Therapeutic Radionuclides: Production and Decay Property Considerations

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Interest in employing unsealed radiotherapeutic agents for treatment of cancer has increased in the past decade, primarily due to the emergence of sophisticated molecular carriers [e.g., monoclonal antibodies (MAbs)] that may provide vehicles for selective deposition of radioactivity in the vicinity of cancer cells. In order to develop effective radiopharmaceuticals for therapy, it is essential to carefully consider the choices of appropriate radionuclides in conjunction with the in vivo localization and pharmacokinetic properties of the radiotracer (*1–5*). Each radiotherapeutic agent will, in most cases, be used for a specific application that requires balancing in vivo targeting and clearance characteristics of the carrier molecules with decay properties of the attached radionuclide.

Selection of an appropriate radionuclide for a particular therapeutic application is directly related to the biolocalization of carrier molecules. Many physiologic and biochemical factors influence the in vivo localization and clearance of tracers which in turn dictate the radiation dosimetry and biologic responses of target cells relative to non-target tissues. This paper discusses the rationales for considering different production and decay properties of radionuclides in formulation of new therapeutic radiopharmaceuticals. No attempt will be made to identify all radionuclides with therapeutic potential since many have been proposed previously (*1–9*). Most of the radionuclides highlighted in this report have relatively short half-lives and, if gamma-rays are emitted, their energies are ≤300 keV and are emitted in low abundance (see Tables 3–5).

MODES OF DECAY

Radionuclides that decay by the following three general categories of decay have been studied for therapeutic potential: beta-particle emitters, alpha-particle emitters, and Auger electron- and Coster-Kronig electron-emitters following electron capture. Each type of particle emitted has a different range, effective distance, and relative biologic effectiveness (RBE). The type of particle emission required for particular applications will depend on the microdistribution of the source of ionizing radiation relative to the radiosensitive target sites (*1,2,7,10–13*) (viz., heterogeneous versus homogeneous deposition in tumors or localization on cell surfaces versus internalization of radionuclides to the cell nuclei or cytoplasm).

Gamma-ray emission may or may not accompany these decay processes. Gamma radiation will contribute little to therapeutic effectiveness and will augment irradiation of non-target tissues. However, if the gamma-ray energy is in the diagnostically useful range, it may be useful for scintigraphic imaging and for determinations of in vivo localization as a function of time.

Alpha-Particle Emitters

Radionuclides that emit alpha particles are attractive for some therapeutic applications (*13–19*). Alpha particles are high-energy helium nuclei that produce high densities of ionization along their linear tracks. These monoenergetic particles deposit their energy over short ranges [e.g., 40–80 μm for 5–8 MeV alpha particles (*10, 14,17*)]. The high LET of alpha radiation limits the ability of cells to repair damage to DNA and is effective in killing cells in hypoxic conditions (*10,18*). The high RBE of this type of radiation results in inactivation of cells with few alpha particles in contrast to gamma radiation or beta particles (*20*). A disadvantage of alpha emitters is that they require binding of the carrier to most cancer cells in a tumor or to their near neighbors for irradiation of all cells (*1*).

Relatively few alpha-emitting radionuclides have been considered for radionuclide therapy (RNT). Bismuth-212 (^{212}Bi) and astatine-211 (^{211}At) (Table 1) are the two nuclides that have been most extensively studied (*10,13–19*). Bismuth-212 is conveniently available in large quantities via a radium-224 generator system (*21*), while ^{211}At is accelerator produced (*22,23*). Be-

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TABLE 1
Alpha-Particle Emitting Radionuclides with Therapeutic Potential

Radionuclide	Half-life	Mean energy alpha particles
^{212}Bi	60.5 min	7.8 MeV
^{211}At	7.2 hr	6.76 MeV
^{255}Fm	20.1 hr	7.0 MeV

cause of the short half-life of ^{211}At, it must be produced in an accelerator near the site of use. The ranges for the alpha particles emitted by both radionuclides are between 40–80 μm. Both a direct 5.87-MeV alpha particle and a 7.45-MeV alpha particle from the polonium-211 (^{211}Po) daughter result from ^{211}At decay. Similarly, a direct 6.0-MeV alpha particle and an 8.9-MeV alpha particle from the ^{212}Po daughter result from ^{212}Bi decay (*6,21*). Beta-particle emissions also occur during these decay processes. The in vitro and in vivo radiation biology experiments performed with these radionuclides showed cytotoxicity to be approximately 10–20 times more biologically effective than low-LET radiations, survival curves to be monoexponential, and cell killing to be dose-rate independent (*17,18*). Despite the high level of in vitro and in vivo cytotoxicity, the 1-hr and 7.2-hr half-lives of ^{212}Bi and ^{211}At impose restrictions on their clinical utility. Astatine-211- and ^{212}Bi-labeled compounds or MAbs are best suited for treatment of rapidly accessible cancer cells or leukemia (*14,16–18*) or for specific target structures in body cavities, such as the peritoneum (*15*). Perhaps the 20.1-hr half-life of fermium-255 (^{255}Fm) (*24*) may allow more flexibility in design of the carrier, if sufficient quantities can be produced at reasonable costs.

Attachment of ^{212}Bi to MAbs requires the use of bifunctional chelating agents (*14,17,18*). In contrast, ^{211}At is a radiohalogen which should have similar chemistry to iodine and can be covalently linked to a carbon atom. Astatine-211 conjugates with MAbs are currently being evaluated as potential therapeutic agents (*25–28*).

Since alpha particles have a high RBE, stringent precautions for safe handling and for administration of RNT agents labeled with alpha emitters to patients will be required. For example, the allowable level of radioactive contamination on package surfaces for these nuclides is a factor of 10 lower than that for beta-emitting radionuclides (10 CFR 0–199, US NRC Rules & Regulations, Vol. III, Parts 70–75). Special facilities or equipment should be available to prevent and monitor laboratory contamination or airborn release of alpha-emitting radionuclides during storage or dispensing. Because of these and other regulatory concerns, extending applications of promising RNT agents labeled with alpha-particle emitters into the clinical setting may be significantly impeded.

Auger-Electron Emitters

Incorporation of Auger-electron emitters within the nucleus of cells produces high radiotoxicity (*1,9,29–31*). This is a result of the deposition of a concentrated amount of energy, emitted in the form of a shower of Auger and Coster-Kronig electrons with energies ranging from a few to several hundred electron volts (*32, 33*), into an extremely small volume within the nuclear DNA (*29*). This type of radiation exposure produces decreasing survival curves with no shoulder at low doses that are relatively independent of oxygen effects (*1,29, 31*). In order to realize this high LET-like response, the Auger emitters must be incorporated into the nucleus of target cells since much less cytotoxicity is produced when these radionuclides are present in the cytoplasm or on the surface of target cells (*1,34*).

RNT agents based on Auger-emitting radionuclides will require incorporation of the therapeutic radiopharmaceutical into the entire tumor cell population. Thus, methods of selective guidance to target cells and subsequent introduction of these radionuclides with good selectivity into the nucleus must be found. One promising approach employs radioactive DNA intercalators, which were shown to be highly efficient in cell killing (*35*). Successful targeting of these types of compounds could produce high therapeutic ratios (*1*). Some of the numerous Auger-emitting radionuclides available (*1,4*) are summarized in Table 2. This wide spectrum of radioisotopes with different chemical properties provides opportunities and challenges in designing RNT agents with the necessary biolocalization properties.

Beta-Particle Emitters

Beta-emitting radionuclides are exclusively used in clinical RNT. As a result of their widespread availability, a large variety of beta emitters have been studied. Negatively charged electrons are emitted as beta parti-

TABLE 2
Selected Radionuclides that Decay by Electron Capture and Emit Low-Energy Electrons*

Radionuclide	Half-life	Source
^{103m}Rh	58 min	^{103}Ru/^{103m}Rh Gen
^{165}Er	10.3 hr	^{165}Ho(p,n)
^{123}I	13.3 hr	^{127}I(p,5n,β^-)
		^{124}Xe(p,pn,EC)
^{119}Sb	1.6 d	^{121}Sb(p,3n,EC)
^{197}Hg	2.7 d	^{197}Au(p,n)
^{97}Ru	2.9 d	^{96}Ru(n,γ)
^{201}Tl	3.1 d	^{203}Tl(p,3n,β^+)
^{67}Ga	3.2 d	^{68}Zn (p,2n)
^{193m}Pt	4.3 d	^{192}Os(α,3n)
		^{192}Pt (n,γ)
^{125}I	60 d	^{124}Xe (n,γ,EC)

* Low-energy electrons consist mainly of Auger and Coster-Kronig electrons.

cles from the nucleus in a continuum of energies (and ranges) up to a maximum value. The average beta-particle energy is approximately one-third of its maximum energy. The range of these high-energy particles is, generally, much greater than alpha particles and the "sparse" ionization density along their tracks accounts for their low LET. The maximum and average range of beta particles can be calculated by the method of Cole et al. (*36*).

PRODUCTION

The primary source for beta-emitting radionuclides are nuclear reactors that use primarily the (n,γ) reaction to produce neutron-rich isotopes; however, some are produced in charged-particle accelerators (*4–8,37*). Most radionuclides produced in reactors have low-specific activities, but high-specific activity is required for some applications (e.g., MAb labeling for radioimmunotherapy (RIT)). High-specific activities of reactor-produced isotopes can be achieved using generator systems, by indirect production schemes and, in some cases, by direct (n,γ)-activation. It is essential that only nuclear reactions and separation schemes be used that result in products with high radionuclidic purities. To this end, enriched stable target nuclides are most often used to eliminate ancillary activation of other stable isotopes in target samples that produce radioisotopes with decay properties (e.g., excessively long-half lives) that adversely affect patient dosimetry.

Direct (n,γ) Activation

Current or projected availability and cost should be an important factor when designing new radiotherapeutic agents. Production of many beta emitters is achieved by direct neutron activation (Table 3) where the quantity of activity produced at half saturation is related to the cross-section, σ (barns); the flux (neutrons/cm^2-sec); ϕ, the number of moles (n); and percent isotopic abundance [A] of the target atoms by the following equation (*6*):

$$\text{Activity (Ci)} = 8\text{nA}\sigma\Phi\cdot\text{x}10^{-14}.$$

Assuming highly enriched targets are available for thermal n-bombardment at a constant ϕ, the specific activities and the quantities that can be obtained are directly dependent on σ. For example, with a 220-barn cross-section for samarium-152 (^{152}Sm), approximately 10 Ci (370 GBq) of ^{153}Sm can be produced by irradiation of 10 mg of >99% enriched $^{152}Sm_2O_3$ at $\phi = 10^{14}$n/cm^2-sec for 46 hr (i.e., half-saturation). [Samarium-152 also has a epithermal resonance integral cross-section of 3,168 barns (*39*) that will increase the production yields further, particularly in reactors with significant epithermal n-fluxes. This consideration is also important for some other (n,γ)-activatable isotopes.] It is clear from this example that abundant quantities of radionuclides can be produced in several domestic reactors at this relatively modest flux with enriched targets having σ's of approximately 10 barns or higher. Most radioactive isotopes produced by (n,γ) reactions in most reactors may not be useful in formulating radioimmunotherapy (RIT) agents because of their low specific activity.

Some promising forms of RNT make use of (n,γ)-produced radioisotopes that do not require high-specific activity. Most of the RNT agents found to be effective for treatment of bone cancers in patients [e.g., phosphorus-32-orthophosphate (*3*), strontium-89-ionic (*40*,

TABLE 3
Beta-Emitting Radionuclides with Half-Lives Less Than 15 Days* Produced in Nuclear Reactors by Direct Neutron (n,γ) Activation of Stable Targets

Radionuclide	Half-life	E_β(max) MeV	E_γ (keV)†	Target nuclide	Cross-section‡ (barns)
^{165}Dy	2.3 hr	1.34	95 (4%)	^{164}Dy	1697
^{109}Pd	13.5 hr	1.03	88 (3.6%)	^{108}Pd	8.8
^{188}Re	17 hr	2.11	155 (15%)	^{187}Re	73.2
^{166}Ho	1.1 d	1.6	81 (6.33%)	^{165}Ho	58
^{153}Sm	1.95 d	0.80	103 (29%)	^{152}Sm	220
^{90}Y	2.7 d	2.27	—	^{89}Y	1.3
^{186}Re	3.7 d	1.07	137 (9%)	^{185}Re	106
^{177}Lu	6.7 d	0.50	113 (6.4%) 208 (11%)	^{176}Lu	2100
^{169}Er	9.6 d	0.34§	—	^{168}Er	2.0
^{32}P	14.3 d	1.71	—	^{31}P	0.18
^{89}Sr	53 d	1.46	—	^{88}Sr	0.006

* Strontium-89 is included since it is used for radiotherapy despite its longer half-life.
† Only gamma-rays with >1% yields are listed (*113,114*).
‡ Cross-sections (σ) for thermal neutrons only (*113*).
§ Energy of the most abundant conversion electron.

41), samarium-153-EDTMP (*42–47*), and rhenium-186-HEDP (*48–50*)] employ low-specific activity beta emitters. Samarium-153-EDTMP and ^{186}Re-HEDP formulations include concentrations of ligand (i.e., EDTMP and HEDP, respectively) that exceed the metal concentration by more than an order of magnitude (*42–44,50*). These types of radiolabeled chelates [including ^{117m}Sn-DTPA (*51*)] exhibit high selective uptake in bone lesions and rapid clearance from nonosseous tissues, demonstrating the feasibility of using metallic radionuclides complexed to appropriate ligands for treatment of primary bone cancer (*52*) and skeletal metastases (*15,50,53–54*).

Radiolabeled particles or microspheres for RNT do not require high-specific activities of the incorporated radionuclide. In these preparations, each particle contains large quantities of the stable isotope(s) precursor of the radionuclide. For example, yttrium-90- (^{90}Y) labeled microspheres have been used for intraarterial RNT of liver tumors (*58–60*). One type of preparation designed to minimize washout of ^{90}Y from the particles and provide for easy production involves the use of glass microspheres doped with stable ^{89}Y (*59*). After (n,γ)-irradiation of these preformed spheres in reactors that activate the trapped ^{89}Y to ^{90}Y, they are ready with no further chemical processing for injection into patients (*59,60*). Despite the 1.3-barn cross-section of ^{89}Y (Table 3), ample quantities of ^{90}Y-labeled glass microspheres can be readily produced for widespread utilization. Preformed microspheres doped with other activatable nuclides [e.g., viz. ^{31}P, ^{152}Sm, ^{165}Ho (holmium), ^{185}Re, ^{164}Dy (dysprosium)] have also been evaluated as intraarterial or intracavitary RNT agents in the (n,γ)-activated forms (*61*). This approach is being extended to biodegradable microspheres of polylactic acid containing activatable dopings of enriched target atoms (*62*).

A few radionuclides produced by direct (n,γ) activation of a stable precursor with high σ and in reactors with high flux, however, will have specific activities that are sufficiently high for preparing radiolabeled MAbs. For example, 1 mg of 95% enriched lutetium-176 (^{176}Lu) bombarded in a reactor with a flux of 2×10^{14} neutrons/cm^2-sec for 6.7 days produces approximately 18.4 Ci (680 GBq) of ^{177}Lu. This translates to a specific activity of 0.17 atoms of ^{177}Lu per atom of all lutetium nuclides, which is similar to the iodine-131 specific activities obtained commercially for routine use in RIT applications.

Production of ^{153}Sm with specific activities $\cong$0.1 are also achievable, but only in the higher flux reactors (i.e., at $\Phi = 2 \times 10^{15}$ n/cm^2-sec for 4 d irradiations, the ^{153}Sm specific activity is approximately 0.08). Assuming conjugation of an average of one samarium atom per MAb molecule, a ^{153}Sm specific activity of 0.08 would provide approximately 450 mCi (33.3 GBq) ^{153}Sm activity in a 10-mg MAb preparation. This should be sufficient for RIT in numerous clinical protocols requiring administration of $\leq$10 mg antibody (*63*). Thus, direct (n,γ) activation of enriched target molecules with $\sigma \gtrsim 100$ barns or more produced in reactors with high thermal neutron fluxes, should provide specific activities appropriate for many RIT applications. Clinical trials with ^{186}Re-MAbs prepared by direct (n,γ) activation of ^{185}Re are currently underway (*64*).

Indirect (n,γ) Production

Indirect reactions can be used for reactor-produced radionuclides at "no-carrier added" (NCA) levels and high total activities. For example, Grazman and Troutner (*65*) isolated NCA rhodium-105 (^{105}Rh) from ruthenium-105 (^{105}Ru) (produced by neutron activation of ^{104}Ru) for use in protein or MAb labeling (*66–68*). Interestingly, large quantities of NCA ^{105}Rh could also be produced inexpensively as a fission product (*6*), if required. Table 4 is a noninclusive listing of several other radionuclides considered to have therapeutic potential that can be produced by indirect neutron activation (*6–9,12,69–71*). The cross-sections of the (n,γ) reactions need not be high since large quantities of activities can be produced by irradiating gram quantities of target nuclei, followed by chemical purification of the desired radionuclide from the parent element. The cross-section for (n,p) production of copper-67 (^{67}Cu) (Table 4) is far too small for reactor production of sufficient quantities for widespread therapeutic applications; however, small quantities of NCA ^{67}Cu can be made for research purposes by this route (*70*).

Generators

NCA beta-emitting radionuclides can also be obtained from generator systems. The shorter-lived radionuclides are obtained from a longer-lived parent when efficient separation of the daughter from parent can be accomplished. A ^{90}Sr/^{90}Y generator system is being used to provide NCA ^{90}Y for RIT (*72–74*). The chelation properties of $^{90}Y^{+3}$ make it attractive for MAb labeling since it forms strong complexes with the same kinds of chelating agents as $^{111}In^{+3}$ (*74,75*). $^{90}Y^{+3}$ will react with MAb conjugates to chelate with the attached ligand(s) [e.g., isothiocyanato-benzyl-DTPA (*74–78*)] with minimal nonspecific binding with the MAbs. Since most of these labeling procedures involve low MAb concentrations with a single conjugated ligand, it is imperative that the $^{90}Y^{+3}$ eluted from the generator not only have high-specific activity, but also be free from contamination from other trace metals that may compete with $^{90}Y^{+3}$ for forming chelates with the limited number of chelating agents in the labeling solutions. This is also a necessary condition for labeling conjugated MAbs with other metallic radionuclides. The use of "preformed" radiometal chelates (*66,78,79*) provides an alternative method for insuring uniformity in chelation chemistry

TABLE 4
Selected Beta-Emitting Radionuclides with Half-Lives Less Than 15 Days Produced in High-Specific Activities

Radionuclide	Half-life	E_β(max) (MeV)	E_γ (keV)†	Source	Cross-section (barns)*
			Nuclear Reactors*		
^{105}Rh	1.4 d	0.57	319 (19%) 306 (5%)	^{104}Ru (n,γ,β) FP‡	0.5
^{77}As	1.6 d	0.68	239 (1.6%)	^{76}Ge (n,γ,β)	0.15
^{149}Pm	2.2 d	1.07	286 (3%)	^{148}Nd (n,γ,β)	1.5
^{67}Cu	2.4 d	0.57	184 (48%) 92 (23%)	^{67}Zn (n,p)	0.0012§
^{199}Au	3.2 d	0.46	158 (37%) 208 (8%)	^{198}Pt (n,γ,β^-)	3.6
^{177}Lu	6.7 d	0.50	208 (11%) 113 (6%)	^{176}Yb (n,γ,β^-)	3.1
^{111}Ag	7.5 d	1.05	342 (6%)	^{110}Pd (n,γ,β^-)	0.36
^{131}I	8 d	0.81	364 (81%) 637 (7%)	^{130}Te (n,γ,β^-) FP‡	0.3
			Accelerators		
^{77}As	1.6 d	0.68	239 (1.6%)	^{80}Se (p,α)	
^{67}Cu	2.4 d	0.57	184 (48%) 92 (23%)	^{68}Zn (p,2p)	
^{47}Sc	3.4 d	0.60	160 (73%)	^{48}Ti (p,2p)	
^{193m}Pt	4.3 d	0.13	—	^{192}Os (α,3n)§	
^{117m}Sn	14 d	0.13, 0.16¶	158 (87%)	^{121}Sb (p,2p,3n)	

* Produced in reactors by indirect n-activation pathways.
† References *113* and *114*.
‡ Produced as a fission product (FP).
§ Reference *70*.
¶ Radionuclides emit conversion electrons; values are major CE energies.

and for reducing the interference of trace metal impurities during RIT labeling procedures.

Other generators for beta-emitting radionuclides also hold potential for RNT applications (Table 5). The tungsten/rhenium (^{188}W/^{188}Re) generators provide some flexibility in designing RNT agents. The ^{188}W parent is produced in low-specific activities by a double-neutron capture reaction. However, the quantities of ^{188}W produced could be markedly increased using reactors with a higher n-flux (ϕ) than currently employed (*80,81*), since the yield of ^{188}W increases proportionately with ϕ^2. Nevertheless, the requirement for double-neutron capture inherently limits the total activity of ^{188}W that can be absorbed on an alumina column as tungstate (*81*). Gel-type generators, in which the tungstate target is processed to form the column mass, permits loading of gram quantities of tungsten into a compact column (*80*). The use of this approach increases the number of reactors worldwide that could produce ^{188}W for use in generators. Rhenium-188, like ^{90}Y, emits a high-energy beta particle (E_{max} = 2.1 MeV) that should be suitable for treatment of diseases requiring long ranges that penetrate many cell diameters (*2, 7,11*). Rhenium-188 agents would be limited to condi-

TABLE 5
Generator Systems for Short-Lived Beta-Particle Emitting Radionuclides

Radionuclide	Half-life	E_β (max)	E_γ (keV)	Parent	Parent ($t_{½}$)
^{115m}In	4.5 hr	0.84 (5%) 0.30 (49%)*	336 (46%)	^{115}Cd	2.2 d
^{188}Re	17 hr	2.1	155 (15%)	^{188}W	69.4 d
^{90}Y	64 hr	2.27	—	^{90}Sr	28.6 yr
^{212}Bi	1 hr	NA†	727 (12%)	^{224}Ra/^{212}Pb	3.7 d

* Energy of most abundant conversion electron.
† Bismuth-212 is used as an alpha-particle emitter (see Table 1), but also emits some high-energy beta particles.

tions requiring relatively rapid localization of the agent in target areas due to its short half-life (17 hr), however, the labeling and chelation chemistry developed for ^{186}Re (*49,82*) and often for ^{99m}Tc (*78*) can be used for ^{188}Re.

Another generator with potential for RNT is the cadmium/indium (^{115}Cd/^{115m}In) (*83*) system, as the 4.5 hr ^{115m}In emits a 300-keV conversion electron with a range of approximately 1 mm in soft tissue (Table 4) which is similar to the particulate emissions from erbium-169 (Table 3). This short range and half-life of ^{115m}In provides advantages for some applications [e.g., radiation synovectomy of small joints (*84*)], however, emission of the 336-keV gamma ray (46% abundant) is a distinct disadvantage.

Accelerators

Several beta-emitting radionuclides that hold potential for RNT can only be produced in accelerators (Table 4). These radionuclides are generally available as NCA products and most require bombardment of enriched stable target nuclei with high energy charged particles (*8,33*). For example, ^{67}Cu is considered desirable for RIT and bifunctional chelating agents have been developed for its conjugation to MAbs (*70,85,86*). Copper-67 emits a medium-energy beta particle (i.e., E_{max} = 0.57 MeV), has a 2.4-day half-life and emits imageable gamma rays (Table 4). Unfortunately, this and other radionuclides requiring high energy/high current production accelerators are not available on a reliable or regular basis in this country due to the lack of a dedicated facility with year-round operation (*87–89*). The HERAC report (*89*) recommended that a national accelerator be built in the U.S. to produce sufficient quantities of these tracers. It is important that a wide range of these radionuclides be available on a regular basis to broaden the scope and promote further development of RNT (*87–89*).

The availability of therapeutic radionuclides with high radionuclidic purity in chemical forms amenable for use in formulating current and new RNT agents is an important factor often overlooked. Most research or clinical laboratories do not usually have the facilities for readily converting short-lived radionuclides in the chemical forms received from suppliers to radiochemically pure species that are suitable for labeling MAb or other compounds. For example, production of ^{105}Rh with high radiochemical radionuclidic purity involves multi-step chemical preparations and purification that prohibit many researchers from using this radionuclide. Similar purification requirements are necessary for other reactor- and accelerator-produced radionuclides (*4–6,8,21,33*). As different radiolabeled chelates or compounds are developed, it is essential that improved chemical processes be developed. These reactions must be carried out at production sites with proper facilities for remote handling of highly radioactive materials so that short-lived radiochemicals in readily usable forms can be supplied to many different research or industrial laboratories.

HALF-LIFE

The physical half-life of the radionuclide is an important consideration in the design of RIT or other RNT agents in that the half-life could have a major influence on the therapeutic ratio of these agents (*1–3, 90*). In order to maximize this ratio, the rate of decay of the radionuclide must be balanced with the rate of biolocalization of the MAb in target tissue along with clearance of radioactivity from normal tissues. If the agent localizes slowly in the tumor but the half-life of the radionuclide is short, most of the radionuclide will have decayed by the time it reaches its target, thus delivering the majority of its dose to non-target organs (*2*). If, on the other hand, the half-life of the radionuclide is long, the agent may localize in the target and then be cleared, thus, causing a less than optimal target-to-non-target dose ratio.

The rates of uptake and clearance of a given MAb in both tumors and normal tissues can be altered dramatically by use of the various antibody fragments (e.g., F(ab')$_2$, Fab, Fv). Covell et al. (*91*) have published an extensive study of various relevant pharmacokinetic parameters for a nonspecific IgG and its F(ab')$_2$ and Fab fragments. These authors point out that the body residence time for the IgG is much longer than that for either of the fragments, which may be an advantage in delivering a sufficient quantity of antibody to the tumor site in order to perform RNT, especially in the case of solid tumors. However, in order to maximize the radiation dose to the tumor, it is important that the half-life of the radionuclide be long enough such that the antibody accumulated on the tumor retains a significant fraction of its radioactivity. Thus, RNT performed using IgGs would seem to be most effective when using some of the longer-lived radionuclides with half-lifes in the 4–8-day range discussed herein (e.g., ^{186}Re, ^{177}Lu, ^{131}I), both in terms of maximizing the dose delivered to the tumor and in minimizing the dose delivered to normal organs. Additionally, recent clinical studies conducted using mouse/human chimeric antibodies (*92*) have shown the rates of both blood and whole-body clearance of radioactivity to be slower than the corresponding murine antibody. This slower rate of clearance from blood and normal tissues adds to the relative advantage of the longer-lived radionuclides. Radionuclides with shorter half-lives (e.g., 1–3 days) would be more effective when utilizing RNT agents with more rapid targeting and normal tissue clearance properties (*2,9*).

The effectiveness of the RNT agents labeled with beta-emitting radionuclides may be sensitive to dose rates since the responsiveness of a tumor cell population

can be influenced by dose rate (*93*). If high concentrations of RNT agents at tumor sites are achieved in a relatively short time, the rate of delivery of the radiation dose may be able to influence the radiotoxicity of the agent. For example, ^{153}Sm-EDTMP concentrates rapidly in canine osteogenic sarcomas while clearing efficiently from blood, bone marrow, and other nonosseous tissues, producing a high target-to-non-target ratio achievable within 1 hr of i.v. administration (*52*). The average integrated radiation dose delivered to some of these tumors from 1 mCi/kg (37 MBq/kg) injection has been estimated to be approximately 2000–10,000 cGy (*46*). Within the first ^{153}Sm half-life (46.3 hr), the average dose rate is in the range (20–100 cGy/hr) where dose rate effects occur when using low-LET radiation (*93*). Continuous, low-dose radiation may offer potential advantages, depending upon the kinetics of localization versus tumor growth (*90*). Clearly, the importance of dose rate on the responsiveness of tumors to systemically administered RNT agents is an important and complex problem but one that requires further study and consideration when designing new RNT agents.

The half-lives of most radionuclides used for RNT are usually relatively short (i.e., usually less than 10 days) and provide opportunities for multi-dose deliveries. If the half-lives are sufficiently short, fractionated dosage regimens may be successful in enhancing the effectiveness of RNT (*90*). This is yet another arena that must be investigated as the development of therapy with internal emitters progresses.

From a practical standpoint, the half-life of the radionuclide should permit widespread distribution from production sites. Generally, radionuclide half-lives of approximately 2 days or longer should provide adequate time for production, processing, formulating the RIT or RNT agent, and shipping to research or clinical sites without excessive physical decay. However, some applications dictate the use of radionuclides not produced by generators with very short half-lives that cannot enjoy widespread distribution. A clear example is ^{165}Dy labeled to FHMA particles, where the 2-hr half-life is beneficial in synovectomy applications (*94,95*). The short half-life permits delivery of high activities to the joint and reduces both subsequent redistribution of the radiolabeled products to normal tissues outside of the joint as well as the amount of time the patient remains radioactive and the time required for hospitalization.

BETA PARTICLE ENERGIES

The penetrating ability of the beta particles emitted from radionuclides can have profound implications on the potential success of RNT (*2,7,11,12,57*). For example, most RNT with MAbs has been performed using beta-emitting radionuclides. The longer range of the beta particle (relative to alphas or Auger electrons) can help to overcome the heterogeneity of uptake of the MAb within the tumor. This heterogeneity arises due to factors such as antigen-negative cells or regions, lack of tumor vascularity, or limited permeability of the carrier MAb. In a detailed analysis of several beta emitters having variable distributions throughout a range of tumor sizes, Howell et al. (*7*) conclude that high-energy beta emitters (e.g., ^{90}Y, ^{188}Re, ^{166}Ho) are most effective in treating large tumors ($d \geq 1$ cm), while for smaller tumors ($d \sim 1$ mm) medium-energy beta emitters (e.g., ^{67}Cu, ^{186}Re, ^{177}Lu, ^{131}I) may be more efficacious. Humm (*11*) has investigated the effect of various size "cold regions" within a tumor and concludes that as the size of the cold region increases, higher energy beta emitters are advantageous in providing a more uniform dose throughout the tumor. Another approach to providing a more uniform dose throughout the tumor is to reduce the number and size of these cold regions. One way to accomplish this is to use a "cocktail" of several MAbs all of which target different antigens within the tumor. Epstein et al. (*96*) have developed a series of MAbs which target nuclear antigens thought to be accessible in dead or dying malignant cells in order to deliver radionuclides to necrotic regions of tumors. Reducing the heterogeneity of uptake within the tumor makes the use of low- and moderate-energy beta emitters more feasible in large tumors as well as the smaller tumors in which they are already better suited. This is important in that many potential patients have multiple metastatic disease with a range of tumor sizes.

The therapeutic ratio may be influenced by beta-particle energy by increasing the radiation dose of normal tissues. Approximately 50% of the i.v.-administered activity of both ^{153}Sm-EDTMP and ^{166}Ho-EDTMP are deposited on bone and the remainder rapidly clears from soft tissues and blood (*43,44,53,57*). The sensitivity of dogs to radiation-induced bone marrow suppression, primarily resulting from radiation doses delivered to marrow from ^{153}Sm localized in normal bone, is less than expected from conventional dosimetry calculations (*47,52,56*), particularly at extremely high i.v. doses of ^{153}Sm-EDTMP where complete marrow ablation is not achievable (*56*). These results indicate that there are pockets of bone marrow outside of the range of the medium-energy beta particles (*56*). In contrast, ^{166}Ho has a high-energy beta emitter (Table 3), produces more pronounced radiation-induced marrow suppression, and is capable of ablating bone marrow (*57*). Interestingly, the medium-energy beta particles from RNT agents designed to treat pain from skeletal metastases originating from soft-tissue cancers [i.e., ^{89}Sr-chloride (*97*), ^{186}Re-HEDP (*50*), ^{153}Sm-EDTMP (*53,54*), and ^{131}I-BDP3 (*98*)] are sufficiently high to be therapeutically effective in a large

majority of patients, even though these agents should not be bound directly to the nonosseous cancer cells.

Most radiolabeled colloids or particulates used for RNT employ high-energy beta-emitting radionuclides. For example, particles labeled with ^{165}Dy and ^{90}Y have been used for radiation synovectomy (*60,97,98,99, 100*). In general, radiation synovectomy using these agents has been shown to be effective for management of chronic rheumatoid arthritis of the knee refractory to medical management (*95*). The ideal radionuclide for radiation synovectomy of the knee is a beta emitter with penetration >5 mm but <10 mm or beta particle energies exceeding 1.2 MeV, since these high-energy particles are required to penetrate thick and inflamed synovium (*95*). In arthritic joints where the inflamed synovial membranes are much thinner (e.g., joints of fingers or toes), a low-energy beta-emitting radionuclide is needed to minimize irradiation of the normal bone below the membrane (*95*). For this reason, ^{169}Er (Table 3) has been used by some investigators (*84*) in small joints despite its rather long half-life. The high-energy beta particles emitted from ^{90}Y microspheres for intra-arterial treatment of hepatic tumors (*58–60*) has a long range (~12 mm). This is important for irradiation of these large tumors due to the necessarily inhomogeneous distribution of radioisotope in the tissue in the form of microspheres deposited in the fine capillary beds.

It is important to recognize that handling of therapeutic doses of high-energy, short-lived, beta-emitting radionuclides poses new risks to radiation workers (e.g., nuclear medicine technologists). In particular, such therapy agents can cause extremity overexposures, especially to the hands, if proper shielding and remote tools are not used. Appropriate precautions must be taken when handling high-energy, low-photon yield beta emitters, since the shielding afforded by syringe or vial walls may not be adequate to attenuate the flux of beta particles to a safe level for direct handling. Beta shields of lucite at least 1 cm thick are sufficient to drastically attenuate the particulate dosage from isotopes such as ^{90}Y, ^{188}Re, or ^{166}Ho (Table 3).

CHEMICAL AND BIOCHEMICAL PROPERTIES

An additional consideration relevant to radionuclide selection for RNT with MAbs has to do with the fate of the radionuclide when the carrier protein is catabolized, either at the tumor site or in normal tissues. Particularly important are the localization and clearance characteristics of RNT agents in non-target tissues, since production of radiotoxic side-effects in these tissues will limit the activity that can be administered to patients (*101–104*). Naruki et al. (*105*) have shown that when radiolabeled MAbs are internalized the rate at which the radionuclide is released can vary greatly, with radioiodine clearing from the cell much more rapidly than a radiometal attached to the protein via a bifunctional chelating agent. Other studies (*103,106,107*) have shown that for radiometals the nature of the bifunctional chelator can also have a significant effect on the rate at which the radionuclide is cleared. Thus, if the MAb to be used for RNT is known to be internalized or, if upon binding, the MAb-antigen complex is shed from the tumor, the rate of that process must be slow relative to the half-life of the radionuclide in order to maximize the radiation dose to the tumor. Increasing clearance of activity from normal tissues (e.g., liver and kidney) can markedly reduce radiation doses to those organs and to other normal tissues as long as the catabolized form of the radionuclide does not redistribute to other radiosensitive non-target tissues (*102,108*).

GAMMA-RAY EMITTERS

There are disadvantages and advantages of using radionuclides where gamma-ray emission accompanies particulate emission during radioactive decay, depending primarily on the gamma-ray yields and photon energies (*2–9,44*). The gamma rays will increase the radiation dose delivered to the whole body and all normal tissues with minimal radiation dose deposition at target sites. In addition, gamma radiation emanating from the body can increase personnel exposure. However, emission of photons for scintigraphic imaging can be useful for following the pharmacokinetics, localization properties, and dosimetry in patients. This information may not only be valuable during safety and efficacy studies performed during the IND phases of drug development, but can be used to estimate radiation doses in tumor sites in individual patients using quantitative SPECT. This information would be invaluable in determining site-specific dose-response relationships in individual patients, particularly if repeat or fractionated dose schedules are used.

Gamma-ray emissions from therapeutic radionuclides should be almost entirely composed of photons in the diagnostically useful energy range (75–250 keV) and have low gamma-ray yields (*2,8,9*). Emission of gamma rays that are outside of the imagable ranges will only increase normal tissue exposure and provide little benefit. Several beta-emitting radionuclides (Tables 3 and 4) with useful gamma-ray emissions include (^{153}Sm, ^{177}Lu, ^{186}Re, ^{67}Cu, etc.). Other radionuclides emitting somewhat higher and less desirable gamma-ray energies (e.g., ^{131}I) are also useful (Table 3). If gamma-ray emitters are used, the gamma-ray abundance should be low; low-abundant photon emissions will provide sufficient photons for imaging since the activities administered to patients for non-sealed source therapy generally exceeds 50 mCi (1850 MBq) of the shorter-lived radionuclides (i.e., ≤ 8-day half-lives). Interestingly, some gamma-ray emission is also useful for assessment of possible radio-

activity contamination by radiation workers and by Radiation Safety Officers in the treatment room following injection of the RNT agent and prior to release of the patient from the hospital.

Iodine-131 RNT Agents

Even though many other beta-emitting radionuclides show promise for therapy, ^{131}I continues to play a central role in RNT despite its emission of a relatively high-energy gamma ray (364 keV), a high yield, and a half-life that is longer than desirable for some applications. Iodine-131 is readily available, inexpensive, emits a medium-energy beta particle and can be directly linked to carbon atoms on molecules by a single covalent bond. This latter property provides a large degree of flexibility for radiolabeling smaller molecules with limited molecular perturbation not usually enjoyed by metallic radionuclides. In addition to current ^{131}I RNT agents [including ^{131}I-iodide (*109*), [^{131}I]MIBG (*110*), and ^{131}I-BDP3 (*98*)], ^{131}I-labeled MAbs continue to be used by virtue of the high rate of clearance of ^{131}I from non-target organs (*4,25–27,102,105,106,111*). Catabolism of ^{131}I-MAbs, prepared via direct labeling, produces [^{131}I]iodide among other products, resulting in increased deposition of activity in the thyroid gland (*98*). Utilization of ^{131}I-phenyl based MAb conjugates essentially eliminates uptake in the thyroid but preserves the desirable clearance rates of ^{131}I from normal tissues (*26–28,112*). The 8-day half-life may also prove desirable when using ^{131}I-whole antibodies for RIT, since these agents typically reach maximal target-to-non-target uptake ratios several days after i.v. injection.

SUMMARY

The development of effective therapeutic radiopharmaceuticals requires careful consideration in the selection of the radionuclide. The in vivo targeting and clearance properties of the carrier molecule must be balanced with the decay properties of the attached radionuclide. Radionuclides for therapeutic applications fall into three general categories: beta-particle emitters, alpha- particle emitters, and Auger and Coster-Kronig-electron emitters following electron capture.

Alpha particles and Auger electrons deposit their energy over short distances with a high LET that limits the ability of cells to repair damage to DNA. Despite their high levels of cytotoxicity, the relatively short range of alpha particles requires binding of the carrier molecule to most cancer cells within a tumor in order to be effective. Because of the extremely short range of Auger electrons, the radionuclide must be carried directly into the nucleus to elicit high radiotoxicity, making it necessary to deliver the radionuclide to every cell within a tumor cell population. These characteristics impose rigid restrictions on the nature of the carrier molecules for these types of particle emitters but successful targeting of these types of radionuclides could result in high therapeutic ratios.

Most beta-emitting radionuclides are produced in nuclear rectors via neutron capture reactions; however, a few are produced in charged-particle accelerators. For radionuclides produced by direct neutron activation, the quantities and specific activities that can be produced are determined in large part by the cross-section of the target isotope and the flux of the reactor. Many applications (e.g., therapeutic bone agents, radiolabeled microspheres, radiocolloids) do not require high-specific activities and can therefore utilize the wide range of radionuclides that can be produced in sufficient quantity by direct neutron activation.

Other applications (e.g., MAb labeling) require high-specific activity radionuclides in order to deliver a sufficient number of radionuclide atoms to the target site without saturating the target or compromising the integrity of the carrier molecule. Most radionuclides, produced at NCA levels in reactors, are produced via indirect reactions (Table 4). High-specific activity beta emitters can also be obtained from radionuclide generator systems where the longer-lived parent radionuclide may be obtained from direct neutron activation, as a fission product, or from charged-particle accelerators.

It is essential that the half-life of a radionuclide used in RNT be compatible with the rates of localization in target tissues and clearance of the carrier molecule from normal tissues. This consideration is especially important for the various MAbs and their fragments that are currently under investigation as carrier molecules for RIT. The proper choice of half-life for a RNT agent has implications on the dose delivered to both target and normal tissue, the dose rate, the feasibility of multidose treatment regimes, and in some cases the widespread availability of the agent.

It is also important that the energy (and thus range) of the beta particles emitted from RNT agents be compatible with the microdistribution of the radionuclide with respect to both target and normal tissues. Too low an energy in combination with an inhomogeneous distribution of the carrier molecule may result in incomplete irradiation of the target. If the range of the beta particles is too large with respect to the size of the target, the result is a decreased dose to the target and an increased dose to adjacent normal tissues. If the adjacent tissue is very radiosensitive (such as bone marrow), this process can limit the efficacy of the agent.

The biochemical nature of the radionuclide is important in determining the sites and rates of any redistribution of radioactivity upon metabolism of the carrier molecule and can thus have an effect on the therapeutic ratio of the agent. The chemical nature of the radionuclide should be a primary consideration in determining the method of attachment of the radionuclide to

the carrier molecule. Favorable chemical and biochemical properties in addition to ready availability at moderate cost are responsible for the continued use of ^{131}I in a variety of RNT applications.

Clearly, there are several radionuclides with a spectrum of chemical and physical properties currently available. These and others form the basis for designing and formulating more sophisticated therapeutic radiopharmaceuticals in the coming decade.

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