3 Radionuclide Half-Life

The radionuclide physical half-life should be well matched with the in vivo biolocalization and clearance properties of the radiolabeled compound. If the half-life is too short, radionuclide depletion resulting from radioactive decay could occur before the radioisotope reaches and has sufficient residence time at the targeted site. Conversely, a long treatment site residence time could cause unnecessary radiation dose to normal tissues. A physical half-life of 1–14 days is often felt to be the optimal half-life range. In light of the explicit need to prepare site-specific radiolabeled compounds of high specific activity to target low-capacity systems such as receptors or antigens, the specific activity of the radionuclide should be high, and for this reason, no-carrier-added (NCA) radionuclides are preferable for these applications.

2.2.4 Radionuclide Decay Products

Ideally, the daughter radionuclide decay product should be stable (nonradioactive) or decay with low-energy emissions and have a short half-life.

2.2.5 Radionuclide Purity

The availability of radionuclides with the highest standard of purity (radionuclidic, radiochemical, elemental, and chemical) is essential for clinical applications for radionuclide therapy. These high purity requirements necessitate the use of nuclear reactions as well as chemical separation and purification schemes that result in products with high radionuclidic purity. To this end, enriched stable target nuclides are most often desirable to preclude ancillary activation of other isotopes in target.

2.2.6 Gamma Emissions

Emission of gamma rays in useful abundance and with optimal energy is usually very advantageous to permit quantification of targeted uptake and biokinetics to allow low-dose imaging, especially during staging, for dosimetry estimates and for monitoring response to therapy. Although gamma radiation

with low abundance is useful for imaging purposes, high abundance as well as high-energy gamma radiation results in poor images and contributes significantly to the whole-body radiation burden of the patient under treatment without significantly increasing the radiation damage to the target tissue.

2.2.7 Radiolabeling Chemistry

The radionuclide chemical properties should permit the opportunity for introduction into a wide range of targeting molecules.

2.2.8 Economic Factors

For projection of widespread and cost-effective dependable availability, the commercial production of the required activity levels of radionuclides with high specific activity and purity is an important aspect for radiopharmaceutical development, and for these reasons, the production of radionuclides is discussed in detail in Chaps. 5, 6, 7, and 8.

Although only a limited number of radionuclides that satisfy the above eight criteria have been found useful in designing therapeutic radiopharmaceuticals, emerging interest is focused on a number of promising radionuclides that may have future importance for radionuclide therapy. The issue of their current and future availability for radionuclide therapy studies warrants continued investigation. A wide range of radionuclides of different radiation emission characteristics, radiobiological effectiveness, and range of action have been used in the treatment of different diseases. The radionuclidic physical and nuclear characteristics must be appropriately matched with the therapeutic application of interest, or the disease under treatment, as discussed below.

2.3 Beta-Particle-Emitting Radionuclides

Radionuclides that decay by β^--particle emission have maximum kinetic energies of 0.3–2.3 MeV with corresponding ranges of ~0.5–12 mm in soft tissue (Fig. 2.1, Chap. 12). Such long penetration range precludes the need for cellular internalization and can be effectively targeted at or near to the cell membrane. The range of β^--particles, as compared to cell diameter, permits β^--particles to traverse several cells (10–1000), a useful therapeutic property that has been termed "crossfire," which ensures sufficient dose delivery to each cell in a large tissue mass. Depending on the size and location of the tissue site for dose delivery, the choice of the β^--emitter may be different. Although β^--particle-emitting radionuclides are effective for medium to large size tumors (Chaps. 9 and 10), for instance, they are less effective in treating smaller metastatic tumors owing to deposition of a larger fraction of the particle energy outside the tumor volume. On the other hand, when the tumor is large in comparison to the range of β^--particle, most of the energy is deposited within the tumor. Various other important clinical applications of β^--emitting radioisotopes are described for bone pain palliation (Chap. 12), nonmelanoma skin cancer therapy (Chap. 13), treatment of arthritis (synovectomy, Chap. 14), and arterial restenosis therapy (Chap. 15).

2.4 Alpha-Particle-Emitting Radionuclides

In contrast, the large positively charged α-particles have soft tissue path lengths (50–80 μm) which are much shorter than β^--particles and characterized by much high linear energy transfer (LET) (~100 keV/μm). The short path length provides a high degree of tumoricidal activity while sparing surrounding normal tissues. Because the high LET of α-particles leads to a high frequency of double-stranded DNA breaks, much of this damage is thus irreparable and accounts for the high kill rate of α-emitting radioisotopes. This property makes them effective in killing cancer cells that are in a hypoxic as well as normoxic tumor cell environments. Their cytotoxic potency is over 100 times greater than that of β^--emitters and, on an atom-by-atom or molecule-by-molecule basis, they are among the most cytotoxic compounds in existence with

fewer than five DNA hits required to kill a cell. The cytotoxicity of α-particles has been reported to be independent of both dose rate and oxygenation status of the cells (Hall 1994). The α-particle emitters are more compatible for use in treatment of tumors with small diameters and where their localization within the tumor is more spatially homogeneous as described in Chaps. 3 and 4.

2.5 Low-Energy Electron Emitters

The majority of low-energy Auger electrons emitted during radioactive decay traverse very short distances in biological tissue generally within a few nm. These short distances result in a highly localized energy deposition in the immediate site of the decaying radionuclide. In order to realize the full potential of Auger electron emitters in radionuclide therapy, it is expected necessary to target the radionuclides target cell nuclear DNA. Most interest in Auger emitters focuses on their potential unique application for cancer therapy, but the clinical use is in its infancy (Chap. 4). The short range of Auger electrons necessitates new and efficient chemical radiopharmaceutical radiolabeling and targeting strategies. However, because of the very short range in order to achieve uniform distribution of absorbed dose, all tumor cells must be targeted. Consequently, targeting approaches more sophisticated than simple radiopharmaceutical cellular internalization are warranted. In contrast to α- and β^--radiation, Auger electron emitters exhibit low cellular toxicity during transit in blood or bone marrow.

The selection of the optimal combination of type and energy of particle emission is largely determined by the size of the lesion or tumor to be treated, delivery site, nature of the tumor (homogeneous or heterogeneous), and required radiation dose. The cytotoxic dose requirement is dependent on the radiation sensitivity of the tissue, type of particle emission (α-particles, β^--particles, or Auger electrons), emitted particle energy, the tumor size, and location. The effectiveness of radionuclide therapy depends largely on the concentration of radionuclide in the tumor for a long duration. Thus, the radiopharmaceutical used for therapy should have fast tumor uptake, high tumor-to-background ratio, prolonged tumor residence time, and fast renal clearance. The aim is thus to reduce the radiation burden to normal nontarget organs, such as the kidney, liver and bone marrow. The major therapeutic radionuclides used in radionuclide therapy for different diseases are summarized and discussed in subsequent Chapters. In order to deliver an effective radiation dose, high target to nontarget ratios must be attained, which includes use of either in ionic species (i.e. thyroid) or by the use of carrier molecules/targeting biomolecules. Therefore, the design and selection of carrier molecules is very important for the development of a clinically useful therapeutic agent. The major therapeutic radiopharmaceuticals based on their chemical forms required for various applications are listed in Table 2.2.

2.6 Radionuclide Production

Production of radionuclides is described in detail in Chap. 5, 6, 7, and 8. The availability of therapeutic radionuclides is the initial major issue in planning the preparation and development of therapeutic radiopharmaceuticals and is also the cornerstone of the success as well as sustainable growth of radionuclide therapy. Production of therapeutic radionuclides involves use of various nuclear reactions conducted by neutron irradiation in a nuclear reactor or from charged particle bombardment in cyclotrons and accelerators. Depending on the production route, either no-carrier-added (NCA) or carrier-added (CA) radionuclides are obtained. The reactor offers large volume for irradiation, simultaneous irradiation of several samples, economy of production, and possibility to produce a wide variety of radioisotopes. The accelerator-produced isotopes relatively constitute a smaller percentage of total use. The accelerators are generally used to produce those isotopes which cannot be produced by reactor or which have unique properties. Because of their in vivo application, strict compliance

Table 2.2 Radiation characteristics of key diagnostic radionuclides with potential applications for Auger electron therapy

Radionuclide	$T_{1/2}$	Auger electrons/decay	IC electrons/decay	Auger energy/decay (keV)	IC energy/decay (keV)	Total energy/decay (keV)	Auger energy in % of total energy/decay	IC energy in % of total energy/decay
^{67}Ga	78 h	4.7	0.3	6.3	28.1	201.6	3.1	13.9
^{99m}Tc	6 h	4.0	1.1	0.9	15.4	142.6	0.6	10.8
^{111}In	67 h	14.7	0.2	6.8	25.9	419.2	1.6	6.2
^{123}I	13 h	14.9	0.2	7.4	20.2	200.4	3.7	10.1
^{125}I	59.4 days	24.9	0.9	12.2	7.2	61.4	19.9	11.8
^{201}Tl	73 h	36.9	1.1	15.3	30.2	138.5	11.0	21.8

IC internal conversion

with the production and quality control protocols of every radionuclide used in therapy has to be ascertained. The chemical, radiochemical, and radionuclidic purity of radionuclides are stringently regulated to meet the stipulated purity standards set forth by various regulatory bodies. Figure 2.1 depicts the various steps of the therapeutic radionuclide production cycle.

2.6.1 Targets for Irradiation

One of the important requirements for radionuclide involves preparation of the targets which are used for either neutron or charged particle activation. In order to maintain a sustainable availability of target material of required purity, advanced procurement is essential in order to ensure the security of the supply for therapeutic radionuclides. Target selection for reactor irradiation is based on number of considerations.

- *Target Material Costs* – Cost-effective availability of target materials is essential to insure affordability of the radionuclide.
- *Chemical Form of Target Material* – The chemical form of the targets must remain stable under the irradiation conditions and should enable easy post irradiation processing and recovery. Usually targets in metallic forms or oxides are preferred.
- *Physical Form of Target Material* – The physical form and geometry of the target material should be compatible for reactor/accelerator irradiation.
- *Target Purity* – The purity of the targets must be ensured to minimize coproduction of unwanted radionuclides.
- *Target Material Recycling* – While the use of enriched target materials constitutes a positive step to augment the radionuclide production yield as well as specific activity, recycling of the enriched target is usually essential, wherever feasible, to minimize radionuclide costs.

In light of the perceived need to maintain the safety of the reactor or accelerator production facility, it is mandatory to calculate the effects of reactivity effects and nuclear heating of the high levels of radioactivity produced in the target. Such practice is useful and in fact mandatory for the safe handling and transport of the irradiated materials as well. For neutron irradiation, the most preferred targets are metals or inorganic salts usually oxide, carbonate, nitrates, sulfates, etc., but not halides. When the sample size for irradiation is large, one must often pay particular attention to self- shielding, such as that encountered during reactor production of ^{188}W (see Chap. 5).

For accelerator production (Chap. 6), considerable efforts are required for target preparation for charged particle irradiations (IAEA 2009; Ruth 2013). The chemical and mechanical designs of the targets are crucial issues owing to the high rate of energy loss of charged particles as they progress through all materials. In general, irradiations are performed in an evacuated chamber, and thus irradiation of liquid and gases targets are more involved but usually surmountable. The target materials used for accelerator production should possess favorable thermal properties such as high melting point or high boiling point and good heat transfer coefficients. It is necessary to provide a cooling system to dissipate the heat energy deposited in the target material during irradiation. Additionally, the target used should have adequate corrosion and radiation resistance. Solid targets in the form of thin foils or deposits on thin backing material of thickness ~0.1–5 mg/cm^2 are generally preferred, but depend, of course on the rate of energy loss of the projectile particles passing through the target material. Various methods have been developed for the preparation of accelerator targets including evaporation, vacuum deposition, electrospraying, electrodeposition, and molecular plating, and a detailed discussion is beyond the scope of this discourse.

In contrast, the common route to obtain ^{223}Ra of current interest for bone pain palliation (Chaps. 8 and 13) is isolation from aging samples of natural uranium (i.e., decay product of ^{235}U). The activity levels of ^{223}Ra that can be obtained through this route are low and therefore inadequate to meet increasing therapeutic demands, requiring the alternative production of ^{223}Ra of

neutron irradiation of ^{226}Ra in a nuclear reactor. This method of production relies upon multiple successive neutron captures on ^{226}Ra requiring the use of high flux reactors, such as the High Flux Isotope Reactor (HFIR) at ORNL (Mirzadeh 1998). This production strategy involves reactor irradiation of ^{226}Ra, followed by chemical isolation of the ^{227}Ac product ($T_{½}$ = 21.8 years), which decays to ^{227}Th ($T_{½}$ = 18.7 days) and then to ^{223}Ra. The separation of pure ^{223}Ra from the irradiated target is a complex process which requires development and use of elaborate radiochemical separation and purification procedures as well as for radioactive waste handling.

2.6.2 Production of Therapeutic Radionuclides

Each radionuclide has unique properties and requires a specific and efficient production process as well as effective methods for isolation and purification from the irradiated target. Production of radionuclides requires a thorough understanding of the relevant nuclear reactions and decay schemes and processing methods rely upon an intimate knowledge of aqueous solution chemistry. A brief overview of production viability of currently used and promising therapeutic radionuclide is provided in this section with the production classified according to the mode of decay.

2.6.3 Auger Electron-Emitting Radionuclides

Interest in the therapeutic use internal radionuclide therapy using Auger electrons has increased over the last several years. Some radionuclides which have established applications in diagnostic nuclear medicine in fact exhibit significant Auger emissions. These include gallium-67 (^{67}Ga), indium-111 (^{111}In), iodine-123 (^{123}I), iodine-125 ^{125}I, technetium-99m (^{99m}Tc), and thallium-210 (^{201}Tl), which have in fact been discussed for specific therapeutic applications. Auger electron-emitting radionuclides have potential for the therapy of small cancers because of their high level of cytotoxicity, low-energy, high LET, and short-range biological effectiveness. In order to realize their therapeutic potential, Auger electron-emitting radionuclides are generally strongly dependent on their close proximity to DNA. Furthermore, many Auger electron emitters also emit γ-radiation, and this property makes Auger-emitting radionuclides an attractive option as therapeutic and diagnostic agents in the molecular imaging and management of tumors. Radiation properties of representative therapeutic radionuclides for Auger electron therapy are depicted in Table 2.2 (Buchegger et al. 2006). The therapeutic use of Auger emitters in both experimental models and in clinical applications is discussed in Chap. 4.

2.6.4 Alpha-Particle-Emitting Radionuclides

In contrast to β^--emitters, the shorter range and higher LET of α-particles allow the delivery of radiation in a highly localized manner and permit for more efficient and selective killing of individual cells of small-volume tumor. Early studies in cell culture have demonstrated that human cancer cells can be killed even after being hit by only a few alpha particles (Akabani et al. 2006) and that unlike other types of radiation, where oxygen is necessary for free radicals to be generated, efficient cancer cell elimination can be achieved even in an hypoxic environment. Although the conceptual advantages of alpha particles have been realized for some time, routine clinical use of these promising targeted radiotherapeutics has only just recently been accomplished with the introduction of ^{223}Ra (Xolfigo®) for treatment of bone pain from prostate cancer refractory to hormone therapy (Chap. 11). Other discussion of other α-emitting radionuclides is confined in Chap. 3 to those which exhibit potential for therapeutic applications and for which preliminary investigations have been reported in humans or animal models. Currently, interest in potential clinical application of α-particles for therapy has primarily focused on actinium-225 (^{225}Ac), astatine-211 (^{211}At), bismuth-212 (^{212}Bi), bismuth-213 (^{213}Bi),

Table 2.3 Characteristics of α-emitting radionuclides considered for radionuclide therapy

Radionuclide	E_{av} (MeV)	Particle(s) emitted	Half-life
^{211}At	6.79	1α	7.2 h
^{212}Bi	6.0	1α, 1β	60.6 min
^{213}Bi	8.32	1α, 2β	46 min
^{223}Ra	5.64	4α, 2β	11.43 days
^{225}Ac	6.83	4α, 2β	10 days

and radium-223 (^{223}Ra) (Allen 2008; Brechbiel 2007; Huclier-Markai et al. 2012; Lindegren and Frost 2011; Kim and Brechbiel 2012; McDevitt et al. 1998; Mulford et al. 2005; Nilsson et al. 2005; Pohlman et al. 2006; Vaidyanathan and Zalutsky 2011) (Table 2.3).

References

Akabani G, Carlin S, Welsh P, Zalutsky MR. In vitro cytotoxicity of 211At-labeled trastuzumab in human breast cancer cell lines: effect of specific activity and HER2 receptor heterogeneity on survival fraction. Nucl Med Biol. 2006;33(3):333–47.

Allen BJ. Clinical trials of targeted alpha therapy for cancer. Rev Rec Clin Trials. 2008;3:185–91.

Brechbiel MW. Targeted alpha-therapy: past, present, future? Dalton Trans. 2007;43:4918–28.

Britton KE. Towards the goal of cancer-specific imaging and therapy. Nucl Med Commun. 1997;18(11): 992–1007.

Buchegger F, Perillo-Adamer F, Dupertuis YM, et al. Auger radiation targeted into DNA: a therapy perspective. Eur J Nucl Med Mol Imaging. 2006;33(11):1352–63.

Chatal J-F, Hoefnagel CA. Radionuclide therapy. Lancet. 1999;354:931–5.

Cuaron JJ, Hirsch JA, Medich DC, et al. A proposed methodology to select radioisotopes for use in radionuclide therapy. AJNR Am J Neuroradiol. 2009;10: 1824–9.

Cutler CS, Hennkens HM, Sisay N, et al. Radiometals for combined imaging and therapy. Chem Rev. 2013;113: 858–83.

Das T, Pillai MRA. Options to meet the future global demand of radionuclides for radionuclide therapy. Nucl Med Biol. 2013;40(1):23–32.

Ehrhardt GJ, Ketring AR, Ayers LM. Reactor-produced radionuclides at the University of Missouri Research Reactor. Appl Radiat Isot. 1998;49:295–7.

Ercan MT, Caglar M. Therapeutic radiopharmaceuticals. Curr Pharm Des. 2000;6:1085–121.

Hall EJ. Radiobiology for the radiologist. 4th ed. Philadelphia: JB Lippincott Company; 1994.

Heeg MJ, Jurisson S. The role of inorganic chemistry in the development of radiometal agents for cancer therapy. Acc Chem Res. 1999;32:1053–60.

Hoefnagel CA. Radionuclide therapy revisited. Eur J Nucl Med. 1991;18:408.

Huclier-Markai S, Alliot C, Varmenot N, et al. Alpha-emitters for immuno-therapy: a review of recent developments from chemistry to clinics. Curr Top Med Chem. 2012;12(23):2642–54.

International Atomic Energy Agency (IAEA). Cyclotron produced radionuclides: physical characteristics and production methods. Technical report series 468. Vienna: IAEA; 2009.

International Atomic Energy Agency (IAEA). Nuclear data for production of therapeutic radionuclides. Technical report series 473. Vienna: IAEA; 2012.

Joensuu H, Tenhunen M. Physical and biological targeting of radiotherapy. Acta Oncol Suppl. 1999;13:75–83.

Karelin YA, Efimov VN, Filimonov VT, et al. Radionuclide production using a fast flux reactor. Appl Radiat Isot. 2000;53:825–7.

Karenlin YA, Toporov YG. RIAR reactor produced radionuclides. Appl Radiat Isot. 1998;49:299–304.

Kim YS, Brechbiel M. An overview of targeted alpha therapy. Tumour Biol. 2012;33(3):573–90.

Knapp Jr FF (R), Mirzadeh S, Beets AL. Reactor-produced radioisotopes from ORNL for bone pain palliation. Appl Radiat Isot. 1998;49:309–15.

Lindegren S, Frost SH. Pretargeted radioimmunotherapy with α-particle emitting radionuclides. Curr Radiopharm. 2011;4(3):248–60.

Mausner LF, Srivastava SC. Selection of radionuclides for radioimmuno- therapy. Med Phys. 1993;20:503–9.

Mausner LF, Kolsky KL, Joshi V, et al. Radionuclide development at BNL for nuclear medicine therapy. Appl Radiat Isot. 1988;49:285–94.

McDevitt MR, Sgouros G, Finn RD, et al. Radioimmunotherapy with alpha-emitting nuclides. Eur J Nucl Med. 1998;25:1341–51.

McDougall IR. Systemic radiation therapy with unsealed radionuclides. Semin Radiat Oncol. 2000;10(2):94–102.

McEwan AJB. Unsealed source therapy of painful bone metastases: an update. Semin Nucl Med. 1997;27: 165–82.

Mirzadeh S. Generator-produced alpha-emitters. Appl Radiat Isot. 1998;49:345–9.

Mulford DA, Scheinberg DA, Jurcic JG. The promise of targeted {alpha}-particle therapy. J Nucl Med. 2005; 46:199S–204.

Neves M, Kling A, Lambrecht RM. Radionuclide production for therapeutic radiopharmaceuticals. Appl Radiat Isot. 2002;57:657–64.

Neves M, Kling A, Oliveira A. Radionuclides used for therapy and suggestion for new candidates. J Radioanal Nucl Chem. 2005;266(3):377–84.

Nilsson S, Larsen RH, Fossa SD et al. First clinical experience with α-emitting radium-223 in the treatment of skeletal metastases, Clin Cancer Res 2005;11: 4451–59

O'Donoghue JA, Bardibs M, Wheldon TE. Relationships between tumor size and curability for uniformly targeted therapy with beta-emitting radionuclides. J Nucl Med. 1995;36:1902–9.

Pohlman B, Sweetenham J, Macklis RM. Review of clinical radioimmunotherapy. Expert Rev Antican. Ther. 2006;6(3):445–61.

Qaim SM. The present and future of medical radionuclide production. Radiochim Acta. 2012;100:635–51.

Qaim SM, Coenen HH. Produktion pharmazeutisch relevanter. Radionuk Pharm Unser Zeit. 2005;34:460–6 (German).

Ruth TJ. Accelerator production of medical radionuclides: a review. Nucl Phys News. 2013;23:30–3.

Ruth TJ, Pate BD, Robertson D, et al. Radionuclide production for biosciences. Nucl Med Biol. 1989;16:323–36.

Serafini AN. Current status of systemic intravenous radiopharmaceuticals for the treatment of painful metastatic bone diseases. Int J Radiat Oncol Biol Phys. 1994; 30:1187–94.

Spencer RP, Seevers RH, Friedman AM, editors. Radionuclides in therapy. Boca Raton: CRC Press; 1987.

Srivastava SC. Therapeutic radionuclides: making the right choice. In: Mather SJ, editor. Current directions in radiopharmaceutical research and development. Dordrecht: Kluwer Academic Publishers; 1996a. p. 63–79.

Srivastava SC. Criteria for the selection of radionuclides for targeting nuclear antigens for cancer radioimmunotherapy. Cancer Biother Radiopharm. 1996b;11:43–50.

Srivastava SC, Dadachova E. Recent advances in radionuclide therapy. Semin Nucl Med. 2001;31(4):330–41.

Stanciu AE. Radionuclide targeted therapy of cancer. Rev Roum Chim. 2012;57(1):5–13.

Stöcklin G, Qaim SM, Rösch F. The impact of radioactivity on medicine. Radiochim Acta. 1995;70/71:249.

Tolmachev V, Carlsson J, Lundqvist H. A limiting factor for the progress of radionuclide-based cancer diagnostics and therapy – availability of suitable radionuclides. Acta Oncol. 2004;43(3):264–7.

Troutner DE. Chemical and physical properties of radionuclides. Int J Radiat Appl Instrum B Nucl Med Biol. 1987;14(3):171–6.

Unak P, Enginar H, Biber FZ, Lambrecht FY, Aslani MA, Ozkilic H. A correlative study between 99mTc-EST-CPTA and 99mTc-MIBI in rats. Appl Radiat Isot. 2002;57(5):733-42.

Vaidyanathan G, Zalutsky MR. Applications of ^{211}At and ^{223}Ra in targeted alpha-particle radiotherapy. Curr Radiopharm. 2011;4:283–94.

Volkert WA, Hoffman TJ. Therapeutic radiopharmaceuticals. Chem Rev. 1999;99:2269–92.

Volkert WA, Goeckeler WF, Ehrhardt GJ, et al. Therapeutic radionuclides: production and decay property considerations. J NucI Med. 1991;32:174–85.

Yeong C-H, Cheng M-H, Ng K-H. Therapeutic radionuclides in nuclear medicine: current and future prospects. J Zhejiang Univ Sci B. 2014;15(10):845–63.

Zhuikov BL. Production of medical radionuclides in Russia: status and future—a review. Appl Radiat Isot. 2014;84:48–56.