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Production of the Auger emitter ^{119}Sb for targeted radionuclide therapy using a small PET-cyclotron

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ABSTRACT

The use of Auger electrons in radionuclide therapy of cancer is a promising tool for specific tumor cell killing of micrometastases and small tumors. The radioisotope ^{119}Sb has recently been identified as a potent Auger-emitter for therapy.

We here present a method for producing this isotope using a low-energy cyclotron. With this method, it will be possible to produce clinically relevant amounts of ^{119}Sb radioactivity with high chemical and radionuclidic purity for cancer therapy.

1. Introduction

The use of Auger electrons in radionuclide therapy of cancer has been shown in the recent years to be a useful strategy for specific cancer cell killing (Janson et al., 2000; Capello et al., 2003; Michel et al., 2003; Behr et al., 2000; O'Donnell, 2006; Chen et al., 2006; Costantini et al., 2007). Auger-electron-emitting isotopes are capable of delivering a high and very localized radiation dose to the target region due to their very short range in biological tissue with a resulting ability to achieve high tumor-to-normal-tissue dose ratios (TNDs). Auger electrons are emitted by isotopes that decay by electron capture (EC) or have internal conversion (IC) in their decay. In each decay of these isotopes, a cascade of very low-energy electrons is emitted (Howell, 1992; Kassis and Adelstein, 2005). The multiplicity and the low energies of these Auger (and Coster-Kronig) electrons with their resulting short ranges in tissue (from a few nm to some μm) give rise to a very high energy density created in the immediate vicinity of the decay site and thus a highly localized absorbed radiation dose to the target region.

Moreover, a low level of damage to surrounding, unlabeled cells, e.g. normal tissue is seen due to the short ranges of the emitted electrons (Chen et al., 2006; Reilly et al., 2000). The biological damage from such radionuclides is highly dependent on the precise location of decays within cells. Auger emitters decaying within the cell nucleus, close to the DNA, are extremely radiotoxic with observed biological effects of high-LET character, but the same type of decay outside the cell is comparatively non-toxic with effects characteristic for low-LET radiation (Adelstein et al., 2003; Humm et al., 1994). An effect that cannot be seen with α- or β-emitting isotopes and thus, cannot be exploited in radionuclide therapy with these isotopes. Hence, by exploiting the high-LET part of the emitted radiation from the Auger-emitter in the tumor cells only, by choosing the proper targeting bio-vector, it will, in theory, be possible to increase the tumor-to-normal-tissue response ratio significantly.

Based on cellular and macroscopic dosimetry calculations, we have recently identified the Auger-electron-emitting isotope ^{119}Sb ($T_{1/2} = 38.19$ h) as a potent nuclide for cancer therapy of micrometastases and small tumors in combination with the isotope ^{117}Sb ($T_{1/2} = 2.8$ h) for patient-specific SPECT-based 3D dosimetry (Thisgaard and Jensen, 2008). In the previous study, calculated TNDs for several Auger emitters were compared resulting in the identification of ^{119}Sb as the most potent nuclide for therapy. However, to our knowledge no attempts have been made previously to produce this isotope for therapy and

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moreover, the main part of the excitation function involved in this production is unknown. Hence, in the current study we developed a complete production method for the ^{119}Sb and ^{117}Sb radioisotopes with a low-energy cyclotron including measurements of the excitation function for the nuclear reaction ^{119}Sn(p,n)^{119}Sb. With the method presented it is possible to produce clinically relevant amounts of ^{119}Sb radioactivity with high chemical and radionuclidic purity for cancer therapy.

2. Materials and methods

2.1. ^{119}Sn(p,n)^{119}Sb excitation function measurements

The excitation function was measured by the standard stacked foil technique using the activation method. 97.4% enriched ^{119}Sn metal (Campro Scientific) was rolled to two thin foils with mean thicknesses of 5.34 and 11.73 mg/cm^2, respectively. The thicknesses were determined from the weight and area of the foils. In the calculations uniformity of the foils was assumed. Three stacks were irradiated for 20 min using the external proton beam of the GE PETtrace Cyclotron equipped with beamline at the Hevesy Laboratory at Risoe National Laboratory. A low, constant intensity of 0.5 μA was used for the irradiations with a primary proton energy of 16 MeV. The beam was collimated to a diameter of 10 mm. The stacks were irradiated in a Faraday-cup-like target holder to determine the collected charge from the incident particles. The energy of the protons was degraded by high purity aluminum foils (Goodfellow).

Precision Cu monitor foils (Goodfellow) were used in all stacks to determine the energy of the beam via the monitor reactions ^{nat}Cu(p, x)^{63}Zn and ^{nat}Cu(p, x)^{62}Zn. The recommended cross sections for these reactions given in the IAEA cross section database for medical radioisotope production were used in the calculations (IAEA, 2007). Any uncertainty contributions stemming from these cross sections were neglected, as no uncertainties are available in the IAEA database. The proton energy was calculated as a weighted average of the two energies obtained from the two reactions in the monitor foil. The energy and measured mean beam current were also checked from the crossing of the calculated beam current versus proton energy curves using the monitor foil as seen in Fig. 1. The beam currents obtained by this method agreed with those of the Faraday-cup measurements within 4%.

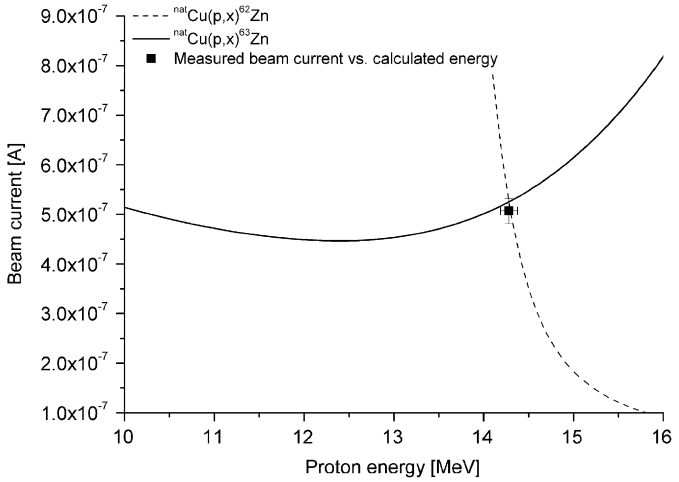

Fig. 1. The calculated beam current in the monitor foil as function of beam energy for both monitor reactions. The intersection of the curves indicates the actual energy and beam current. The measured beam current from the Faraday-cup-like target holder is also shown.

The activity measurements of the irradiated foils were done using three different setups. A calibrated Ge detector (Princeton Gamma-Tech, LGC 5) with the detector software Genie 2000 (version 3.0) was used for measuring the monitor foils and the enriched ^{119}Sn foils for any produced ^{118m}Sb and other impurities. The energy and efficiency calibrations were done using ^{152}Eu and ^{133}Ba point sources (AEA Technology). For accurate determination of the activity each target was measured several times with a distance of either 100 or 20 cm (depending on the dead-time) from the detector in the time interval from 20 min to 62 h after end of bombardment (EOB).

For determining the produced ^{119}Sb activities either a calibrated Si(Li) detector (Princeton Gamma-Tech, S-80-4-19) or a low-energy Ge detector (Canberra, GL0055P) was used. This setup made it possible to discriminate the 23.87 keV γ-ray stemming from the ^{119}Sb decay from the characteristic X-rays simultaneously emitted from both the ^{119}Sb and impurities with EC- or IC-decay if present. The energy and efficiency calibrations were done using ^{241}Am and ^{210}Pb point sources (AEA Technology). The ^{119}Sb activity was calculated from the 23.87 keV γ-ray using Genie 2000. Each target was measured several times with a distance of 4.5 cm from the detectors in the time interval from 2 h to several weeks after EOB. The ^{119}Sb activities were corrected for any simultaneously produced ^{119m}Sn ($T_{1/2} = 293.1$ d), which emits a single γ-ray of the same energy (23.87 keV), by measuring the targets after the ^{119}Sb had decayed. The attenuation of the 23.87 keV γ-ray in the ^{119}Sn foils was calculated to be maximum 8%.

Errors due to counting statistics, peak fitting and background subtractions were taken as reported by the Genie software. Errors in the measured activities due to recoil effects were negligible (<1%) compared to other experimental uncertainties (the aluminum foil right behind the first ^{119}Sn foil was checked for pick up of recoiling Sb activity).

The cross sections were calculated using the activation formula. The decay data were taken from the WWW Table of Radioactive Isotopes (Table of Radioactive Isotopes, 2004). The total uncertainty of each cross section (6–7%) was calculated by combining the contributing errors in quadrature: beam current (5%), target foil thickness (3%) and activity measurement (4–6%); the latter includes detector efficiency (3%) and nuclear data (3–5%).

The particle energy in the middle of each foil in the stack was calculated based on the stopping powers taken from the software SRIM 2006 by Ziegler et al. (2006). In the total energy uncertainties, contributions stemming from beam straggling effects and errors in target thickness measurements have been included.

2.2. Irradiations and Sb/Sn-separation

The separation of the produced antimony activity from the bulk target material was performed by chromatography using a column (0.8 × 20 cm) packed with weakly basic anion exchange resin (Bio-Rad AG4-x4, 100–200 mesh, free base form). For developing the separation method the tin and antimony activities were obtained in two ways. Initially, 211 mg of ^{nat}SnO was sealed in a quartz ampoule and irradiated for 13 days with a neutron flux of 10^{13} cm^{-2} s^{-1} in the nuclear reactor at Institute for Energy Technology in Norway. After two months cooling time to allow the decay of ^{125}Sn to ^{125}Sb, the sample—now containing ^{113}Sn ($T_{1/2} = 115.09$ d) and ^{125}Sb ($T_{1/2} = 2.7582$ y), was dissolved in concentrated HCl and used for the separations. H_2O_2 was added