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Radionuclides used for therapy and suggestion for new candidates

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Targeted radiotherapy has the potential to provide radiation doses from a wide range of radionuclides, some of them suitable for killing single cells while others are more suitable for killing tumor cell clusters of various sizes. A list of 64 radionuclides, including 20 new potential candidates for therapy (^{73}Ga, ^{75}Se, ^{87m}Sr, ^{97}Ru, ^{103}Ru, ^{113}Sn, ^{113m}In, ^{117}Sb, ^{123}Sn, ^{131}Cs, ^{139}Ce, ^{141}Ce, ^{149}Eu, ^{167}Tm, ^{170}Tm, ^{173}Tm, ^{195}Au, ^{195m}Pt, ^{197}Pt and ^{197}Hg) were analyzed in terms of the suitability of their energies for killing tumor cells which grow as single, small, intermediate and large clusters. In addition, their possible production routes were studied.

Introduction

Radiopharmaceuticals are used extensively in diagnostic imaging and have shown a rapid growth in the past few years in therapy (oncology, bone palliation, synovectomy, etc.). The recent revival of interest on radionuclide therapy or targeted radiotherapy (TR), is a consequence of improvements in tissue specific biomolecules (monoclonal antibodies (mAbs), bone-seeking bisphosphonates, etc.) and its potential advantages over external radiotherapy, particularly for patients with inoperable or multi-site disease as neuroendocrine tumors and disseminated bone metastases. In benign disorders TR provides an alternative to surgery or medical treatments and in cancer treatment combines target selectivity with that of being systemic. TR has the potential to eradicate disseminated tumor cells and small metastases, being an effective complement or alternative to chemotherapy. On the other hand, bulky tumors and large metastases have to be treated surgically or by external radiation therapy.[1] Although long-term cure or complete remission is so far rare, TR promises to expand the usefulness of radiation techniques to a successful treatment of widespread cancer.

TR is based on the selective deposition of cytotoxic ionizing radiation from radionuclides attached to specific biomolecule that damages or destroys cells. Since TR requires the administration of significantly higher activities than for diagnostic applications, a larger number of exigencies are necessary: high target binding, uniform target distribution, minimum irradiation of critical organs, effective biologic dose-response, precise estimation of radiation dosimetry, radiation protection safety, etc. Therefore, substantial efforts in several research areas as: radionuclide production, radio-pharmaceutical chemistry, medical physics, radiation biology and oncology are required.

For many years TR has played a relatively small role in nuclear medicine practice, being restricted to the use of ^{131}I, developed more than 50 years ago for treatment of thyroid cancer. At present, TR has a great potential in oncology, due to its limited toxicity which influence patient survival time and/or quality of life in comparison with other cancer therapies. With more than ten million new cases and six million deaths each year, cancer has become one of the most devastating diseases worldwide. According to international agencies these numbers will double by 2020.[2] Cancer treatment, aiming at increased survival time and improvement of the quality of life is one of the fastest-growing cost segments of the health economy. It also accounts for the rising prevalence of cancer in an ageing society of industrialized countries as well as in developing countries. In addition to the devastating effects on patients and their families, the economic costs of cancer are enormous in terms of direct medical care resources for its treatment and in the loss of human capital due to early mortality. Pain relief and palliative care are the main feasible interventions and constitute a humanitarian duty. Although improvements in terms of survival time and quality of life of cancer patients have been achieved during the past decades, solutions for those suffering from distant metastases at the time of diagnosis still have to be developed. The opportunities for translating new insights in cancer biology into therapeutic advances in this field have never been better than at present.

Radiopharmaceutical uptake into tumors or disseminated cells is based on the fact that targeted receptors or antigens are over-expressed in cancerous cells. At present, in TR simple ions and small molecules, which follow physiological pathways as natural substrates or analogues, are used for biological targeting. Clinically valuable results obtained so far are: the long-time therapy with ^{131}I in differentiated thyroid cancer cells, incorporation of the calciummimetic element ^{89}Sr

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in areas of increased bone metabolism, bone mineral affinity of radiolabeled bisphosphonates, accumulation of the catecholamine analogue ^{131}I-MIBG (meta-iodobenzylguanidine) in phenochromocytomas and neuroblastomas, and radiolabeled somastotatin analogues for neuroendocrine tumors expressing somastotatin receptors. A new promising radioimmunotherapy mAb for treatment on non-Hodgkins's B-cell lymphoma is Ibritumomab Tiuxetan labeled with ^{90}Y (Zevalin™). Ibritumomab is a mAb directed against the CD20 antigen of B-cell lymphocytes, and Tiuxetan is the linker-chelator for the radionuclide. A recent publication reports on the radiobiology, radiation safety and future directions in radioimmunotherapy of B-cell lymphoma.[3]

Several approaches have been described to improve the radiopharmaceutical uptake in tumor cells as: (1) biological response modifiers that might regulate receptors and cell surface antigen, (2) retention and internalization by using indirect halogen labeling or metal retention and (3) intranuclear localization including transport of the radiolabeled receptor complex to the cell nucleus, DNA-binding or antisense molecules that recognize tumor specific cells, as reported by CARLSSON et al.[1] Results from research in basic tumor biology as over-expression of oncogene molecules, mutations, apoptosis, cell cycle regulation, cell surface molecules, etc., could yield valuable information for the design of new targets for therapy of different tumor cell types. This would allow to obtain tailored radiopharmaceuticals that could lead to long-term survival or even cancer cure. To design a radiopharmaceutical that selectively binds to tumor tissue and disseminated cells is a fundamental issue of scientific research and considerable efforts are necessary. Since differences in radiosensibility between tumor cells types could decide on the success or failure of targeted radiotherapy, the following additional aspects have to be considered: (1) appropriate radiation absorbed dose (which should match the biologic desirable effect), and consequently the properties of the radionuclides emissions (type of radiation, energy and half-life), (2) biological response, i.e., the response of cells to radiation as radiosensitivity, repair capacity and proliferation rate or repopulation, and (3) continuous refinement of nano- and microdosimetry in order to increase the accuracy and the dose/response correlations.

Selection of radionuclide

In conventional radiotherapy, the terms low, medium and high dose rates (LDR, MDR and HDR, respectively) are still common, but in TR these terms have no more specific meaning since it is possible to exploit subtle differences in the radiation doses provided by a wide range of radionuclides. The role of a radionuclide is to deliver a cytotoxic radiation dose, sufficient to overcome the cell response in terms of repair and proliferation. In addition, only a minimum radiation dose should be delivered to the surrounding healthy tissue. The radiation dose delivered to the cancer cells by a radionuclide should be intrinsically related to the radiobiology response in terms of the relative ability of different tissues to recover from radiation damage and the absolute ability to control concurrent tumor regrowth. As each human cancer has its own cellular cytoxicity and cytoprotective response to ionizing radiation, a certain energy threshold has to be surpassed to achieve the cell death. This means that a tailored radionuclide should exist that is able to provide the desired therapeutic effect. The energy threshold depends on several chemical/biochemical factors (carrier molecule, target affinity, cell distribution, biokinetics, route of administration, radiation safety, etc.) although the radionuclide properties play one of the most important roles. TR relies on the biological effects during the delivery of radiation. Different half-lives imply different dose rates, resulting in very different clinical response for a given total dose if the surviving cells in the irradiated volume are continuously proliferating, and the sublethal damaged cells can be repaired during the protracted dose delivery. Therefore, the principles of radiobiology, dose rate and absorbed radiation doses are the most important in order to predict the radiation effects. Radionuclide selection for TR should not be done only on the basis of their availability, but through an analysis of what would be best in terms of radiobiology. The linear-quadratic radiobiological model could be applied in TR optimization, to select a near-optimal radionuclide physical half-life.[4] Related experience in other radiotherapy procedures, could support researchers in a radiobiological selection linking physics and radiobiology, as the following examples elucidate:

(a) In interstitial permanent seeds implants the general concept is to use radionuclides with short half-lives, as ^{103}Pd, which are more efficient in case of fast growing tumors, while radionuclides with long half-lives as ^{125}I are advantageous for slow growing tumors. Radionuclides with half-lives in the range of 4–17 days are likely to be significantly better for a wide range of tumor types for which the radiobiologic characteristics are not precisely known in advance.[5]

(b) The radionuclide selection for transperineal permanent brachytherapy of prostate cancer (recommendations of the American brachytherapy society), is based on the Gleason criteria using ^{125}I in lower grade and ^{103}Pd for higher grade malignancy (both have significant difference half-lives: 59.4 and 17 days, respectively). This criterion based on radionuclide dose rate and cell doubling time was observed in vitro studies.[6]

(c) Yttrium-90 with a higher beta-energy (2.3 MeV) and longer path length (5–10 mm) than ^{131}I does (0.8 MeV and 1–2 mm, respectively), may be preferred in treating large tumors accompanied by areas of necrosis, which requires tumor-cell sterilization through a "crossfire" effect from neighboring cells that have been targeted by antibodies. This crossfire effect may be lost, however, as the tumor mass decreases, and so tumors less than 1 cm or micro- metastases might be more effectively treated using ^{131}I.[7]

In TR these concepts could probably be applied, but since a large number of radionuclides are available, it is likely and desirable to find an appropriate radionuclide for each tumor type.

Electrons and α-particles

A large number of potential therapeutic radionuclides that emit low energy (conversion and Auger), intermediate and high energy electrons (β^--emitters), or α-particles are known.[8–12] Our interest concerning therapeutic radionuclides stems from work published about two decades ago showing that ^{109}Pd and ^{166}Ho are radionuclides with physical and chemical characteristics for synoviotherapy.[13] The linear energy transfer (LET) of identical values of radiation doses by β^--emitters and α-particles produces different biologic effects, which is known as the relative biological effectiveness (RBE). It means that electrons and α-particles (highest RBE) differ in energy deposition and cytotoxicity. With decreasing tumor size the potential advantage of α-particles – producing high densities of ionization compared to electrons emitters – should increase. Due to their high energy and short range they offer cell specific targeting of pre-angiogenic microscopic lesions, tiny clusters of cancer cells, leukaemia, lymphomas, or malignancies spread on body compartments surfaces.[12] In general, it is assumed that TR of small targets like single cells or small clusters of cells require short-range high-LET radiation. An example is astatobenzylguanidine labeled with ^{211}At, proposed for the targeted therapy of micrometastatic neuroblastoma.[14] Radioimmunotherapy with α-particles has the advantage of high energy deposition in a short path length, which produces significant cellular damage close to the site of the radionuclide deposition.

Emitters of Auger electrons with energies below 40 keV and short sub-cellular path length (2–12 μm) such as ^{125}I and ^{111}In are attractive to TR. According to ADELSTEIN et al.[15] the radiobiological response to Auger electrons depends particularly on the location at which the decay is taking place. This refers not just to the site within the cells but also within the nucleus in the fine structure of chromatin. As radiopharmaceuticals are never deposited to 100% on the targeted organ or tissue, the choice between α- and β^--emitters should also taken into consideration, the possibility that critical organs might be targeted and submitted to high ionization radiation doses.

The use of positron emitters radionuclides such as ^{64}Cu, ^{114m}In, ^{123}I, ^{149}Tb, ^{195m}Hg, etc., for TR is questionable because the interaction of positrons in tissues results in the 511 keV annihilation photons. These constitute a major contribution to the absorbed dose in the surrounding healthy tissues. Nevertheless, positron emitters may be valuable for the selection of radio-immunotherapy candidates by confirming tumor targeting and/or estimating radiation doses. For example, ^{89}Zr labeled mAbs were proposed for scouting therapeutic doses of ^{90}Y labeled mAbs, while ^{124}I was proposed for scouting therapeutic doses of ^{131}I or ^{186}Re mAbs in squamous cell carcinoma studies.[16]

Radionuclides and cell clusters

According to O'DONOGHUE et al.,[8] a linear correlation occurs between optimal cure tumor diameter and the equilibrium dose constant (EDC), and this parameter could be used as a predictor of optimal cure size. According to MIRD parameters, the average energy deposited in a target organ is the product of the EDC and the absorbed fraction ϕ. Considering the same organ or tissue, i.e., the same absorbed fraction values the average energy deposited in a target organ is, therefore, directly proportional to the EDC. Average energies (or EDC values) could be grouped into low, medium and high energy electron emitting radionuclides and correlated with tumor sizes. ZWEIT[17] claims that low energy electron emitting radionuclides are best suited for small tumors ($d \approx 1$–2 mm), high electron emitting radionuclides for large tumors ($d \geq 1$ cm) and medium electron emitting radionuclides for intermediate sizes. On the other hand, CARLSSON et al.[1] consider a list of radionuclides with therapeutic interest based on the type and energy of emission suitable for killing tumor cells when the cells growing as single and small, intermediate or large clusters corresponding to intervals 10^4–10^6, 10^6–10^8 and 10^8–10^{10} tumor cells per cluster, respectively. Based on the 22 potential therapeutic radionuclides examined by O'DONOGHUE et al.,[8] a direct correlation between E_{aver} (keV) and EDC (g Gy/MBq day) is demonstrated in Fig. 1. The plot is extended to other potential therapeutic radionuclides proposed by several authors,[9–11,13,18–22] using the average energies of β^-, conversion electrons and Auger radiation data, obtained from the "Radionuclide Decay Data in the MIRD Format", IAEA Nuclear Data Centre http://www-nds.iaea.org.mird. In addition, we included into Fig. 1, further potential radionuclides for therapy, (which could be extended to intracavitary, intratumoral and permanent implants) as: ^{73}Ga, ^{75}Se, ^{87m}Sr, ^{97}Ru, ^{103}Ru, ^{113}Sn, ^{113m}In, ^{117}Sb, ^{123}Sn, ^{131}Cs, ^{139}Ce, ^{141}Ce, ^{149}Eu, ^{167}Tm,

^{170}Tm, ^{173}Tm, ^{195}Au, ^{195m}Pt, ^{197}Pt and ^{197}Hg (low, intermediate and high electron emission). These radionuclides are electron and photon emitters with average energies ranging from 5.02 to 523.0 keV and 4.17 to 497.6 keV, respectively, and are selected from a Radionuclide Table scanning considering that X-rays and photons should be less than 500 keV. Their half-lives range from 0.07 days (≈100 min) to 129.20 days (Table 1). From theoretical considerations the half-lives of ^{170}Tm and ^{123}Sn appear to be too long (128.60 and 129.20 days, respectively), but could be appropriated or even desirable to treat a specific cell tumor type or in intracavitary, intratumoral or permanent implants.

Despite current trends to limit the list of radionuclides to a small number of selected radionuclides a more extended list might have substantial advantages. Covering a wide range of half-lives and electron energies offers the possibility to tailor the radiopharmaceutical to various kinds of applications. Some of the additional radionuclides proposed by us are related to radioisotopes of the same element or chemically similar already reported as being in use or of potential interest in imaging/radiotherapy as **^{73}Ga**/^{67}Ga, **^{113m}In**/^{111}In, **^{113}Sn+^{123}Sn**/^{117m}Sn/^{121}Sn, **^{139}Ce+^{141}Ce**/^{134}Ce, the radiolanthanides **^{149}Eu**, **^{167}Tm, ^{170}Tm,** and **^{173}Tm**/^{134}Ce/^{143}Pr/^{149}Pm/^{153}Sm/^{165}Dy/^{161}Ho/^{166}Ho/^{169}Er/^{177}Lu, **^{195}Au**/^{198}Au, **^{195m}Pt+^{197}Pt**/^{191}Pt. In bold letters, the proposed radionuclide; no-bold, the same element or chemically similar elements are proposed. The remaining proposed radionuclides have been already reported for imaging as **^{75}Se, ^{87m}Sr, ^{97}Ru, ^{103}Ru, ^{117}Sb** and **^{197}Hg**, offering an advantageous combination of image and therapy.[23,24] These radionuclides overcome the difficulties of estimating absorbed dose distributions, because they can be considered as scouting radionuclides for therapeutic doses. In addition, presenting identical chemical properties, the optimization of radiopharmaceuticals procedures involved in labeling of biospecific molecules, could be achieved more easily. The estimated values of EDC for the 64 radionuclides as well as their half-lives and average electron and photon energies are listed in Table 1. This table, includes the radionuclides selected by CARLSSON et al.[1] as suitable for killing tumor cells for different cluster sizes. We extended this classification to further radionuclides considering that the intervals are somewhat arbitraries. This list yields valuable informations for a first approach to radionuclide selection, particularly when biological data as tumor or/and cell cluster size are available. Therefore, the choice of a radionuclide results from matching physical with biological data, in spite of the fact that other radiobiological issues as re-oxygenation, cell cycle redistribution, re-population, bystander effects, induction of apoptosis, etc., could give an important contribution to the design of tailored radiopharmaceuticals. Therefore, radiobiology and microdosimetry are very important issues in radionuclide therapy design.

Radionuclide viability production

A short overview of the proposed radionuclide viability production is outlined, without considering aspects of carrier-free or production with high specific activities which are very important aspects and should be analyzed separately.

Ga-73

For the production of ^{73}Ga two cyclotron-based routes have been investigated. In the case of the bombardment of natural Ge by protons using the ^{nat}Ge(p,*x*)^{73}Ga reaction, a maximum cross section of 4.99 mbarn at a proton energy of 94.2 MeV has been reported.[25] The drawback is the simultaneous production of other radioactive Ga isotopes (^{65}Ga, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{72}Ga) in similar quantities. ^{73}Ga can also be generated using the ^{76}Ga(α,p) ^{73}Ga reaction as reported by ROTBARD et al.[26] for 26 MeV α-particles.

Se-75

The production of ^{75}Se by thermal neutron capture (σ_{th} = 68.9 barn, RI = 582 barn) is hampered by the low natural abundance of ^{74}Se (0.9%). The use of isotopically enriched material is, therefore, of advantage and also reduces the contamination by the long-living ^{79}Se ($T_{1/2} \leq 65000$ y). The cyclotron-based production using the proton and deuteron-induced reactions ^{75}As(p,n)^{75}Se and ^{75}As(d,2n)^{75}Se with maximum cross sections of 880 mbarn at 11.5 MeV and 700 mbarn at 19 MeV, respectively, is an alternative.[27,28]

Sr-87m

This radionuclide is usually obtained from an ^{87}Y/^{87m}Sr generator.[29] ^{87}Y can be easily produced at cyclotrons irradiating rubidium or strontium targets. Natural rubidium targets may be used for the ^{85}Rb(α,2n)$^{87m+g}$Y reaction, since the abundance of ^{85}Rb is high.[30] The maximum cross section of 1325 mbarn for this reaction occurs for 26.6 MeV helium ion energy.[31] The ^{87}Sr(p,n)^{87}Y and ^{88}Sr(p,2n)^{87}Y reactions using natural or enriched strontium targets are an alternative approach although the cross sections are not as well known as for the Rb-based production.[29,32]

Ru-97

Excitation functions for the production of ^{97}Ru using helium ion beams impinging on natural molybdenum targets have been investigated by GRAF and MÜNZEL.[33]

Table 1. Therapeutic radionuclides, half-lives, photon and electron average energies, equilibrium dose constant (Δ) and cluster size

Radionuclide	Half-life, day	E_{ph}, keV	E_e, keV	Δ, g·Gy/MBq·day	Cluster size
Cr-51	27.70	32.9	3.65	0.050	
Cs-131	**9.69**	**22.9**	**5.02**	**0.069**	
Ce-134	3.16	27.9	5.48	0.076	
Se-75	**119.8**	**389.3**	**13.9**	**0.192**	
Ru-97	**2.9**	**248.6**	**15.2**	**0.210**	
I-125	59.4	42.3	16.6	0.229	
Eu-149	**93.1**	**65.5**	**19.2**	**0.265**	
Os-189m	0.24	-	21.5	0.297	
Sb-119	1.59	23.1	22.7	0.313	
I-123	0.553	172.3	26.6	0.367	
Ho-161	0.10	57.8	27.7	0.382	
Sb-117	**0.117**	**185**	**28.1**	**0.388**	
Ce-139	**137.6**	**160**	**32.1**	**0.443**	
In-111	2.80	406	32.2	0.444	Single cells
Rh-103m	0.04	1.7	35.3	0.487	
Ga-67	3.26	160	35.7	0.489	and
Tl-201	3.04	92.7	36.4	0.502	
Pd-103	16.99	16.3	40.2	0.556	
Au-195	**186.1**	**84.7**	**42.4**	**0.585**	small clusters
Hg-197	**2.67**	**99.1**	**64.2**	**0.888**	
Sr-87m	**0.117**	**321**	**64.7**	**0.893**	*10^4 – 10^6 tumor*
Pt-191	2.80	293	65.6	0.905	*cell per cluster*
P-33	25.34	-	76.4	1.059	
Er-169	9.40	0.165	103.0	1.421	
Ru-103	**39.26**	**497.9**	**103.3**	**1.425**	
Yb-169	32.0	334.3	114.5	1.580	
Au-199	3.14	95.2	115.0	1.587	
Sn-121	1.13	-	116.0	1.600	
Tm-167	**9.25**	**147.2**	**124.2**	**1.714**	
Yb-175	4.19	38.9	129.4	1.786	
In-113m	**0.07**	**260**	**132.0**	**1.822**	
Sn-113	**115.1**	**284**	**137.0**	**1.891**	
Lu-177	6.65	33.4	147.0	2.028	
Rh-105	1.47	77.3	153.0	2.121	
Sn-117m	13.60	158	156.0	2.153	
Cu-67	2.58	115	156.0	2.153	
Sc-47	3.35	109	162.0	2.247	
Pt-195m	**4.02**	**75.4**	**169.1**	**2.333**	
Ce-141	**32.51**	**76.7**	**170.0**	**2.346**	
I-131	8.02	383.1	192.3	2.658	
Tb-161	6.88	36.0	196.1	2.706	
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As-77	1.62	8.31	225.0	3.130	
Pt-197	**0.83**	**25.1**	**251.0**	**3.470**	
Sm-153	1.94	63.5	269.2	3.720	Intermediate
Gd-159	0.77	56.6	308.5	4.257	clusters
Tm-173	**0.34**	**388**	**310.0**	**4.278**	
Pr-143	13.57	-	315.0	4.347	*10^6 – 10^8 tumor*
Au-198	2.70	403	328.0	4.526	cell per cluster
Tm-170	**128.60**	**4.17**	**328.0**	**4.526**	
Re-186	3.72	20.8	334.8	4.620	
Ag-111	7.45	26.5	350.7	4.839	
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Pd-109	0.57	11.8	436.2	6.019	
Ga-73	**0.20**	**340.5**	**446.7**	**6.164**	
Dy-165	0.10	26.3	448.3	6.187	Large clusters
Pm-149	2.21	11.9	450.7	6.220	
Sn-123	**129.20**	**6.89**	**523.0**	**7.286**	*10^8 – 10^{10} tumor*
Sr-89	50.53	-	585.0	8.073	cell per cluster
Ho-166	1.12	30.1	694.5	9.584	
P-32	14.26	-	695.0	9.591	
Re-188	0.71	61.1	778.2	10.740	
Pr-142	0.80	58.1	809.0	11.164	
Ir-194	0.80	90.9	810.5	11.185	
In-114m/In-114	49.51	82.54	917.0	12.655	
Y-90	2.67	-	934.0	12.889	

In bold, new proposed therapeutic radionuclides, and underlined those referred as suitable for single, small, intermediate and large clusters treatment by CARLSSON et al.[1]

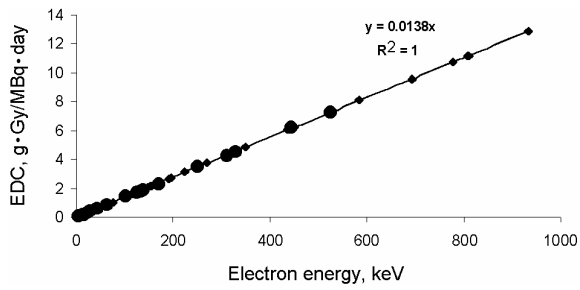

Fig. 1. Relationship between equilibrium dose constant (EDC) and average electron energy; ♦ Therapeutic radionuclides, ● proposed 20 new therapeutic radionuclides

They have reported cross sections of up to 1290 mbarn for the ^{95}Mo(α,2n)^{97}Ru reaction. A drawback is the simultaneous production of ^{103}Ru, which has a half-life of 39.3 days, in targets with natural isotopic composition. Therefore, the use of targets enriched in ^{95}Mo (natural abundance 15.92%) seems advisable.

Ru-103

Although the production of this isotope is in principle possible using cyclotrons, as indicated in the previous paragraph, thermal neutron capture is the more suitable method. The reaction ^{102}Ru(n,γ)^{103}Ru has a thermal cross section and resonance integral of σ_{th} = 1.23 barn and RI = 4.06 barn, respectively.[34] Thermal capture reactions in other ruthenium isotopes lead either to stable isotopes or radioisotopes with a half-life significantly shorter than that of ^{103}Ru.

Sn-113

The production of ^{113}Sn by thermal neutron capture via the reaction ^{112}Sn(n,γ)^{113}Sn has a moderate thermal cross section of σ_{th} = 1.14 barn and a resonance integral of RI = 29.7 barn.[34] The use of the reaction is hampered by the low abundance of ^{112}Sn (0.97%) in natural tin. Although, the other tin radioisotopes, produced during the thermal neutron irradiation of natural tin targets, have half-lives that are much shorter than that of ^{113}Sn, the use of enriched targets is recommended. Alternatively, the isotope can be obtained at cyclotrons by irradiating natural indium targets with protons or deuterons. The energy dependence of the ^{113}In(d,2n)^{113}Sn reaction cross section shows a plateau-like behavior with a $\sigma \approx 1$ barn between 11 and 19 MeV deuteron energy.[35] For the ^{nat}In(p,2*x*)^{113}Sn reactions a maximum cross section of 780 mbarn at 27.8 MeV proton energy has been reported.[36]

In-113m

The isotope ^{113m}In is obtained from a ^{113}Sn/^{113m}In generator.[37] For the production of ^{113}Sn see the preceding paragraph.

Sb-117

The only feasible production route for ^{117}Sb is the irradiation of natural tin targets with protons. KORMALI et al.[38] reported a cross section of 309 mbarn at 18.8 MeV incident proton energy for the ^{nat}Sn(p,*x*)^{117}Sb reactions.

Sn-123

The only feasible production route for ^{123}Sn is the thermal neutron capture reaction ^{122}Sn(n,γ)^{123}Sn. The relatively low thermal neutron cross section (σ_{th} = 0.183 barn) and resonance integral (RI = 0.886 barn) in combination with the low natural abundance of ^{122}Sn (4.63%) make it necessary to use isotopically enriched targets for the production of ^{123}Sn in useful quantities.[34]

Cs-131

The isotope ^{131}Cs can be obtained from the decay of ^{131}Ba which may be produced by thermal neutron capture.[39] Despite its reasonably high thermal cross section (σ_{th} = 11.3 barn) and resonance integral (RI = 175 barn), the use of the reaction ^{130}Ba(n,γ)^{131}Ba is hampered by the low natural isotopic abundance of ^{130}Ba (0.106%).[33] An alternative is the cyclotron production via the ^{127}I(α,γ)^{131}Cs reaction that exhibits a cross section of 176 mbarn at a helium ion energy of 15.7 MeV.[40]

Ce-139

Although ^{139}Ce can be produced by thermal neutron capture the simultaneous production of ^{141}Ce and ^{143}Ce during the irradiation of natural cerium targets and the low natural isotopic abundance of ^{138}Ce (0.25%) renders this method problematic. The reaction ^{139}La(p,n)^{139}Ce which has a cross section of about 300 mbarn at 10 MeV proton energy is the more suitable method for obtaining this isotope.[41]

Ce-141

Thermal neutron capture via the reaction ^{140}Ce(n,γ)^{141}Ce with its moderate thermal cross section and resonance integral of σ_{th} = 0.575 barn and RI = 0.281 barn, respectively,[34] is hampered by the competing reaction ^{142}Ce(n,γ)^{143}Ce. On the other hand, the distinct lower half-life of ^{143}Ce ($T_{1/2}$ = 33.0 h) allows to reduce this radiocontaminant to less than 0.1% within about two weeks of cooling time and a moderate (25%) loss of ^{141}Ce activity. Carrier-free ^{141}Ce may be obtained from irradiation of lanthanum with helium ions using the ^{139}La(α,pn)^{141}Ce reaction. A cross section of 29 mbarn was measured for an incident helium ion energy of 38.5 MeV.[42] Alternatively the ^{142}Ce(α,nα)^{141}Ce reaction can be used for which a maximum cross section of 87 mbarn at 39.3 MeV was reported.[43]

Eu-149

This isotope can only be obtained using cyclotron-based production paths. The reactions ^{151}Eu(p,*x*)^{149}Eu and ^{151}Eu(d,*x*)^{149}Eu have been investigated by WEST et al.[44] The maximum reaction cross sections of 150 mbarn and 100 mbarn, respectively, are both reported for 34.5 MeV energy of the incident beam.

Tm-167

As reported by MARTIN and PILGER,[45] the production of ^{167}Tm is possible using the ^{165}Ho(α,2n)^{167}Tm reaction. The maximum cross section (ca. 700 mbarn) for this reaction occurs for helium ion energies between 26.7 and 28.0 MeV. The cross section of the competing ^{165}Ho(α,n)^{168}Tm reaction is about an order of magnitude lower and other reactions producing Tm isotopes have a higher threshold energy. An alternative offers the irradiation of natural erbium with protons.[46] The ^{nat}Er(p,*x*)^{167}Tm reactions exhibit a maximum cross section of 1700 mbarn at an incident proton energy of 22 MeV.

Tm-170

Thermal neutron capture is the only possibility to obtain ^{170}Tm in sufficient quantities by the reaction ^{169}Tm(n,γ)^{170}Tm. The large thermal cross section and resonance integral of $\sigma_{th} = 109$ barn[47] and RI = 1548 barn,[48] respectively, and ^{169}Tm being the only natural isotope of thulium guarantee the easy production of large quantities even at reactors with moderate powers.[49]

Tm-173

In contrast to ^{170}Tm, the production of ^{173}Tm in larger quantities is difficult. A feasible accelerator-based method employs the ^{176}Yb(p,α)^{173}Tm reaction with a cross section of 4.1 mbarn for 18 MeV protons.[50] For the fast neutron induced reaction ^{173}Yb(n,p)^{173}Tm a cross section value of 8.2 mbarn has been measured at a neutron energy of 14.6 MeV.[51] Unfortunately, no cross section values for this reaction at uranium fission spectrum energies are available to estimate the viability of reactor-based production.

Au-195

The production of ^{195}Au is only feasible using ^{197}Au(α,*x*)^{195}Au reactions. Cross sections up to 840 mbarn were observed in the energy interval from 70 to 80 MeV helium ion energy.[52] Other Au isotopes produced in the irradiation have significantly lower half-lives and lower cross sections. On the other hand, with half-lives between 1.58 days (^{194}Au) and 6.18 days (^{196}Au) a relatively long cooling time is required to obtain a sufficiently pure ^{195}Au ($T_{1/2} = 186.1$ d).

Pt-195m

The only feasible production method for ^{195m}Pt, is the irradiation of highly enriched ^{194}Pt targets in a high flux nuclear reactor, since the thermal cross section of the ^{194}Pt(n,γ)^{195m}Pt reaction is small (0.09 barn) compared to the ^{195m}Pt(n,γ)^{196}Pt burn-up cross section reaction (13,000 barn).[53]

Pt-197

The most convenient production method is the thermal neutron capture by the reaction ^{196}Pt(n,γ)^{197}Pt. ^{196}Pt has a thermal cross section and resonance integral of $\sigma_{th} = 0.74$ barn and RI = 8 barn, respectively.[54] As most important radiocontaminant occurs, ^{199}Pt that decays with a half-life of 30.80 minutes into the easily separable ^{199}Au. The activity contributions of ^{191}Pt and ^{193}Pt can be neglected due to the low isotopic abundance of ^{190}Pt in natural platinum and the long half-life of ^{193}Pt ($T_{1/2} = 50.7$ y), respectively. In principle ^{197}Pt can also be produced by the ^{197}Au(n,p)^{197}Pt reaction by fast neutrons but the cross sections in the fission spectrum region are unknown. For neutron energies between 12 MeV and 20 MeV, cross sections in the order of a few mbarn have been reported.[55]

Hg-197

Carrier-free ^{197}Hg can be obtained using the ^{197}Au(p,n)^{197}Hg reaction. The reaction yields ^{197}Hg in the ground and metastable state. ^{197m}Hg decays with a half-life of 23.8 hours into ^{197}Hg.[56] The maximum cross section for the production of both, ^{197m}Hg and ^{197g}Hg is 148 mbarn at 10 MeV incident proton energy.[57] For alpha-particles incident on a Au target also the reaction ^{197}Au(α,3np)^{197m}Hg can be taken into account with a maximum cross section of 25 mbarn at 51.7 MeV.[58] Thermal neutron capture using the ^{196}Hg(n,γ)^{197}Hg reaction is also feasible. Due to the very high thermal cross section and resonance integral of $\sigma_{th} = 3079$ barn and RI = 420.1 barn, respectively, large quantities can be produced at nuclear reactors. The major drawbacks are the low abundance of ^{196}Hg (0.14%) in natural mercury and the occurrence of the radiocontaminant ^{203}Hg with a half life of $T_{1/2} = 46.6$ days[55] due to thermal neutron capture in ^{202}Hg (abundance: 29.80%, $\sigma_{th} = 4.96$ barn and RI = 3.12 barn).[59]

Conclusions

A selection of 20 additional radionuclides is considered to present physical characteristics useful for targeted radiotherapy. In addition, they also can be considered appropriate for intracavitary, intratumoral or permanent implants. The newly proposed radionuclides and those previously referred by other authors, a total of

64, were tabulated according to their average electron energies. Average photon energies, half-lives and equilibrium dose constants were included. The additionally proposed radionuclides increase the number of options for suitable radionuclides for killing tumor cells when they grow as small, intermediate and large clusters. A short analysis of the production possibilities of the proposed additional radionuclides has been outlined.

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