Optimization of irradiated proton energy window for high-purity Actinium-225 production from Thorium-232 target

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1. Introduction

Actinium-225 has been considered one of the most promising and effective alpha-emitting radionuclides in targeted alpha therapy (TAT) by showing its efficacy in early clinical trials [1]. The ^{225}Ac radioisotope decays into stable ^{209}Bi by emitting four alpha and two beta particles with a half-life of 9.9 days, which is appropriate for medical applications. Therefore the demand of ^{225}Ac has been greatly increased for clinical studies. Several research groups reported [2] that the high energy proton spallation reaction on natural thorium metal targets has been utilized to produce millicurie quantities of ^{225}Ac, having less than 0.1 % of ^{227}Ac as a byproduct. In order to reduce the product of ^{227}Ac, IRIS will employ the energy range of 40-70 MeV protons irradiated onto the Th target and discuss the calculation results in this work.

2. Methods and Results

To meet growing clinical demand for ^{225}Ac from ^{232}Th spallation, two nuclear reaction routes are being developed via ^{232}Th(p,x)^{225}Ac and ^{232}Th(p,x)^{225}Ra → ^{225}Ac with 70 MeV cyclotrons as shown in figure 1. The accelerator-produced method is always contained ^{227}Ac at activity levels of 0.1 to 0.2 % relative to that of ^{225}Ac at production. The ^{227}Ac cannot be chemically separated from ^{225}Ac and has a long half-life of 21.8 years (^{227}Ac → ^{227}Th; mostly beta-emitting).

2.1 Two nuclear reaction routes for developing Actinium-225 radioisotope

Accelerator-based methods for increasing global ^{225}Ac production capacity have focused on the high energy (>100 MeV) proton irradiation of thorium, despite the coproduction of the undesirable ^{227}Ac byproduct at 0.1−0.3 % of the ^{225}Ac activity. Recently TRIUMF[3] have reported the production of a ^{225}Ra/^{225}Ac generator from irradiated thorium that results in an ^{225}Ac product with reduced ^{227}Ac content (< 7.5×10^{-5} %), while providing a directly produced Ac product with measured ^{227}Ac content of 0.15 %. The ^{225}Ra-derived ^{225}Ac showed improved quality compared to the directly produced ^{225}Ac product in terms of chemical purity. However the production yield of ^{225}Ac is estimated ~10 % of that from the direct production.

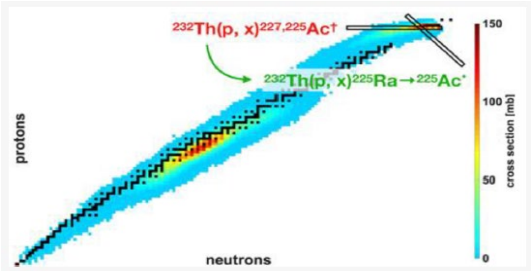

Fig. 1. The ^{225}Ac radioisotope production routes from Thorium target by irradiating protons [3]

2.2 Yields of Actinium-225 and other RIs produced during irradiation

The production yields of ^{225,226,227}Ac, ^{223,225}Ra, and ^{227,229}Th are calculated from natural thorium dioxide (ThO_2) targets, primarily through nuclear reactions induced by 40~70 MeV protons irradiation using Radionuclide Yield Calculator (RYC) program [4]. This program is dedicated to radioisotope production with the use of the cyclotron. The cross-section for ^{232}Th(p,x)^{225}Ac nuclear reaction was imported from TENDL (TALYS-based evaluated nuclear data library) as shown in Figure 3. The yellow region indicated the selected proton energy window. The model used for yield calculations is a cylindrical target with a diameter of 25 mm and a thickness of 5 mm, with a thorium dioxide density of 9.86 g/cm^3.

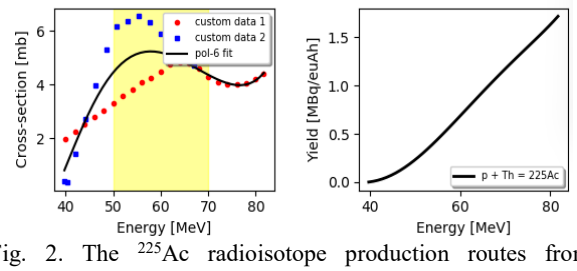

Fig. 2. The ^{225}Ac radioisotope production routes from Radionuclide Yield Calculator (RYC) program [4]. Cross-sections for ^{225}Ac radioisotope production are shown in left and the production yields is indicated as a function of proton beam energies in right.

The proton beam is perpendicularly incident on the center of the cylindrical target. Cross sections of other radionuclides such as ^{225,226,227}Ac, ^{223,225}Ra, and ^{227,229}Th in ^{232}Th targets irradiated with protons in the energy

range 40-70 MeV have used libraries in RYC. Based on these data, the production yields of radioisotopes have been calculated. ^{225}Ac and ^{223}Ra are two prospective alpha-emitters for targeted therapy. The impurities of ^{227}Ac and ^{227}Th are important and need to be assessed for further medical applications.

2.3 Cross-Sections for ^{232}Th(p,x)^{225}Ac and ^{232}Th(p,x)^{227}Ac reactions

Although spallation of ^{232}Th is considered one of the most advanced methods for ^{225}Ac production, its primary limitation is the simultaneous co-production of ^{227}Ac. Consequently, a series of multi-step chemical separation processes is required to separate ^{225}Ac from ^{227}Ac and other radionuclide impurities. However, achieving complete separation of these isotopes is not practical. Therefore, the impact of this isotopic impurity must be reasonably reduced when producing ^{225}Ac. To minimize impurities and enhance the radionuclide purity of ^{225}Ac, the energy range of the incident proton beam can be optimized. In this study, the presence of ^{227}Ac as a contaminant was evaluated with existing data shown in figure 3. The production yield values of ^{225}Ac and ^{227}Ac were obtained from the IAEA medical isotope portal.

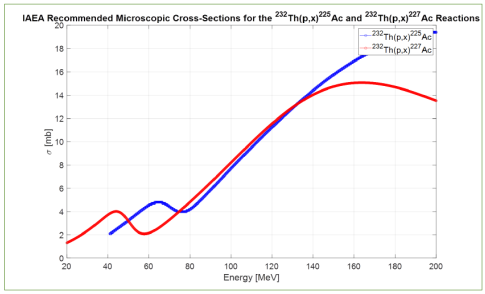

Fig. 3. The recommended Cross-sections for ^{232}Th(p,x)^{225}Ac and ^{232}Th(p,x)^{227}Ac reactions. The cross-section for the ^{225}Ac is high and ^{227}Ac is low at proton energy of 60 MeV. [ref: https://nds.iaea.org/relnsd/vcharthtml/MEDVChart.html]

2.4 Enhanced the Ratio of ^{225}Ac/^{227}Ac

With the proton energy range of 40~70 MeV, the ratio of ^{225}Ac and ^{227}Ac are enhanced to be below 0.07 % (see figure 4). Ratios are also increased with higher proton energies (left) and irradiation times (right). The ^{227}Ac/^{225}Ac ratio was lower than 0.04 % at the end of beam (EOB) within 90 hours. From the figure 4, higher energy proton and longer radiation exposure time also leads to increased contamination of ^{225}Ac with ^{227}Ac.

An objective of this work is to ensure, under the thorium irradiation with 70 MeV protons, the ^{225}Ac radiochemical purity with respect to ^{227}Ac does not exceed several hundredths percent of ^{225}Ac's activity. The narrow energy range of 40 to 70 MeV could be selected by the irradiation of thorium powder capsule with a thickness of 3 to 5 mm under a current of at least 100 uA. After the irradiation with 100 uA current for 2 days, more than 100 mCi of ^{225}Ac will be produced.

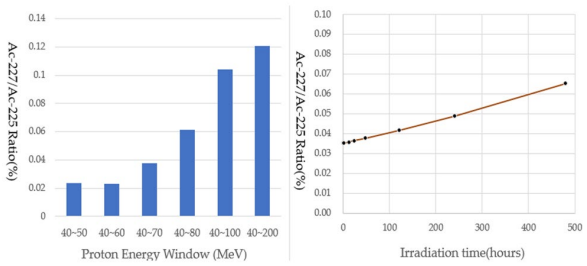

Fig. 4. Activity ratios (%) of ^{227}Ac to ^{225}Ac for a Th target as a function of proton beam energy window(left) and irradiation time (hours)

3. Conclusions

Targeted alpha therapy (TAT) is an active area of radiopharmaceutical developments for cancer treatment. TAT involves the selective delivery of α-emitting radionuclides to cancerous tissues. The therapeutic effect stems from the emission of alpha particles in close proximity to the cancerous cells. In particular, the demand for ^{225}Ac is reported to far exceed its supply, hampering clinical trials [1]. It is expected a large ^{225}Ac supply-and-demand mismatch is likely to continue. Efforts by larger proton accelerators will likely reduce this mismatch but not completely satisfy the growing demands. In this work, the improved method from the specified energy range (40~70 MeV) leads to a sharp increase the radiochemical purity of ^{225}Ac in relation to ^{227}Ac.

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REFERENCES

[1] Mengqi Shi, Vivianne Jakobsson, Lukas Greifenstein, Pek-Lan Khong, Xiaoyuan Chen, Richard P. Baum, Jingjing Zhang, Alpha-peptide receptor radionuclide therapy using actinium-225 labeled somatostatin receptor agonists and antagonists, frontiers in Medicine 9 (2022) 1034315.

[2] J.R. Griswold et al., Large scale accelerator production of ^{225}Ac: Effective cross sections for 78-192 MeV protons incident on 232Th targets, Appl. Rad. Iso. 118 (2016) 366.

[3] Robertson A.K.H., McNeil B.L., Yang H., Gendron D., Perron R., Radchenko V., Zeisler S., Causey P., Schaffer, P., ^{232}Th-Spallation-produced ^{225}Ac with reduced ^{227}Ac content. Inorg. Chem. 59 (17), (2020) 12156–12165.

[4] Radionuclide Yield Calculator (v.2) program, GIP ARRONAX [http://www.cyclotron-nantes.fr/].