BNL-63016
CONF-9603186--1

Therapeutic Radionuclides: Making the Right Choice

RECEIVED
JUL 15 1996
OSTI

Suresh C. Srivastava
Medical Department
Brookhaven National Laboratory
Upton, New York 11973

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

Address for Correspondence:
Brookhaven National Laboratory
Medical Department, Building 801
P.O. Box 5000
Upton, NY 11973-5000
Tel: (516) 344-4459
FAX: (516) 344-5962
E-mail: SRIVAST1@BNL.GOV

MASTER

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

Introduction

Recently, there has been a resurgence of interest in nuclear medicine therapeutic procedures (1-4). Using unsealed sources for therapy is not a new concept; it has been around since the beginnings of nuclear medicine. Treatment of thyroid disorders with radioiodine is a classic example. The availability of radionuclides with suitable therapeutic properties for specific applications, as well as methods for their selective targeting to diseased tissue have, however, remained the main obstacles for therapy to assume a more widespread role in nuclear medicine (4,5). Nonetheless, a number of new techniques that have recently emerged, (e.g., tumor therapy with radiolabeled monoclonal antibodies, treatment of metastatic bone pain, etc.) appear to have provided a substantial impetus to research on production of new therapeutic radionuclides (4-7). Table 1 lists the various categories of therapeutic procedures involving the use of internally administered radionuclides. Although there are a number of new therapeutic approaches requiring specific radionuclides, only selected broad areas will be used as examples in this article.

Selection Criteria

The selection criteria for therapeutic radionuclides have to include the physical and chemical characteristics of the radionuclide, feasibility of large-scale production, and the biological factors governing its in-vivo distribution (4,7).

DISCLAIMER

Portions of this document may be illegible in electronic image products. Images are produced from the best available original document.

Physical properties that are important to consider include half-life, and the type, energy, branching ratio and abundances of particulate and gamma-ray emissions. Ideally, the physical half-life should be matched with the in-vivo pharmacokinetics of the radiolabeled compound. If the half-life is too short, most decay will have occurred before the compound has reached maximum target/background ratio. Conversely, too long a lifetime would cause unnecessary radiation dose to normal tissues following the processing of the labeled compound. The nature of the particulate emission is also important to maximize therapeutic effectiveness. The potent lethality of high-LET (linear energy transfer) Auger and low-energy conversion electrons is well documented (8). This effect, however, can best be achieved with intranuclear localization of the labeled compound. Beta particles on the other hand are less densely ionizing and thus have a longer range but much lower LET. Their distribution requirements are, therefore, less restrictive for effective radiotherapy. The gamma-ray energies and abundances are also important since the presence of gamma rays allows low dose biodistribution studies by external imaging for determining biodistribution and dosimetry. Biodistribution data combined with the physical properties of the radionuclide, and with assumptions about tumor size, etc., can be used to calculate radiation absorbed dose at the cellular level (7,9-11).

The important chemical criteria for selecting a radionuclide for radiotherapy are the specific activity, radiochemical purity, trace metal contamination, the number of metal atoms that can be attached per molecule of the compound without compromising biological activity, and in-vivo stability of the radionuclide

attachment. The specific activity is dictated primarily by the method of production. Trace metal contaminants are a concern as they can compete for binding sites on the compound being labeled.

The various above physical and chemical criteria have then to be matched with the in-vivo pharmacokinetics of the labeled compound. For example, substantial variations in localization of radiobioconjugates and the kinetics of their uptake and excretion have been reported (3,11). For monoclonal antibodies (MAb), it is generally observed that 0.5-3 days are necessary to reach maximum tumor concentration although optimum tumor to normal tissue contrast may take longer. Despite the numerous available antigen sites on cancer cells, a non-uniform cellular distribution of the MAb results in most cases (12). These facts reduce the general attractiveness of short-ranged Auger and alpha-emitting radionuclides for radioimmunotherapy (RIT) with MAbs except in specific situations such as for treating blood tumors and micrometastases. Also, short-ranged particles are more attractive if the radiobioconjugate gets internalized into tumor cells, and binds to nuclear components, thus making it possible to target nuclear antigens (13). The longer range of beta particles, on the other hand, allows more uniform tumor irradiation despite the heterogeneity of radioactivity distribution within the tumor tissue. Ultimately, it becomes a trade-off as to which radionuclide is best for a particular application.

Alpha, Auger, and Conversion Electron Emitters

As mentioned above, nuclides that emit high-LET radiations can be most effective in tumor cell killing (8,9,13). If the nuclide used is an Auger electron or a low-energy conversion electron emitter it will deposit the maximum dose within the targeted tumor cells. The radionuclide will be most effective, however, if it is transported across the cell membrane, and localizes into the nucleus or in close proximity to it. Representative examples of radionuclides (halogens and metals) that emit alpha, Auger, or conversion electrons, and are suitable for therapeutic use with this approach, are shown in Table 2.

Attractive radionuclides with short range Auger and conversion electron emission are ^{67}Ga, ^{77}Br, ^{117m}Sn, ^{123}I, and iodine-125. Alpha particles that have a high LET effective in cell killing and a range of several cell diameters (40-80 μm) are also very attractive. Examples of alpha emitters include ^{212}Bi, ^{211}At, and ^{255}Fm. It has been calculated that the dose advantage for ^{211}At compared to ^{90}Y (a long-range beta emitter) increases from a factor of 9 for a 1-mm-diam tumor to a factor of 1200 for a single tumor cell (10). However, a high degree of selectivity and uniform intracellular localization are necessary to achieve maximum therapeutic advantage. It should be noted that a number of nuclides from this category, in particular ^{123}I, ^{125}I, ^{67}Ga, and ^{201}Tl are commercially available and should be tested for effectiveness to target nuclear antigens.

Beta Emitters

There are a number of beta emitters especially radiometals that possess various particle ranges and chemical properties and thus offer a much wider choice for specific applications (4,7,11). Candidate beta emitters can be arbitrarily grouped into two classes: 1) those emitting low to intermediate energy beta particles and gamma emission suitable (>10%) for imaging; and 2) those with higher beta energy and little (<10%) or no gamma emission (Table 3). This distinction is only arbitrary since many radionuclides in the second category allow imaging at high dose administrations. Low-dose biodistribution and imaging experiments are possible with radionuclides in the first group before administering a therapeutic dose of the exact same preparation. Because it has been observed that the biodistribution can be influenced by the choice of radionuclide alone, even with the same antibody system (14), this would be a real advantage. Clinically, it is considered highly desirable, even necessary, to image each patient prior to therapy in order to assess biodistribution and antigenic status and to calculate tumor and normal tissue doses.

From among the radionuclides listed in Table 3, ^{47}Sc, ^{67}Cu, ^{117m}Sn, ^{153}Sm, and ^{188}Re appear particularly attractive because of their favorable chemistry and/or ease of production. Copper-67 has given promising results in preliminary studies for the RIT of lymphoma (15). However, scaled-up accelerator production of ^{67}Cu of high specific activity, required for many applications, has turned out to be problematic (16). Scandium-47 is considered a better substitute for ^{67}Cu since it can be

reactor-produced in larger quantities and also because its nuclear and chemical properties are favorable for developing radiobioconjugates and other labeled compounds (17). Tin-117m and ^{153}Sm that are being developed for bone pain palliation therapy are discussed in a later section. The current specific activity of reactor-produced ^{117m}Sn, although not a problem with its use for bone pain palliation therapy, is not acceptable for developing radioimmunoconjugates. Rhenium-188 is attractive since it is a generator product from the decay of the 69.4 day parent, tungsten-188 (18). It has shown promise in initial investigations as a therapeutic label for MAbs and other vehicles, e.g., somatostatin analogs.

The use of ^{90}Y for various radiotherapeutic procedures has been popular because of its high-energy beta particle, suitable half-life, and availability. Since ^{90}Y is unsuitable for quantitative imaging, ^{111}In biodistribution data are utilized to predict dose from ^{90}Y-labeled immunoconjugates. However, it has been shown that although the intravascular kinetics in patients are often similar for many ^{90}Y and ^{111}In labeled MAbs, there are significant differences in the tumor uptake and tissue biodistribution properties of these radionuclides (19). A similar approach has been taken for the pair ^{99m}Tc and ^{186}Re, the former for imaging, and the latter for therapy. These radionuclides share very similar chemistries for radiolabeling MAbs and other compounds.

Radiobioconjugates for Tumor Therapy

Research on radiobioconjugates (used here in a generic sense to include radiolabeled monoclonal antibodies, peptides, receptor specific and other bioactive molecules) has experienced rapid growth due to the promise of a number of these compounds to serve as selective carriers of radionuclides to tumor-associated and other specific antigens/receptors in vivo (1-4). However, although radiobioconjugate therapy has shown initial promise for certain types of tumors, practical benefits of this approach have not matched the expectations that were raised more than ten years ago (1). Radioimmunotherapy (RIT, used here in a generic sense for all radiobioconjugates) is considered best suited for treating tumors that cannot be easily resected or for treatment of small disseminated lesions and/or secondary micrometastases. From various considerations, especially dosimetry, the choice of the optimum radionuclide is a very important factor for a successful exploitation of this technique. Although ^{131}I is marginally suited for RIT, most therapy trials have so far utilized this isotope due to its commercial availability at low cost, the well understood chemistry of iodine, and the experience from the use of ^{131}I in treating thyroid disorders.

The radionuclides listed in Tables 2-3 are among the most promising for RIT. Those in Table 2 require the labeled molecule to be not only efficiently internalized into the tumor cells but to also preferably bind to nuclear antigens. A number of monoclonal antibodies have been observed to internalize into tumor cells of various types and bind to nuclear components (13). Various other important factors

involved in radiobioconjugate development include the convenience, efficiency, and gentleness of different radiolabeling procedures as well as the stability of the radionuclide attachment to the immunoconjugate. These topics are outside of the scope of this article but a very brief discussion at this point is considered appropriate.

RIT requires a stable attachment of the radionuclide to the MAb since free radionuclide may target normal tissues thus increasing normal organ and whole body doses. Radiolabeling techniques range widely from well established protein halogenation schemes, simple direct labeling of ^{186}Re, to the use of general purpose bifunctional chelating agents such as the bicyclic anhydride of DTPA (DTPA-DA) for ^{90}Y, ^{109}Pd, and ^{153}Sm, to the use of more structurally complex in-house synthesized bifunctional chelating agents for ^{186}Re, ^{67}Cu, ^{47}Sc and ^{90}Y (13,14).

Due to the chemical similarity between Tc and Re, strategies for labeling MAbs with ^{186}Re have directly paralleled those for ^{99m}Tc. Direct labeling with ^{188}Re has been demonstrated utilizing free sulfhydryl groups on the MAb; these groups can be generated either by chemical reduction of MAb disulfide bonds or by the reaction of lysines on the MAb with 2-iminothiolane. A more selective approach involves chelation of ^{186}Re to a N_3S-amide mercaptide ligand (MAG_2-GABA) prior to conjugation to MAbs (20). While less convenient, this approach allows more control over radiolabeling and may have wider applicability with various MAb systems. Antibodies have been labeled with ^{90}Y using DTPA-DA; however, in clinical trials these preparations showed high bone uptake of ^{90}Y. Substantially reduced bone uptake in mice was shown using p-isothiocyanantobenzyl DTPA (the

coordination sites on this ligand are 8 compared to 7 for DTPA-DA); however, it was still higher than what is generally observed with the corresponding ^{111}In labeled MAb (21). In mice the bone uptake of ^{90}Y has been reduced to the levels of ^{111}In using the macrocyclic bifunctional chelating agent p-bromoacetamidobenzyl-DOTA (22). Biodistribution studies in mice of ^{47}Sc labeled MAb prepared using DTPA-DA have shown high levels of radioactivity in the liver. Carrier-free ^{47}Sc has been prepared at BNL and successfully attached to MAbs 17-1A and anti-CEA F(ab')$_2$ using the semi-rigid bifunctional chelating agent 4-isothiocyanato-cyclohexyl EDTA (4-ICE) and others (17). Using the preorganized ligand approach, the biodistribution in normal and tumor mice of the ^{47}Sc labeled preparations was comparable or better than that of the corresponding ^{111}In labeled antibodies (23). Antibodies prepared using 4-ICE have shown higher tumor uptake with a three to four-fold reduction in the retention of ^{111}In in the liver compared to DTPA-immunoconjugates in mice (24), and similar results were obtained with scandium-47 (23).

Copper labeled DTPA-immunoconjugates are not stable in serum. Even though the serum stability of Cu labeled 4-ICE-immunoconjugates is substantially higher they are still unstable in-vivo and produce high nonspecific retention of copper-67. Stable Cu labeled immunoconjugates result only by using derivatives of the macrocyclic polyaminocarboxylates p-aminobenzyl-TETA (25) and DOTA or derivatized cyclic polyamines (cyclams) (26). Preliminary studies in patients with pharmacological doses of ^{67}Cu labeled Lym-1 MAb prepared using parabromo-acetamidobenzyl-TETA have given promising results (15). Little work has been done on ^{153}Sm as an antibody label, however. In one study in mice, ^{153}Sm labeled

K-1-21 murine IgG (labeled using DTPA-DA) gave a slightly lower tumor uptake with higher bone and liver uptake compared to ^{131}I or ^{111}In labeled K-1-21 (27). The use of bifunctional chelator 4-ICE did not improve the ^{153}Sm labeled 17-1A biodistribution compared to ^{153}Sm labeled DTPA-17-1A (28). This may be due to the fact that since Sm is a lanthanide with f valence electrons having no specific coordination geometry, it does not need a preorganized chelation cavity. A higher number of coordination sites on the ligand is more important for samarium. The macrocyclic polyaminocarboxylate DOTA (eight coordination sites) produced much better results with samarium-153 (28).

The experience with the above mentioned radiometals has been valuable in terms of understanding the chelation chemistry for attachment to immunoconjugates, and will serve to improve our current methodology to produce stable radioimmunoconjugates with these and other promising radiometals listed in Tables 2 and 3.

Treatment of Metastatic Bone Pain

A number of radiopharmaceuticals appear to offer advantages over narcotic or other conventional treatments for bone pain from osseous metastases in cancer patients (29). This concept is not new, and ^{32}P has been investigated for over three decades for this purpose (30). However, the recent FDA approval of ^{89}Sr chloride (Metastron) has opened up a new era for the development of unsealed

sources for bone pain palliation therapy. Introduction of ^{89}Sr has catalyzed the development of newer competitive agents that may offer improvements in efficacy or reduced myelosuppression. The radionuclides under investigation include β-emitters ^{186}Re (31) and ^{153} Sm (32), and the conversion-electron emitter tin-117m (33,34). Physical and nuclear properties of the various radionuclides for bone pain palliation therapy are summarized in Table 4.

The primary concern from the therapeutic use of this class of bone-seeking radiopharmaceuticals is the absorbed dose to the red marrow. The energy of the beta particles seems to be an important factor because the dose to the marrow depends on the range of penetration of the particles into the marrow from the deposited radioactivity on to the bone surfaces. In this respect, ^{117m}Sn may offer a distinct advantage because of the discrete limited range (0.2-0.3 mm) of its conversion electrons in tissue (33-35). It remains to be seen which one of these agents eventually will become the agent of choice.

Radionuclides that appear promising for this application (Table 4) are all reactor-produced and there does not seem to be a supply/demand problem for most cases. Tin-117m could be considered an exception since a high-flux reactor is required for producing it in sufficient quantities and there are only a few reactors worldwide with such a capability. However, future production in sufficient quantities now appears feasible (36).

Radiation Synovectomy

Radiation synovectomy is an attractive alternative to chemical or surgical synovectomy for the treatment of inflammatory synovial disease, including rheumatoid arthritis. The procedure entails a single injection of a beta-emitting radiopharmaceutical directly into the synovium to control and ablate inflammation. The injected agents, typically colloids or larger aggregates, are assumed to be rapidly phagocytized by synoviocytes and then distributed within the synovium, primarily at the surface. Most commonly used agents have comprised radiocolloids or macroaggregates employing high-energy beta emitters, ^{90}Y, ^{198}Au, ^{165}Dy, and ^{186}Re (37). While these agents have shown good treatment efficacy, they are not widely used especially in the United States. All display some degree of leakage of the radionuclide from the joints leading to an increased radiation dose to normal organs. The size of these raidolabelled particles cannot be adequately controlled during formation, and it is assumed that small (< 10 μm) particles leak from the synovium over time. However, a new type of particle, made from hydroxyapatite (HA), a natural constituent of bone, has become commercially available in various controlled sizes ranging from 1 - 80 μm. Research interest has thus focused recently on incorporating HA particles into new agents for radiation synovectomy. Initial studies in rabbits with antigen-induced arthritis (AIA) using ^{153}Sm labeled HA, showed minimal leakage of activity (0.09% over four days) from the treated joint compared to leakage rates obtained with other radiocolloid agents (5-45%); results

with ^{186}Re-HA, however, showed slightly higher leakage (3.05% over four days) (38).

The presumed heterogeneous distribution of radionuclide within the synovium has limited existing agents to only those labeled with high energy beta emitters. It is presumed that the longer range of these particles is necessary to treat medium to large sized joints. However, low-energy beta emitters may be equally or more effective in reducing inflammation for small to medium joints since a much larger radiation dose could be delivered to the synovium without excessive irradiation of surrounding tissue. This could be analogous to the effectiveness of the short range conversion electrons from ^{117m}Sn for bone pain palliation, compared to the high-energy beta emitter ^{89}Sr (35). The only clinical example to date for treating synovial inflammation using a low-energy beta emitter is the use of ^{169}Er (β^-_{avg} 111 keV) colloids to treat inflammation in the small finger joints (37). Based on various considerations, appropriate sized particles labeled with ^{47}Sc, ^{117m}Sn, ^{153}Sm, and ^{169}Er would seem to be the agents of choice for radiation synovectomy.

Radionuclide Production

A detailed description of production methods, in particular those that can be implemented on an economic scale, is not within the purview of this article. However, it is considered important to provide a summary of the current status in this area including problems and concerns related to isotope availability.

Radionuclides are primarily produced using a nuclear reactor or a charged-particle accelerator (mainly cyclotrons), and their properties depend upon a number of factors that include targetry, irradiation conditions and processing chemistry (5,6,39). The production and supply of many routine imaging and some therapeutic radionuclides that have a commercial market have continued at a satisfactory level (5,39).

In terms of the radionuclides listed in Table 2 that are particularly attractive for targeting nuclear antigens (13), only ^{123}I, ^{125}I, ^{67}Ga and ^{201}Tl are available commercially. Although the production methodology for others has been worked out to some extent, they are not readily available in sufficient quantities on a regular basis. A notable exception is ^{117m}Sn which has been discussed above for bone pain palliation therapy in cancer patients. The current specific activity ($\sim$8 mCi/mg), however, that is adequate for this application is not high enough for radiobioconjugate development. Its use as a target for nuclear antigens will have to await the development of methods that could provide a no-carrier-added product (40). Additional radionuclides in Table 2 that have been investigated to some extent include ^{124}I (41), ^{211}At (42), and bismuth-212 (43). Their properties are suitable for targeting nuclear antigens using MAb systems or other vehicles that are shown to be internalized into the tumor cells. However, the production, the availability, and the conjugation chemistry of these radionuclides remain to be developed further.

Reactor Production

Table 5 lists some therapeutic radionuclides that can be produced in a nuclear reactor in quantities sufficient for widespread clinical use (4,6). It is noteworthy that many of the β^- or β^-/γ emitters discussed in this article are best produced using neutron bombardment reactions.

In reactor production, there are three types of reactions that are employed: (i) neutron capture, (n,γ); (ii) neutron capture followed by decay; and (iii) fission. The n,γ reaction using thermal neutrons is the most widely employed technique. The reasons are that elemental targets can be used and the yields are generally high. However, separation from the bulk of the stable element is not possible and thus the specific activities can be low unless the cross sections are very high. No-carrier added radionuclides are not producible using the n,γ reaction. The other reactions allow improvement in specific activity, and can often be used (n,γ→β^- decay, n, f, etc.) under certain situations such as when an intermediate nuclide decays to the product of interest. In general, high chemical purity reagents and enriched stable element targets have to be employed in reactor production of radionuclides.

Accelerator Production

The cyclotron is the most widely used accelerator for producing radionuclides. A wide variety of cyclotrons now exist ranging from "baby"

cyclotrons of energies as low as 3 MeV to very large isochronous synchrotrons with energies in excess of 500 MeV. The variety of accelerated particles ($p,d,^3He,\alpha$) and the energy range available make cyclotrons very flexible for radionuclide production. Commercial cyclotrons commonly have a range of 5-30 MeV particles and many are used exclusively for isotope production.

Certain radionuclides that can be produced only using high-energy linear accelerators (e.g., spallation reactions) or whose production is more cost effective when made this way are either scarce or not available (5). One of the main reasons for this is that high-energy machines are very expensive to build and operate and isotope production is usually in conflict with their primary mission which is physics research (44). Consequently, isotope production in these machines has been undertaken only as an intermittent and parasitic activity. This situation has created considerable concern within the radioisotope research community that includes nuclear medicine as well as basic physical and life science investigators (44,45). This is especially in view of the fact that a number of high-energy produced radionuclides are emerging as being potentially useful and in some cases unique for applications (mostly imaging, some therapeutic) in nuclear medicine. With the recent rapid growth in biotechnological and immunological approaches to treatment of cancer, bone pain, and other diseases, there is an urgent need at least in the U.S. for a continuous and reliable availability of certain high-energy produced radionuclides (5).

At the present time, there are about six high-energy accelerators world-wide that engage in isotope production for distribution. These are located in the U.S.

(BLIP and LAMPF), Canada (TRIUMF), Switzerland (PSI), South Africa (NAC), and Russia (45). A few others also have the capability for isotope production but are utilized rarely or very little for this purpose. It must be emphasized that the cost of production is a critical factor and unless there is a commercial market, high-energy produced radionuclides are not produced in any consistent fashion.

Generator Systems

A number of relatively short-lived therapeutic radionuclides, especially β^- emitters, can be obtained through generator systems. These are listed in Table 7. The $^{90}Sr/^{90}Y$ generator system has been utilized for quite some time; it has a number of practical advantages. The chemistry of yttrium, as mentioned earlier, is also favorable for labeling MAbs and other bioactive molecules. A number of therapeutic protocols have employed ^{90}Y with significant success (46). Another generator system, $^{188}W/^{188}Re$ (18), has also been developed and investigated for antibody labeling and other applications. The results are still preliminary but quite promising. Large-scale production of ^{188}W can be accomplished in a high-flux reactor. The generator system for the alpha emitter ^{212}Bi has been available on an experimental basis only (43). The use of this isotope because of the 1 h half-life is possible only in special situations. The $^{115}Cd/^{115m}In$ generator system should be useful for applications where a short range (it emits a 300 keV conversion electron with $\sim$1 mm range) and a short half-life are advantageous.

The remaining generator systems listed in Table 7 primarily procedure daughter radionuclides with short t½ and high β^- energies. There is an inverse relationship between t½ and β^- decay energy and therefore, there are only a few radionuclides that have both a several-day t½ and a high β^- energy. To circumvent this problem one could use the approach of labeling with an intermediate t½ radionuclide that decays in-vivo to a much shorter t½ daughter with high β^- emission. Since the daughter will be in equilibrium with the parent, it will exert an in-situ cytotoxic effect over a prolonged period, essentially as an "in-vivo generator" (47). However, a number of critical questions will have to be answered before his approach can be applied successfully for radiotherapy (e.g., the fate of the daughter nucleus following the uptake of the parent by the tumor - will it translocate to other tissues before decay? etc.). A theoretical test of the feasibility of this approach has been attempted with encouraging results (48).

Conclusion

There are a number of potential candidate radionuclides for tumor therapy and for other therapeutic applications. This article has attempted to provide a brief discussion of the criteria for selecting radionuclides for specific applications. The choice of the radionuclide best suited for a particular application depends upon a number of factors that include: (1) Half-life; (2) Type of emission (α, β, γ, Auger or conversion electrons); (3) Specific activity; (4) Chemistry; (5) Route of

administration; (6) Internal dosimetry; (7) Radiation safety and environmental concerns; (8) Vehicle used as the carrier; (9) In-vivo biopharmacokinetics of the labeled carrier and the free radionuclide; and (10) Cost of production and availability.

The various important therapeutic applications, where radionuclide therapy may have an important role to play in, and the radionuclides that are considered best suited for the application, are summarized in Table 8. It should be noted that this listing is not meant to be exhaustive, and additional radionuclides can be added based on present and future work as well as various other considerations. At times, the cost and availability, especially if the radionuclide is "new" and/or difficult to produce, become issues of paramount importance.

In summary, there are a number of therapeutic radionuclides that are presently under investigation, and some of these may eventually turn out to be ideal or best-suited for specific applications. Although issues relating to cost and availability of many of these are yet to be addressed to everybody's satisfaction, there does not seem to be a dearth of new therapeutic radionuclides. As new needs and applications develop, appropriate radionuclides will follow. The substantial progress of investigations in certain areas, for example, tumor radioimmunotherapy and bone pain palliation, offer renewed hope and promise for the widespread use of internally administered radionuclides for various novel and effective therapeutic approaches.

Acknowledgements

This work was supported by the United States Department of Energy, Office of Health and Environmental Research, under Contract No. DE-AC02-76CH00016. The author is thankful to Ms. Susan Cataldo for excellent secretarial assistance during the preparation of this article.

References

1. Srivastava SC (ed): Radiolabeled Monoclonal Antibodies for Imaging and Therapy, New York, Plenum Press, 1988, 876 pp

2. Britton KE, Mather SJ, Granowska M: Radiolabelled monoclonal antibodies in oncology III. Radioimmunotherapy. Nucl Med Commun 12:333-347, 1991

3. Larson SM, Digvi CR, Scott A, et al: Current status of radioimmunotherapy. Nucl Med Biol 21:785-792, 1994

4. Mausner LF, Srivastava SC: Selection of radionuclides for radioimmunotherapy. Med Phys 20:503-509, 1993

5. Srivastava SC, Mausner LF: Production and supply of radioradionuclides with high-energy particle accelerators: Current status and future directions: in: Proc 21st Japan Conf Radiat and Radionuclides, Feb. 2-4, 1994, Japan Atomic Industrial

Forum, B-550, pp 1-11

6. Volkert WA, Goeckler WF, Ehrhardt GJ, et al: Therapeutic radionuclides: production and decay property considerations. J Nucl Med 32:174-185, 1991

7. O'Donoghue JA, Bardies M, Wheldon TE: Relationships between tumor size and curability for uniformly targeted therapy with beta emitting radionuclides. J Nucl Med 36:1902-1909, 1995

8. Adelstein SJ, Kassis AI: Radiobiologic implications of the microscopic distribution of energy from radionuclides. Nucl Med Biol 14:165-169, 1987

9. Jungerman JA, Yu Kin-Hung P, Zanelli CI: Radiation absorbed dose estimates at the cellular level for some electron emitting radionuclides for radioimmunotherapy. Int J Appl Radiat Isot 35:883-888, 1984

10. Humm JL: Dosimetric aspects of radiolabeled antibodies for tumor therapy. J Nucl Med 27:1490-1497, 1986

11. Wessels BW, Rogus RD: Radionuclide selection and model absorbed dose calculations for radiolabeled tumor-associated antibodies. Med Phys 11:638-645, 1984

12. Griffith MH, Yorke ED, Wessels BW, et al: Direct dose confirmation of quantitative autoradiography with micro-TLD measurements for radioimmunotherapy. J Nucl Med 10:1795-1809, 1988

13. Srivastava SC: Criteria for the selection of radionuclides for targeting nuclear antigens for cancer radioimmunotherapy. Cancer Biother Radiopharm 11: 43-50, 1996

14. Srivastava SC, Mease RC: Progress in research on ligands, nuclides,

and techniques for labeling monoclonal antibodies. Nucl Med Biol 18:589-603, 1991

15. DeNardo GL, DeNardo SJ, Meares CF, et al: Pilot therapy of lymphoma with fractionated Cu-67-BAT Lym-1. J Nucl Med 34:93P, 1993

16. DasGupta AK, Mausner LF, Srivastava SC: A new separation procedure for Cu from proton irradiated Zn. Int J Appl Radiat Isot 42:371-376, 1991

17. Mausner LF, Kolsky KL, Mease RC, et al: Production and evaluation of Sc-47 for radioimmunotherapy. J Labelled Compds Radiopharm 32:388-390, 1993

18. Ehrhardt G, Ketring AR, Turpin TA, et al: An improved tungsten-188/rhenium-188 generator for radiotherapeutic applications. J Nucl Med 28:656, 1987

19. Carasquillo JA, Kramer B, Fleisher T, et al: In-111 versus Y-90 T101 biodistribution in patients with hematopoietic malignancies. J Nucl Med 32:970, 1991 (abstr)

20. Breitz H, Ratliff B, Schroff R, et al: Phase I studies of ^{186}Re whole MoAb and F(ab')$_2$ fragment for radioimmunotherapy in solid tumors. J Nucl Med 31:724-725, 1990

21. Roselli M, Schlom J, Gansow OA, et al: Comparative biodistribution of yttrium- and indium-labeled monoclonal antibody B72.3 in athymic mice bearing human colon carcinoma xenografts. J Nucl Med 30:672-689, 1989

22. Adams GP, DeNardo SJ, Deshpande SV, et al: Dual isotope pharmacokinetics of an anti-lymphoma antibody (LYM-1) with a new bifunctional chelating agent. J Nucl Med 31:823, 1990

23. Mausner LF, Joshi V, Kolsky KL, et al: Evaluation of chelating agents for radioimmunotherapy with scandium-47. J Nucl Med 36:104P, 1995 (abstr)

24. Srivastava SC, Mease RC, Meinken GE, et al: Reduction in non-specific uptake of indium-111 from using semi-rigid cyclohexyl EDTA immunoconjugates. J Labelled Compds Radiopharm 35:303, 1994

25. Moi MK, Meares CF, McCall MJ, et al: Copper chelates as probes of biological systems: Stable copper complexes with a macrocyclic bifunctional chelating agent. Anal Biochem 148:249, 1985

26. Macke H, Ruser G, Koch P, et al: New bifunctional chelators for antibody labeling with metallic radionuclides. J Labelled Compds Radiopharm 30:318, 1991

27. Boniface GR, Izard ME, Walken KZ, et al: Labeling of monoclonal antibodies with samarium-153 for combined radioimmunoscintigraphy and radioimmunotherapy. J Nucl Med 30:683-691, 1989

28. Srivastava SC, Mausner LF, Mease RC, et al: Development and evaluation of ^{67}Cu and ^{153}Sm labeled conjugates for tumor radioimmunotherapy. Int J Radiopharmcognosy, 33:92-101, 1995

29. McEwan AJB: Radiopharmaceuticals for palliative treatment of painful bone metastases. New Perspectives in Cancer Diagnosis and Management. 2:24, 1994

30. Silberstein EB, Elgazzar AH, Kapilivsky A: Phosphorus-32 radiopharmaceuticals for the treatment of painful osseous metastases. Semin Nucl Med 22:17-27, 1992

31. Maxon HR, Schroder LE, Hertzberg VS, et al: Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: results of a double-blind crossover comparison with placebo. J Nucl Med 32:1877-1881, 1991

32. Goeckler WF, Edwards B, Volkert WA, et al: Skeletal localization of samarium-153 chelates: potential therapeutic bone agents. J Nucl Med 28:495-504, 1987

33. Srivastava SC, Meinken GE, Richards P, et al: The development and in-vivo behavior of tin containing radiopharmaceuticals. I: Chemistry, preparation, and biodistribution in small animals. Int J Nucl Med Biol 12:167, 1985

34. Atkins HL, Mausner LF, Srivastava SC, et al: Human biodistribution of Sn-117m(4+)DTPA: A new agent for palliative therapy of painful osseous metastases. Radiology 186:279-283, 1993

35. Atkins HL, Mausner LF, Srivastava SC, et al: Tin-117m(4+)-DTPA for palliation of bone from osseous metastases: A pilot study. J Nucl Med 36:725-729, 1995

36. J. Lister-James, Diatide, Inc., personal communication, 1996.

37. Deutsch E, Bordack JW, Deutsch KF. Radiation syovectomy revisited. Eur J Nucl Med 20:1113, 1993, and references therein

38. Chinol M, Vallabhajousula S, Goldsmith SJ, Klein MJ, Deutsch KF, Chinen LK, Brodack JW, Deutsch EA, Watson BA, Tofe AJ. Chemistry and biological behavior of samarium-153 and rhenium-186-labeled hydroxyapatite particles: Potential radiopharmaceutical for radiation synovectomy. J Nucl Med 34:1536, 1993

39. Lamb JF, Kramer HH: Commercial production of radionuclides for nuclear medicine, in Rayudu GVS (ed): Radiotracers for Medical Applications Volume I. Boca Raton, FL, CRC, 1983

40. Mausner LF, Mirzadeh S, Maher R, et al: Production of high specific activity ^{117m}Sn with the Szilard-Chalmers process. J Labelled Compds Radiopharm 16:177-178, 1989

41. Larson SM, Pentlow KS, Volkow ND, et al: PET scanning of I-124-3F9 as an approach to tumor dosimetry during treatment planning for radioimmunotherapy in a child with neuroblastoma. J Nucl Med 33:2020-2023, 1992

42. Zalutsky MR, Garg PK, Friedman HS: Labeling monoclonal antibodies and $F(ab')_2$ with the α-particle-emitting nuclide astatine-211: preservation of immunoreactivity and in-vivo localizing capacity. Proc Natl Acad Sci USA 86:7149-7153, 1989

43. Atcher RN, Friedman AM, Hines JJ: An improved generator for the production of ^{212}Pb and ^{212}Bi from ^{224}Ra. Int J Appl Radiat Isot 39:283-286, 1988

44. Radionuclides for Medicine and the Life Sciences, Adelstein SJ, Manning FJ (ed): Washington, DC, National Academy Press, 1995, pp 1-132

45. Srivastava SC: Is there life after technetium: (What is the potential for developing new broad-based nuclides)?. Semin Nucl Med, 1996 (in press)

46. Hnatowitch DJ, Chinol M, Siebecker DA, et al: Patient biodistribution of intraperitoneally administered yttrium-90 labeled antibody. J Nucl Med 29:1428-1435, 1988

47. Mausner LF, Straub RF, and Srivastava SC: Production and use of prospective radionuclides for radioimmunotherapy. In: Radiolabeled Monoclonal Antibodies for Imaging and Therapy, Srivastava SC, Editor, Plenum, New York, 1988, pp. 149-163

48. Mausner LF, Straub RG, Srivastava SC: The in-vivo generator for radioimmunotherapy. J Labelled Compds Radiopharm 16:498-500, 1989

Table 1. Radiotherapy Using Unsealed Sources

- Tumor therapy
  - Radiolabeled monoclonal antibodies
  - Non antibody methods
- Receptor-binding radiotracers for tumor and other specific therapies
  - Bioactive peptides
  - Antibody derived agents
  - Molecular recognition units
  - Conventional in-vivo receptors
- Bone pain palliation therapy
- Radiation synovectomy
- Miscellaneous therapies
  - Microspheres, colloids (for ascites, etc.)
- Radioimmunoguided surgery

Table 2. Nuclear and Physical Characteristics of Some Alpha, Auger, and Conversion Electron Emitting Radionuclides for Targeting Nuclear Antigens.

	Halogens			Metals		
Radionuclide	Bromine-77	Iodine-125	Astatine-211	Tin-117m	Thallium-201	Bismuth-212
Half-life	57.0h	60.1d	7.2h	13.6d	3.04d	61m
Decay mode	EC,β^+	EC	EC,α	IT	EC	α,β^-
Principal γ KeV	$\gamma \pm 511$	35.5	None	159	167	727
% Abundance	1.5	6.7	---	86	11	6.7
Principal α KeV	None	None	5868	None	None	6051
% Abundance	---	---	41	--	--	25
Auger Electrons, #	15	20	20	5	18	1
Range, KeV	0.1-12	0.7-30	3.2-87	0.6-24	2.7-77	2.7
Total % per decay	376	479	95	281	253	30
Conver. Electrons, #	11	6	Negligible	9	20	3
Range, KeV	149-508	3.7-36	---	127-158	1.6-167	25-40
Total % per decay	1.5	93	---	114	115	25

Table 3. Potential Beta-emitters for Radiotherapy

Radionuclide	Half-life (d)	Electron energy (keV avg)	Gamma photon keV(%)
	Group I. >10% Gamma Emission		
Scandium-47	3.4	162	159 (68)
Copper-67	2.6	141	185 (49)
Rhodium-105	1.5	190	319 (19)
Tin-117m	13.6	127*	159 (86)
		152*	
Iodine-131	8.0	181	364 (81)
Samarium-153	1.93	225	103 (28)
Lutetium-177	6.7	133	208 (11)
Rhenium-188	0.71	764	155 (15)
Iridium-194	0.80	808	328 (13)
Gold-199	3.1	86	158 (37)
		143*	
	Group II. <10% Gamma Emission		
Phosphorus-32	14.3	695	----
Arsenic-77	1.6	228	239 (1.6)
Strontium-89	50.5	583	----
Yttrium-90	2.7	935	----
Palladium-109	0.56	360	88 (3.6)
Silver-111	7.5	350	342 (6.7)
Praseodymium-142	0.80	860	158 (3.7)
Promethium-149	2.2	364	286 (3.1)
Gadolinium-159	0.77	311	363 (8.0)
Holmium-166	1.1	666	80 (6.2)
Rhenium-186	3.71	329	137 (9.2)

*Conversion electron

Table 4. Physical Characteristics of Radionuclides for Bone Pain Palliation Therapy

Radionuclide	Maximum Eβ (MeV)	Weighted Average Eβ (MeV)	Average Range (mm)	Half-Life (days)	Gamma Photons (MeV (%)
Strontium-89	1.46	0.583	2.4	50.5	None
Rhenium-186	1.08	0.329	1.05	3.71	0.137 (9.2)
Samarium-153	0.81	0.225	0.55	1.93	0.103 (28)
Tin-117m	0.127[1] 0.152[1]	-- --	0.21[2] 0.29[2]	13.6	0.159 (86)

[1] Monoenergetic conversion electron
[2] Discrete travel of emitted conversion electron (not an average)

Table 5. Reactor Production of Therapeutic Radionuclides

Radionuclide	Nuclear Reaction
Scandium-47	$^{47}Ti(n,p)$
Yttrium-90	$U(n,f)^{90}Sr \rightarrow \beta$
Rhodium-105	$^{nat}Ru(n,\gamma)^{105}Ru \rightarrow \beta$
Palladium-109	$^{108}Pd(n,\gamma)$
Silver-111	$^{110}Pd(n,\gamma) \rightarrow \beta$
Tin-117m	$^{117}Sn(n,n'\gamma)^{117m}Sn$
Iodine-131	$^{235}U(n,f)$
Praseodymium-142	$^{141}Pr(n,\gamma)$
Promethium-149	$^{148}Nd(n,\gamma)^{149}Nd \rightarrow \beta$
Samarium-153	$^{152}Sm(n,\gamma)$
Gadolinium-159	$^{158}Gd(n,\gamma)$
Holmium-166	$^{165}Ho(n,\gamma)$
Lutetium-177	$^{176}Lu(n,\gamma)$
Rhenium-186	$^{185}Re(n,\gamma)$
Rhenium-188	$^{186}W(n,\gamma)^{187}W(n,\gamma)^{188}W \rightarrow \beta$
Iridium-194	$^{193}Ir(n,\gamma)$
Gold-199	$^{198}Pt(n,\gamma)^{199}Pt \rightarrow \beta$
	$^{197}Au(n,\gamma)^{198}Au(n,\gamma)$

Table 6. Accelerator Production of Therapeutic Radionuclides

Radionuclide	Nuclear Reaction
Scandium-47	^{48}Ti (p,2p)
Copper-67	^{68}Zn (p,2p)
Bromine-77	$^{79}Br(p,3n)^{77}Kr\beta^{+}\rightarrow$
Arsenic-77	^{80}Se (p,α)
Tin-117m	^{121}Sb (p,2p,3n)
Platinum-193m	^{192}Os (α,3n)

Table 7. Generator Systems for Therapeutic Radionuclides

Daughter				Parent	
Radionuclide	T½	β⁻max, MeV	γ, keV (%)	Radionuclide	T½
Copper-66	5.1 min	2.63	1039 (9)	Nickel-66	2.3 d
Zinc-69	55 min	0.90	---	Zinc-69m	0.6 d
Yttrium-90	64 h	2.27	---	Strontium-90	28.6 yr
Silver-112	3.2 h	3.94	617 (41)	Palladium-112	0.9 d
Indium-115m	4.5 h	0.83 (5%) 0.30 (49%)[1]	335 (50)	Cadmium-115	2.2 d
Cesium-128	3.6 min	2.89 (β^+)	441 (27) 511 (110)[2]	Barium-128	2.4 d
Iodine-132	2.3 h	2.12	773 (89)	Tellurium-132	3.2 d
Rhenium-188	17 h	2.1	155 (15)	Tungsten-188	69.4 d
Bismuth-212[3]	60 min	----	727 (11)	Radium-224/ Lead-212	3.7d

[1]Conversion electron
[2]$\gamma \pm$ from β^+ emission
[3]Alpha emitter, also has some β^- emission

Table 8. Choice of Radionuclides for Principal Therapeutic Applications

Application	Route of Administration	Best-suited Radionuclide(s)[1]
I. Tumor Therapy		
(i) Solid Tumors		
a. Large lesions	i.v.	Sc-47, Y-90, I-131, Re-188
	intra-tumoral	Sc-47, Sm-153, Re-188
b. Micrometastases	i.v.	Sc-47, Sn-117m, Sm-153, Auger emitters
(ii) Leukemias, lymphomas	i.v.	Sc-47, Cu-67, Sn-117m, I-131
II. Palliation		
(i) Soft tissue	i.v.	Y-90, I-131, Ho-166, Re-188
(ii) Bone pain	i.v.	Sr-89, Sn-117m, Sm-153, Re-186
III. Non-Oncology and Other		
(i) Synovectomy	Regional	Sc-47, Sn-117m, Sm-153, Er-169
(ii) Marrow ablation	i.v.	Sn-117m, Ho-166
(iii) Microspheres	i.v. or regional	Y-90, lanthanides
(iv) Receptor-positive, nuclear antigens	i.v.	Auger, conversion electron, and short-range β^- emitters

[1]Based, partially, on a Therapy Isotope Workshop sponsored by Nordion International, Inc., at the 43rd Annual Meeting of the Society of Nuclear Medicine, Minneapolis, MN, June 11, 1995. The order of listing of isotopes here is based on atomic mass and not necessarily their degree of effectiveness for a particular application.