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(54) **PRODUCTION OF THORIUM-229 FROM THORIUM-230**

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(57) **ABSTRACT**

A method for producing ^{229}Th uses ^{230}Th as a target material. ^{229}Th can be formed from ^{230}Th using energetic particles, including neutron, gamma ray, proton or deuteron bombardment.

PRODUCTION OF THORIUM-229 FROM THORIUM-230

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional of U.S. patent application Ser. No. 10/938,044 filed on Sep. 10, 2004, which claims the benefit of U.S. Provisional Application No. 60/503,149 entitled Process For Production of Thorium-229 filed on Sep. 15, 2003, the entirety of both being incorporated herein by reference in their entireties.

STATMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] The United States Government has rights in this invention pursuant to Contract No. DE-AC05-00OR22725 between the United States Department of Energy and UT-Battelle, LLC.

FIELD OF THE INVENTION

[0003] The invention relates to methods for producing thorium-229.

BACKGROUND OF THE INVENTION

[0004] The goal in the treatment of cancerous tumors and micrometastases has long been to kill the cancerous cells without killing healthy cells. Today, in the development of new short-range, site-specific therapies, there is increasing interest in using radioisotopes which decay with the emission of alpha particles. Indeed, recent clinical trials have shown the effectiveness of the alpha-emitter bismuth-213 in killing cancer cells in patients with acute myeloid leukemia. In addition, lung tumors in mice have been effectively treated for the first time by using an antibody radiolabeled with bismuth-213, targeting the lung vascular endothelial cells.

[0005] Alpha-particles are of interest in site-specific therapy because of their short range. Bismuth-213emits an 8 MeV alpha particle which penetrates only 6 to 10 cell layers nearby, killing the cells in its short path (~80 μm), including cancer cells. In addition to bismuth-213, there are only eight other known alpha-emitters with potential for this type of application, namely, astatine-211, bismuth-212, lead-212, radium-223, radium-224, radium-225, actinium-225, and fermium-255.

[0006] There are a number of factors that need to be considered in using any radioisotope in humans, especially those radioisotopes emitting alpha particles. These factors include availability, cost, nuclear characteristics, chemistry, and in vitro and in vivo stability of the biomolecules labeled with alpha-emitters. The first two alpha-emitters to be used in human trials are bismuth-213 and astatine-211; the other seven radioisotopes mentioned above are under more preliminary investigations. Bismuth-213 is currently being used in human trials at Memorial Sloan-Kettering Cancer Center (New York) and is generated in-house from the decay of actinium-225. This radioisotope is produced from the decay of radium-225, which is the daughter of thorium-229, which, in turn is the alpha decay daughter of uranium-233.

[0007] Currently, uranium-233 is the only viable source for high purity thorium-229. However, the anticipated growth in demand for actinium-225 may soon exceed the levels of thorium-229 present in the aged uranium-233 stockpile (in fact, there have been occasions that supply has not been able to keep up with the current demand). It is estimated that only ~45 g or ~9 curies of thorium-229 (^{229}Th specific activity is 0.2 mCi/mg) can be extracted from entire uranium-233 stockpile at the Oak Ridge National Laboratory (hereinafter "ORNL"). The uranium-233 stockpile at ORNL is about 50% of the high quality uranium-233 available in the world which provides reasonably low quantities of both Th-228 and Th-232. This stockpile is only about eighty times the current thorium stock. Large quantities of Th-228 or Th-232 can make the use of a uranium-233 stockpile impractical. Considering the rather low annual production rate of thorium-229 from uranium-233 (0.92 mCi/kg) and the increasing difficulties associated with uranium-233 safeguards, large-scale routine processing of uranium-233 is, at a minimum, problematic.

[0008] A number of approaches have been identified as alternative routes for the production of ^{229}Th ($t_{1/2}$=7340 y), or for direct production of ^{225}Ra ($t_{1/2}$=15 d), and ^{225}Ac ($t_{1/2}$=10 d). These approaches include a) production of ^{229}Th in a nuclear reactor by thermal neutron transmutation of ^{226}Ra targets, b) direct production of ^{225}Ac from proton and deuteron irradiation of ^{226}Ra targets via the [p,2n] and [d,3n] reactions, respectively, at accelerators, and c) indirect production of ^{225}Ac from the decay of ^{225}Ra which in turn is produced by high energy γ-ray irradiation of a ^{226}Ra target, [γ,n] reactions. The alternate route (a) noted above produces a low yield of ^{229}Th.

SUMMARY OF THE INVENTION

[0009] A method for producing ^{229}Th includes the steps of providing ^{230}Th as a target material, and bombarding the target material with energetic particles to form ^{229}Th. The energetic particles can comprise neutrons sufficient to result in a ^{230}Th[n,2n]^{229}Th reaction to form ^{229}Th. The energetic particles can comprise gamma rays having energies sufficient to result in ^{230}Th[γ,n]^{229}Th reaction to form ^{229}Th, such as having an energy of from 8 MeV to about 12 MeV. The energetic particles can comprise protons or deuterons having energies sufficient to result in ^{229}Pa, the ^{229}Pa decaying or transmuting into ^{229}Th. When protons are used, the energy of the protons can be from 8 MeV to about 16 MeV. When deuterons are used, the energy of the deuterons can be from 16 MeV to about 28 MeV.

DETAILED DESCRIPTION OF THE INVENTION

[0010] The invention provides methods for the production of thorium-229 using thorium-230. The methods have good yields and generally lower contamination levels as compared to known methods for production of thorium-229 other than by decay of U-233.

[0011] In one embodiment, Thorium-229 is produced via neutron bombardment of a thorium-230 target. Thorium-230 with a half-life of 7.5×10^4 y, is a part of the uranium-238 decay chain, and depending on the geological location the amount of ^{230}Th in uranium mines is about 16 g per ton of uranium.

[0012] The ^{230}Th[n,2n]^{229}Th reaction has a threshold energy of 6.8 MeV and a cross section of 1.34 barns at 14

MeV. These assumptions translate to a production rate of ~2.5 nCi of ^{229}Th per day per gram of ^{230}Th at neutron flux of $\mathbf{10}^{11}$ n $s^{-1}\cdot cm^{-2}$ with an energy of 14 MeV. The 14 MeV neutrons can be produced in a cyclotron through a number of nuclear irradiations, the most common being the irradiation of a Be target with deuterons having an energy of ~30 MeV, generating a neutron flux of $\sim 3\times 10^{10}$ n.$s^{-1}\mu A^{-1}$ at 0-20° solid angle. For a 10 μA deuteron beam, the total neutron flux in the forward direction would be $\sim 3\times 10^{11}$, distributed over an area ~2 cm^2. By controlling the incident deuteron energy below ~35 MeV, production of higher energy neutrons (>20 MeV) will be substantially minimized, and hence the production of unwanted ^{228}Th which is produced via ^{230}Th[n,3n]^{228}Th can be substantially reduced. It is noted that the threshold for the ^{230}Th[n,3n]^{228}Th reaction is about 12 MeV. As noted above, high energy neutrons can be obtained from reactors such as High Flux Isotope Reactors. Alternatively, 14 MeV neutrons can be readily obtained from D-T fusion reactions. Also, high energy neutrons can be produced in charged particle accelerators via fission, fusion, pick-up, spallation, and other reactions.

[0013] Alternatively, high-energy neutrons available from a nuclear reactor can be used, where the flux of neutrons with energy >7 MeV is on the order of 5×10^{13} n $s^{-1}\cdot cm^{-2}$. The fission averaged cross section of ^{230}Th[n,2n]^{229}Th reaction is 10.66 mb. The yield of ^{229}Th from reactor irradiation of ^{230}Th would be on the order of 10 nCi per gram of target per day or 3.7 μCi per gram per year of irradiation. The main disadvantage of the ^{230}Th[n,2n]^{229}Th reaction would be the generation of fission products as the fission averaged cross section of ^{230}Th is rather significant (163 mb).

[0014] In another embodiment, thorium-229 is produced via gamma ray bombardment of a thorium-230 target via the ^{230}Th, [γ,n] reaction. No excitation function for the ^{230}Th [γ,n]^{229}Th reaction is currently known. However, from the reported excitation functions for ^{232}Th[γ,n] reactions, a threshold energy of ~6 MeV can be expected, and a maximum cross section of ~440 millibarns at ~11.5 MeV. The maximum incident energy of the incident gamma ray for this reaction is about 12 MeV in order to minimize the production of unwanted ^{228}Th by the ^{230}Th[γ,2n]^{229}Th reaction. Production of ^{231}Th via the ^{232}Th[γ,n] reaction is known to be 22 mCi/h/g of ^{232}Th in a 10 kW electron accelerator producing 25 MeV electrons. If ^{229}Th is produced from ^{230}Th at the same rate, the product activity of ^{229}Th will be 0.21 μCi/d/g of ^{230}Th.

[0015] In another embodiment, thorium-229 is produced via proton and deuteron irradiation of thorium-230 targets, such as in an accelerator. Both reactions are believed to actually proceed through production of relatively short-lived protactinum-229 having a half life of only 1.5 day, ^{230}Th [p,2n]^{229}Pa (EC, $t_{1/2}$=1.5 d) ^{229}Th and ^{230}Th [d,3n]^{229}Pa (EC, $t_{1/2}$=1.5 d)^{229}Th reactions, respectively. No excitation functions for these reactions are reported. In the case of the proton-induced reaction, from the reported excitation function for a similar reaction using a thorium-232 target, ^{232}Th[p,2n] reaction, a threshold energy of ~10 MeV can be expected, a maximum cross section of ~400 millibarns at ~15 MeV, and a cross section of ~200 mb at 20 MeV. However, in order to minimize the production of unwanted ^{228}Th by the ^{230}Th[p,3n]^{228}Pa (EC, $t_{1/2}$=22 h)^{228}Th reaction, the maximum energy of the incident proton used for this reaction is limited to about 16 MeV. Assuming an average cross section of 200 mb, bombarding a foil of ^{230}Th with a thickness of 0.5 mm (~0.55 g/cm^2, range of protons 16→10 MeV) translates to a production rate of ~0.6 μCi of ^{229}Th per day at a 100 μA current of protons with an incident energy of 16 MeV.

[0016] In the case of the deuteron-induced reaction, from the reported excitation functions of for a similar reaction using a bismuth-209 target, ^{209}Bi[d,3n] reaction, a deuteron threshold energy of ~16 MeV can be extrapolated. Above the threshold, the cross section sharply increases to a maximum of ~1.5 barn, then drops off rapidly to ~500 mb at 32 MeV. The maximum energy of the incident deuteron for this reaction is about 28 MeV, in order to reduce the probability of the evaporation of an additional neutron which results in the production of unwanted ^{228}Th by the ^{230}Th[d,4n]^{228}Pa (EC, $t_{1/2}$=22 h) ^{228}Th reaction. In this case, assuming an average cross section of 700 mb, bombarding a foil of ^{230}Th with a thickness of 0.7 mm (~0.78 g/cm^2, range of deuterons 28→16 MeV) results in a production rate of ~3 μCi of ^{229}Th per day at a 50 μA current of deuterons with an incident energy of 28 MeV.

[0017] The necessary fast turn-around for processing of the Ra target in the direct production of ^{225}Ra and ^{225}Ac (a few days post-irradiation) is the main disadvantage for proton, deuteron and gamma ray irradiation of a radium target via ^{226}Ra[p,2n]^{225}Ac, ^{226}Ra[p,pn]^{225}Ra ($t_{1/2}$=15 days, β^-)^{225}Ac, or ^{226}Ra[γ,n]^{225}Ra ($t_{1/2}$=15 days, β^-)^{225}Ac reactions. The main drawback in the reactor approach for the production of ^{229}Th using a ^{226}Ra target is the significant contamination of ^{229}Th with ^{228}Th ($t_{1/2}$=2.8y) that generally results. The approaches for production of ^{229}Th via alpha or ^{3}He bombardment of a radium-**226** target described above generally provides thorium-229 with significantly reduced levels of ^{228}Th contamination. The fast neutron irradiation of a thorium-230 target, or neutron capture by ^{228}Ra generally also provides thorium-229 with significantly reduced levels of ^{228}Th contamination as compared to the reactor approach using a ^{226}Ra target.

[0018] The thorium-229 generated using the invention must be separated from the target material and other by-products generated for most uses. Radiochemical procedures can be used for the separation of thorium-229 from target materials and by-products. The chemical processing of U, Th, Ac and Ra has been studied extensively in the past 70 years and is well known. In summary, after irradiation, the target can be dissolved and Th selectively retained on anion exchange resin (e.g. MP1 resin, BioRad Inc.) from 7.5 M HNO_3 as the Th $(NO_3)_6^{2-}$complex, while U (VI), Ac (III), Fe (III), Al (III), Ra (II) and Pb (II) and a number of fission products are eluted. Subsequent to the elution of Th from the column with O.1 M HNO_3, the Th is further purified by hydroxide precipitation in the presence of the Fe^{+3} carrier to eliminate Tc and I. Thorium is then separated from the Fe^{+3} carrier by retaining $FeCl_4^-$on an anion exchange column in 10 M HCl. After allowing ^{225}Ra and ^{225}Ac to reach their equilibrium values (~45 days), they are separated from Th using anion exchange resin and 7.5 M HNO_3 as described above. Separation of Ac from Ra is accomplished by one of two methods, both based on cation exchange resin from nitric acid media. In the first method, using 1.2 M HNO_3 as eluent, Ra^{+2} is eluted ahead of Ac^{+3} with a small overlap.

When the eluent is changed to 0.15 M NH_4Cl and 0.1 M NaEDTA, pH ~5, (the second method), Ac is eluted quantitatively whereas Ra remains adsorbed on the resin (reverse phase chromatography). Both methods have been tested extensively for the separation of carrier-free ^{225}Ac from ^{224}Ra and ^{225}Ra and they work well.

[0019] Thorium-229 produced using the invention is expected to be used for a variety of medical applications, such as for killing cancer cells. With appropriate biological targeting molecules, bismuth-213 can be used not only in cancer therapy but also for autoimmune diseases, organ transplantations, bone marrow ablations, and vasculature irradiation following restenosis.

[0020] For example, the invention can be used for cell-directed radiation therapy. In this method, millions of cancer seeking antibodies guide radiation to the cancer. Energetic radioactive isotopes (radioisotopes which are capable of depositing a significant amount of energy in a short distance in the tissue) according to the invention are attached to the antibodies. As the cancer hunting antibodies flow though the blood stream, the radioactive isotopes ride. along. The antibodies target cell surface binding sites specific to the cancer cells. When the antibodies reach a cancer cell, they attach. Radiation from these bound radioisotopes then destroys the cancer cells that make up the malignant tumor.

[0021] This invention can be embodied in other forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be had to the following claims rather than the foregoing specification as indicating the scope of the invention.

We claim:

1. A method for producing ^{229}Th, comprising the steps of:

providing ^{230}Th as a target material, and

bombarding said target material with energetic particles to form ^{229}Th.

2. The method of claim 1, wherein said energetic particles comprise neutrons sufficient to result in a $^{230}Th[n,2n]^{229}Th$ reaction to form ^{229}Th.

3. The method of claim 1, wherein said energetic particles comprise gamma rays having energies sufficient to result in $^{230}Th[\gamma,n]^{229}Th$ reaction to form ^{229}Th.

4. The method of claim 3, wherein an energy of said gamma rays is from 8 MeV to 12 MeV.

5. The method of claim 1, wherein said energetic particles comprise protons having energies sufficient to result in ^{229}Pa, said ^{229}Pa decaying or transmuting into ^{229}Th.

6. The method of claim 5, wherein an energy of said protons is from 8 MeV to 16 MeV.

7. The method of claim 5, wherein said deuterons are used, an energy of said deuterons being from 16 MeV to 28 MeV.

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