Feasibility of medical radioisotope production based on the proton beams at China Spallation Neutron Source

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Abstract

The utilization of a proton beam from the China Spallation Neutron Source (CSNS) for producing medical radioisotopes is appealing owing to its high current intensity and high energy. The medical isotope production based on the proton beam at the CSNS is significant for the development of future radiopharmaceuticals, particularly for the α-emitting radiopharmaceuticals. The production yield and activity of typical medical isotopes were estimated using the FLUKA simulation. The results indicate that the 300-MeV proton beam with a power of 100 kW at CSNS-II is highly suitable for proof-of-principle studies of most medical radioisotopes. In particular, this proton beam offers tremendous advantages for the large-scale production of alpha radioisotopes, such as 225Ac, whose theoretical production yield can reach approximately 57 Ci/week. Based on these results, we provide perspectives on the use of CSNS proton beams to produce radioisotopes for medical applications.

Full Text

Preamble

Feasibility of Medical Radioisotope Production Based on Proton Beams at the China Spallation Neutron Source

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Abstract: The utilization of proton beams from the China Spallation Neutron Source (CSNS) for medical radioisotope production is highly attractive due to its high current intensity and energy. This application is significant for developing future radiopharmaceuticals, particularly α-emitting compounds. Production yields and activities of typical medical isotopes were estimated using FLUKA simulations, revealing that the 300-MeV, 100-kW proton beam at CSNS-II is highly suitable for proof-of-principle studies of most medical radioisotopes. Notably, this beam offers tremendous advantages for large-scale production of alpha radioisotopes such as ^{225}Ac, with a theoretical production yield reaching approximately 57 Ci/week. Based on these results, we provide perspectives on using CSNS proton beams for medical radioisotope production.

Key words: CSNS proton beam; Medical isotope production; α-emitting radionuclides; Nuclidic purity analysis

1. Introduction

Nuclear medicine employs radioisotopes as special carriers that use radiation to provide diagnostic information about organ function or deliver therapeutic effects [**?**]. Since the discovery of nuclear medicine' s diagnostic and therapeutic capabilities last century, numerous medical radioisotopes have been studied and developed to enhance cancer and disease treatment. Currently, over 40 million nuclear medicine procedures are performed annually, with radioisotope demand increasing by up to 5% [**?**]. For instance, diagnostic radioisotopes like technetium-99m (^{99} Tc) and therapeutic isotopes such as actinium-225 (^{225}Ac) are increasingly utilized in radiopharmaceuticals, requiring minimum pharmaceutical activities of 40 mCi and 0.1 mCi, respectively. Radioisotope production has gained strategic importance for national economic and healthcare development due to extensive applications in nuclear technology, particularly nuclear medicine. In China, the Medium- and Long-Term Development Plan for Medical Isotopes (2021–2035) was officially issued by eight ministries in June 2021, establishing medical radioisotope production and application as a national strategic priority. The plan aims to achieve key technological development for isotopes including ^{99}Mo, ^{68}Ge/^{68}Ga, ^{123},^{124}I, ^{64},^{67}Cu, ^{89}Zr, ^{103}Pd, ^{111}In, and ^{225}Ac, while mastering core competencies in irradiation structure design, parameter optimization, target post-processing, and essential raw material recovery. This initiative is crucial for enhancing radioisotope industry capacity and supporting the Healthy China strategy, which encompasses public health services, environmental management, the Chinese medical industry, and food and drug safety [**?**].

Radioisotopes can be produced through stable isotope target irradiation in nuclear reactors or particle accelerators [**?**]-[**?**]. As an effective complement to reactor-based production, accelerator irradiation provides a new pathway for generating neutron-deficient nuclides and developing innovative medical radioisotopes. Using high-intensity proton or gamma-ray facilities, appropriate targets undergo proton- or photon-induced nuclear reactions to produce new ra-

dioisotopes such as ^{99} Tc and ^{225}Ac [?][?]. While over 3,000 low-energy medical cyclotrons worldwide produce traditional isotopes like ^{18}F, only a few proton accelerators with energies exceeding 100 MeV are used for radioisotope production. To meet pharmacopoeial purity requirements, several dedicated facilities have been constructed at high-energy accelerator centers globally. For example, Switzerland' s 1.4-GeV CERN-MEDICIS facility delivered its first radioactive ion beam in December 2017 to support research on non-conventional radioisotopes including ^{149},^{152},^{155}Tb, ^{153}Sm, ^{165},^{167}Tm, ^{169}Er, ^{175}Yb, and ^{225}Ac [?]. In Canada, TRIUMF' s ISAC facility serves as a powerful source for research quantities of promising therapeutic radioisotopes [?]. In China, the 100-MeV compact cyclotron CYCIAE-100 at CIAE drives the Beijing Radioactive Ion-beam Facility (BRIF) [?][?], offering high beam currents up to 520 μA that make it highly suitable for radioisotope production.

The China Spallation Neutron Source (CSNS) is a proton-driven complex providing multidisciplinary research platforms [?]-[?]. In CSNS Phase I (CSNS-I), a tungsten-coated tantalum spallation target is bombarded with a 1.6 GeV, 100 kW proton beam at 25 Hz repetition rate. An important upgrade, CSNS Phase II (CSNS-II), is currently underway to increase proton power to 500 kW, with parallel design studies for beam quality improvement and intensity/energy upgrades. A 300-MeV proton beam can be extracted from the H^- linear accelerator end at CSNS-II for irradiation experiments, providing at least 100 kW power for radioisotope production—offering competitive advantages among international facilities. This study analyzes the feasibility of medical radioisotope production using CSNS proton beams.

The remainder of this paper is organized as follows: Section 2 describes CSNS proton beams in detail; Section 3 presents simulation methods and target material irradiation for medical isotope production; Section 4 presents in-target production yields of typical medical isotopes; and Section 5 provides conclusions.

2. Medium Proton Beams at CSNS

The CSNS facility comprises an H^- linear accelerator (LINAC), proton rapid cycling synchrotron (RCS), target station, and multiple neutron spectrometers [?]-[?]. Medium-energy proton beams extracted from the LINAC end are suitable for proton irradiation applications, particularly medical radioisotope production. Basic parameters of CSNS proton beamlines are summarized in Table 1 , with detailed descriptions in the following subsections.

Table 1. Basic parameters of the proton beams at CSNS.

The Associated Proton Beam Experiment Platform (APEP) beamline is the first proton irradiation facility utilizing naturally stripped protons from the CSNS H^- LINAC. Accelerated H^- ion beams interact with residual gas in the vacuum tube, with a small fraction being stripped to protons and transported to

the LINAC end. Physical design details for APEP, including proton transport, beam collimation, and radiation shielding, are available in [**?**].

Figure 1 [Figure 1: see original paper] shows the APEP beamline schematic, with an actual length of approximately 14.5 m. Two experimental irradiation points—the vacuum test point (VTP) and air test point (ATP)—are located at flight path lengths of approximately 9.3 m and 10 m from the extraction position, respectively. A wedge degrader enables continuous proton energy adjustment within the 10–80 MeV range. To meet various experimental requirements, a cascading collimation system with three graphite collimators controls spot sizes ranging from 10 mm × 10 mm to 50 mm × 50 mm at irradiation points.

Fig.1. Layout of the APEP.

Using the degrader for energy adjustment, irradiation experiments can be performed on medical isotopes of interest—including ^{123},^{125}I, ^{103}Pd, ^{99} Tc, ^{82}Sr, ^{68}Ge, ^{64}Cu, and ^{62}Zn—at both VTP and ATP with appropriate target materials. These isotopes are extensively used medically and exhibit relatively high production cross-sections at low proton energies, making them ideal for verification experiments under current APEP conditions.

Tables 2 and 3 list medical isotopes with potential for APEP production and research. For 80-MeV (CSNS-I) and 300-MeV (CSNS-II) APEP beamlines, recommended medical isotopes and corresponding reaction channels are provided along with suitable medical applications.

APEP-produced medical isotopes are not limited to those listed. These isotopes are widely used in medical applications [**?**][**?**][**?**]. Generally, the 80-MeV APEP meets production experiment requirements for most medical isotopes and proof-of-principle studies of innovative alpha isotopes (see Table 2). With appropriate gamma spectroscopy, two experiment types are currently feasible at 80-MeV APEP: (1) quantitative analysis of end-of-bombardment (EOB) activity in irradiated targets; and (2) proton-induced reaction cross-section measurement via activation analysis. EOB activity of specific isotopes is deduced from characteristic γ-ray counts of decay products, while reaction cross-sections are calculated from EOB activity and incident proton intensity, typically measured using monitoring targets irradiated simultaneously with experimental targets. The CSNS-I APEP line began operation in 2021, with user experiments already underway. A recent ^{100}Mo target irradiation experiment at APEP yielded ^{99} Tc experimental yields conforming to theoretical calculations. Based on APEP, 2-hour irradiation of multi-layer ^{100}Mo targets can produce approximately 60 MBq of ^{99} Tc and 18 MBq of ^{99}Mo, sufficient for pre-clinical studies. Further details are available in [**?**].

Table 2. Typical medical isotopes produced by proton beam with energy up to 80 MeV (CSNS-I, APEP).

After CSNS-II completion in 2028, the APEP line' s maximum proton energy will reach 300 MeV with approximately 333.3 μA beam current (see Table 1),

significantly expanding producible isotope variety. To fully utilize this energy, isotopes of interest will be generated via spallation (p, x) reactions at 300-MeV APEP. High-energy protons produce isotopes across a wide mass range, enabling study of rare radioisotopes. Considering production reaction cross-sections and impurity content, appropriate target materials are essential for generating nuclides with different mass numbers. Table 3 lists potential medical isotopes producible with 300-MeV proton beams. Irradiating thorium or tantalum targets with 300-MeV protons yields various products, including crucial alpha-emitter isotopes and lanthanide isotopes ideal for medical applications.

Table 3. Potential medical isotopes that can be produced by the 300 MeV proton beam (CSNS-II, APEP).

3.1 Simulation Code

Several codes accurately simulate particle transport through matter, including FLUKA [**?**] and GEANT4 [**?**]. This study employed FLUKA due to its convenient information extraction features and comprehensive reaction cross-section libraries. The code's proton reaction cross-section data are parameterized based on primary energy and target nucleus rather than integrated channel-by-channel cross-sections. Based on existing APEP experimental results and simulation experience, FLUKA-calculated isotope production rates using theoretical cross-sections provide reliable experimental guidance [**?**][**?**][**?**]. The code facilitates acquisition of proton-induced nuclear reaction parameters, including reaction product types, radioactive isotope decay, and induced radioactivity from nuclear interactions. In FLUKA simulations, the coalescence process and new fragmentation model were activated—critical for residual nuclei calculations. Decay radiation generation and transport are embedded using a dedicated database based primarily on NNDC information [**?**]. To investigate in-target isotope activity as a function of irradiation time, the following decay law was embedded in the code, where variables represent numbers of produced isotopes, parent isotopes, and target isotopes, with corresponding decay constants for parent and produced isotopes.

The first right-hand term represents parent nucleus decay contribution, the second term represents proton-target nuclear reaction contribution, and the third term represents loss through produced isotope decay. Using FLUKA, we obtained residual production results, their time evolution, and residual doses from decays in simulation. These procedures ensure qualified simulation results for radioisotope yields from CSNS proton beams.

3.2 Simulation Method

To analyze CSNS proton beam isotope production feasibility, reaction process simulations were performed to determine different isotope activities under specific conditions. Irradiation target thickness and density were considered uniform. Target material isotope abundances were included while impurities were

ignored. In practice, experimental activities may be lower than simulated results, with product species proportions differing slightly between experiment and simulation due to target material impurities. The irradiated target geometry was a solid cylinder composed entirely of target material, with 2 cm diameter determined by APEP beam spot size (2 cm × 2 cm).

For different target materials, proton utilization efficiency was improved by adjusting target thickness in simulation to ensure complete proton energy deposition in targets. In simulations, protons vertically incident on targets produced various isotopes through target nucleus interactions. Parameters of interest—including proton number Z, neutron number N, and mass number A for all products—were acquired and recorded. The influence of secondary particles from proton bombardment (neutrons and gamma-rays) on simulated yield was also considered, with detailed results discussed in the following section.

3.3 Alternative Targets

Target material selection depends on physical and chemical properties as well as reaction-generated impurities. Target fabrication techniques are not discussed in this paper. This study focused on physical analysis of proton reactions with different target materials, including radioisotope activities and corresponding impurities, plus various factors influencing purity.

Table 4 lists alternative target materials for CSNS isotope production. Several reaction channels can produce medical isotopes, including proton-induced (p, x), (p, n), (p, 2n) reactions. The (p, x) reaction can generate isotopes across a wide mass range, though with small cross-sections and difficult separation due to numerous produced nuclides. Some classic medical isotopes can also be produced via (p, n), (p, 2n), or other reactions with lower energy and higher cross-sections, though these require specifically designed target materials. Generally, single reaction channels like (p, n) and (p, 2n) exhibit resonance energies where cross-sections reach maxima, as listed in Table 4. However, (p, x) reactions show no distinct resonance peaks due to multiple channel combined effects. Notably, isotopes listed in the table are accompanied by substantial impurity production, requiring detailed impurity analysis before production. Particularly, medical isotopes generated through 300 MeV proton (p, x) reactions produce hundreds of simultaneous impurities, making subsequent chemical separation a significant challenge.

As listed in Table 4, ideal spallation reaction target materials include uranium, thorium, tantalum, yttrium, and titanium. These materials are not prohibitively radioactive, pose fewer radiological hazards, and are readily available. Existing facilities and methods have demonstrated capability to fabricate, irradiate, and process these targets [**?**][**?**]. Considering target fabrication difficulty and high-purity germanium detector counting limitations, we recommend target thicknesses between 100 µm and 1 mm for verification experiments. At CSNS-II, alpha-emitter radioisotope ^{225}Ac is expected to be produced using thorium tar-

gets—an isotope of particular interest at 300-MeV APEP due to high proton energy and urgent domestic market demand.

Table 4. Typical targets for isotope production by proton beams at CSNS APEP.

4. Analysis of Recommended Radioisotopes for Production at CSNS-II

Radiological diagnosis and therapy utilize various radioactive emissions to image or destroy cancer cells, including gamma (γ), alpha (α), beta (β^- and β^+), and Auger electrons. Diagnostic radioisotope procedures are now routine, with gamma- and positron-emitting radionuclides extensively used (e.g., ^{99} Tc (γ-emitter) and ^{18}F (β^+-emitter)) [**?**][**?**]. Alpha-emitter radioisotopes like ^{225}Ac, ^{223}Ra, and ^{211}At are gaining interest for targeted α therapy [**?**]-[**?**]. β^- radioisotopes including ^{90}Y and ^{177}Lu have been applied clinically [**?**][**?**]. Auger electron-emitting radioisotopes such as ^{165}Er and ^{67}Ga are also under consideration for targeted therapy [**?**][**?**].

This section discusses recommended radioisotopes for CSNS research and production. Comprehensive analysis of all potential irradiation targets and corresponding isotopes is beyond scope; we focus on several medically significant radioisotopes that are either promising or extensively used. The 300-MeV CSNS-II proton beam' s producible radioisotope types are of great interest due to high proton intensity and production capacity.

4.1 Alpha-Emitting Radioisotopes

Targeted Alpha Therapy (TAT) represents one of the most promising future tumor therapies, with radiopharmaceutical development emitting alpha particles being an active global academic and commercial research field [**?**]. Alpha radiation can kill cancer cells resistant to beta/gamma irradiation and chemotherapeutic drugs. Additionally, alpha radiation has shorter tissue range than beta or gamma radiation, reducing damage to surrounding healthy tissue. Typically, α-particles have 50-100 m tissue range with high linear energy transfer (LET) averaging 100 keV/ m, providing more specific tumor cell killing with less normal tissue damage than β^- particles [**?**]. Only a few alpha-emitting radioisotopes are suitable for TAT, including ^{225}Ac, ^{223}Ra, ^{212},^{213}Bi, and ^{211}At. These candidates with suitable half-lives possess favorable properties for cancer therapy, detailed in the following subsections.

4.1.1 ^{225}Ac/^{213}Bi Actinium-225 (^{225}Ac) has become increasingly prominent due to its suitable half-life ($T_1/_2$ = 9.9 d) and short tissue range. The long half-life allows gradual decay during production and delivery. ^{225}Ac' s alpha particles have high LET and approximately 50-90 µm range in biological tissue, effectively killing tumor cells while minimizing normal tissue damage. However,

^{225}Ac-radiopharmaceutical applications face significant challenges including limited isotope supply and chemical separation difficulties. Four main production routes are proposed: (1) decay from ^{229}Th sources; (2) ^{226}Ra(p, 2n) reaction with proton energies above ~16 MeV; (3) ^{232}Th(p, x) or ^{238}U(p, x) spallation reactions via high-energy protons; (4) ^{226}Ra(γ, n) producing ^{225}Ra which subsequently decays to ^{225}Ac. Further details are available in literature [**?**][**?**][**?**].

At CSNS, the third route is recommended for ^{225}Ac production experiments due to high proton energy and researchers' adept ^{232}Th target-making techniques. Based on previous experience, ^{232}Th targets can be prepared via cold or hot pressing with ^{232}Th metal powder depending on required thickness [**?**][**?**]. Comparing existing ^{232}Th(p, x) cross-section data at different energies [**?**], we found the 300-MeV proton beam highly suitable for ^{225}Ac production.

Figure 2 [Figure 2: see original paper] shows ^{225}Ac and ^{213}Bi generation and decay schemes. ^{225}Ac is produced through proton-induced ^{232}Th spallation, followed by three α-particle decays to ^{213}Bi—another important medical alpha-emitting radionuclide.

Fig.2. Generation and decay scheme of ^{225}Ac to ^{213}Bi.

To evaluate in-target production rates, the 300-MeV proton and ^{232}Th reaction process was simulated using FLUKA with the geometric model described in Section 3.2. Beam intensity was set to 333.3 μA based on CSNS-II design parameters. ^{232}Th target thickness was evaluated using SRIM code [**?**] to ensure full proton energy deposition in the target, serving as FLUKA input. Irradiation time was set to 6 days based on CSNS operational status. Key parameters discussed include weekly ^{225}Ac production activity, activity evolution over time, and ^{225}Ac radionuclidic impurities.

Figure 3 [Figure 3: see original paper] shows main ^{225}Ac isotope activity evolution in irradiated thorium targets with 10 cm thickness. ^{225}Ac activity increased to approximately 57 Ci after 6 days continuous irradiation, indicating CSNS-II APEP can produce 1,710 Ci ^{225}Ac annually during 30 weeks of dedicated operation. Figure 3(a) shows the ^{227}Ac impurity ratio increased with irradiation time, reaching 0.146% after 6 days and 0.216% after 20 days continuous irradiation. After appropriate irradiation periods (6 days), targets should be promptly removed for chemical separation. Figure 3(b) shows the ^{225}Ac activity to total activity ratio peaks at approximately 10–20 days cooling time, which can estimate optimal cooling time for practical production.

Fig.3. ^{225}Ac activity evolution with irradiation time (a) and cooling time (b) in irradiated thorium target (thickness = 10 cm), accompanied by major impurity activity evolution. Dashed lines represent ^{227}Ac/^{225}Ac (a) and ^{225}Ac/total (b) activity ratios, with corresponding values on right axes. Note (b) corresponds to 6-day irradiation.

As shown in Figure 2, short-lived daughter nuclide ^{213}Bi ($T_1/_2$ = 46 min) is obtained through three α-particle emissions from ^{225}Ac, subsequently undergoing

alpha and beta decay to produce ^{209}Tl (2%) and ^{213}Po (98%), respectively, with ~8.4 MeV α-energy and ~85 µm short tissue range. ^{213}Bi is a promising alpha-emitting radioisotope for TAT applications and can be conveniently produced using a ^{225}Ac-^{213}Bi generator with high specific activity. Detailed ^{213}Bi descriptions are provided in [**?**][**?**][**?**]. Figure 4 [Figure 4: see original paper] reveals ^{213}Bi production yield is nearly equivalent to ^{225}Ac, primarily due to ^{225}Ac' s notably longer half-life compared to ^{213}Bi. Simulation results demonstrate CSNS can provide substantial ^{225}Ac and ^{213}Bi quantities for drug research and clinical studies.

Fig.4. Evolution of ^{213}Bi activity with irradiation time (a) and cooling time (b) in irradiated thorium target (thickness = 10 cm), accompanied by ^{225}Ac activity evolution. Note (b) corresponds to 6-day irradiation.

4.1.2 ^{223}Ra Radium-223 (^{223}Ra, $T_1/_2$ = 11.4 d) is considered among the most promising alpha-emitting radioisotopes based on its decay characteristics. Its long half-life allows ample time for transportation, drug preparation, and patient injection. As a bone-seeking radiopharmaceutical, Xofigo ($^{223}RaCl_2$) has been clinically used to treat skeletal metastases from breast and prostate cancers [**?**]-[**?**], representing the world' s first TAT radiopharmaceutical.

At CSNS-II, ^{223}Ra production is also expected using ^{232}Th target nuclei. As shown in Figure 5 [Figure 5: see original paper], proton spallation on thorium can directly produce ^{223}Ra, which can also form via decay of simultaneously produced ^{227}Th and ^{227}Ac from spallation reactions. Subsequently, ^{223}Ra decays to stable lead through a series of short-lived daughter radionuclides, emitting four alpha particles. In the ^{223}Ra decay chain, 94% of total decay energy is released via alpha particles [**?**], enabling effective cancer cell killing.

Fig.5. Generation and decay scheme of ^{223}Ra.

^{223}Ra can also be generated from ^{227}Ac/^{227}Th and purified using Ac-resin, which immobilizes both ^{227}Ac and ^{227}Th, as previously described [**?**]. Figure 6 [Figure 6: see original paper] illustrates radioactive activity variation with irradiation and cooling times for these three nuclides. As shown, EOB activity after one-week irradiation was approximately 14.5 Ci. However, with increased cooling time, ^{227}Ac and ^{227}Th from spallation continued decaying to ^{223}Ra, increasing ^{223}Ra production. After ~20 days cooling, ^{223}Ra reached maximum activity of approximately 24 Ci, maintaining relatively high yield for extended periods, providing sufficient time for chemical separation.

Fig.6. Evolution of ^{223}Ra activity with irradiation time (a) and cooling time (b) in irradiated thorium target (thickness = 10 cm), accompanied by ^{227}Ac and ^{227}Th activity evolution. Note (b) corresponds to 6-day irradiation.

4.1.3 ^{211}At Astatine-211 (^{211}At) has attracted significant attention as a therapeutic α-particle emitter for treating microscopic diseases such as micrometastases and monocellular malignancies [?][?]. Typically, ^{211}At ($T_1/_2$ = 7.2 h) is more suitable for production via alpha accelerators using the ^{209}Bi(α, 2n) reaction with ~1 b cross-section at Eα = 29 MeV [?], restricting ^{211}At production due to limited global alpha accelerator availability.

Recently, researchers discovered that bombarding Th or U targets with high-energy protons to produce ^{211}Rn ($T_1/_2$ = 14.6 h), the parent isotope of ^{211}At, offers an attractive ^{211}At production pathway [?]. A ^{211}Rn/^{211}At generator system is recommended for ^{211}At production. As shown in Figure 7 [Figure 7: see original paper], at CSNS-II, ^{211}At and ^{211}Rn can be generated through proton thorium irradiation. Simultaneously, ^{211}At is produced via electron capture (EC) decay of ^{211}Rn with ~73% probability. Subsequently, ^{211}At decays to ^{207}Bi and ^{211}Po through α decay (42%) and EC decay (58%), respectively.

Fig.7. Generation and decay scheme of ^{211}At.

Activity evolutions of ^{211}At and ^{211}Rn were calculated, with results shown in Figure 8. Six-day thorium target irradiation with 333.3 μA proton beam intensity can produce maximum ^{211}At activity of approximately 163.5 Ci. However, due to ^{211}At' s short half-life, activity reaches maximum quickly, meaning prolonged irradiation does not effectively increase yield (Fig. 8 Figure 8: see original paper), while frequent irradiation can improve production yield.

Fig.8. Evolution of ^{211}At activity with irradiation time (a) and cooling time (b) in irradiated thorium target (thickness = 10 cm), accompanied by ^{211}Rn activity evolution. Note (b) corresponds to 6-day irradiation.

Other alpha-emitting isotopes such as ^{212}Pb and ^{212}Bi, potential TAT candidates, may not be optimally produced via proton accelerator irradiation. However, we discovered considerable in-target yields of these isotopes could also be obtained using thorium targets at CSNS-II, adequate for proof-of-principle studies and pre-clinical drug research.

Weekly production yields for these and aforementioned isotopes are listed in Table 5 . Currently, two main methods separate alpha-emitting isotopes from thorium targets. Using ^{225}Ac separation as an example, a three-step procedure including liquid-liquid and solid-phase extraction chromatography can achieve >85% ^{225}Ac recovery [?]. A two-step method using 1 M oxalic acid at pH 2 to remove bulk thorium can yield ^{225}Ac with >98% recovery, suitable for radiolabeling or generator applications [?][?]. Additionally, alpha-emitting radioisotopes can be separated via online isotope separation based on mass-to-charge ratio. Based on existing CERN MEDICIS (2.0 GeV, 6.7 μA) [?] and TRIUMF ISAC (500 MeV, 100 μA) [?] experiences, CSNS APEP (300 MeV, 333.3 μA) has potential to provide sufficient yields for clinical experiments via online isotope separation. In summary, the 300 MeV CSNS-II proton beam is highly suitable

for alpha-emitting isotope production and provides an excellent experimental platform for isotope production.

Table 5. In-target production yield of alpha-emitter radioisotopes at CSNS-II.

4.2 Neutron-Deficient Lanthanide Isotopes

Lanthanide radionuclides are highly favorable for several reasons: (1) they can emit different particle types and possess all radiation characteristics suitable for radiotherapy and diagnosis; (2) different lanthanide isotopes have similar chemical properties offering unique advantages for molecular tracer labeling. Neutron-rich lanthanide nuclides like ^{141}Ce, ^{143}Pr, and ^{153}Sm are typically produced by bombarding ^{238}U with high-energy protons. Neutron-deficient lanthanide isotopes such as ^{169}Yb, ^{167}Tm, ^{149}Tb, and ^{152}Tb can be produced by bombarding tantalum targets.

This study evaluated evolution of various neutron-deficient lanthanide radioisotopes suitable for CSNS-II production using FLUKA code with ^{181}Ta target material. The tantalum target was bombarded by a 300 MeV, 100 kW proton beam for 6 days. To maximize in-target production yield, Ta target thickness (8 cm) was maintained to ensure complete proton energy deposition.

Figure 9 [Figure 9: see original paper] shows variation trends for some lanthanide isotopes over time, with specific weekly yields summarized in Table 6 . Several listed isotopes are already used clinically, while others are in pre-clinical research but show promising applications. Lanthanide isotopes release different particle types during radiotherapy or diagnosis. For example, ^{177}Lu is used for beta therapy, ^{149}Tb for alpha therapy, and ^{152}Tb for PET. ^{165}Er is a promising Auger electron therapy candidate, and ^{169}Yb is commonly used for SPECT.

Fig.9. Evolution of lanthanide isotope activity with irradiation time in irradiated tantalum target (thickness = 8 cm).

Table 6. In-target production yield of neutron-deficient lanthanide isotopes at CSNS-II.

As shown in Table 6, various lanthanide isotopes can be obtained via proton-tantalum reactions, though some can be produced in higher yields using other targets and reaction channels. Therefore, we prefer utilizing CSNS for centralized production of one or a few medical radioisotopes, such as the aforementioned ^{225}Ac. For other isotopes, we are committed to providing adequate quantities for verification rather than large-scale production.

4.3 Other Medical Radioisotopes

Beyond alpha and lanthanide isotopes, we explored feasibility of using other materials as irradiation targets for medical isotope production. Based on target material selection principles from Section 3.3, stable and naturally abundant

isotopes such as Y and Ti can serve as target nuclei. Theoretical weekly yields of isotopes from these targets reacting with 300-MeV proton beams were evaluated using FLUKA, with results listed in Table 7 . These data provide valuable references for future research and significantly broaden the range of medical isotopes studiable at CSNS-II.

Table 7. In-target production yield of other medical radioisotopes at CSNS-II.

4.4 Ongoing Research

The next focus of CSNS radioisotope research will be alpha-emitter radioisotope production and separation. As described in Section 4.1.1, alpha-emitter radioisotopes' unique radioactive properties make them particularly advantageous for cancer treatment, and their supply has become a major issue in international commercial applications and academic research. Fortunately, CSNS-II' s 300-MeV, 100-kW proton beam provides ideal conditions for studying these nuclides in China. High-energy proton spallation reactions with various targets produce numerous rare nuclides, offering unique opportunities for studying and collecting pre-clinical and, in some cases, clinical quantities of innovative medical radioisotopes. To fully utilize the CSNS beam, an irradiation program related to ^{225}Ac production—including irradiation target physical design, thermal analysis, and impurity analysis—is currently in progress.

5. Conclusion

This study evaluated CSNS proton beam isotope production feasibility. Using FLUKA code, we analyzed medical isotope types and yields from CSNS proton beams. Results demonstrate that CSNS APEP facility provides unique opportunities for producing a wide range of medical radioisotopes, especially alpha-emitting isotopes. Using specific target materials, APEP can generate sufficient desired radioisotope quantities for researchers to conduct proof-of-principle experiments and even commercial applications. ^{225}Ac and ^{223}Ra will become key alpha-emitter medical isotopes studied at CSNS due to urgent domestic market demand; therefore, production and separation of these isotopes will be our primary future focus. We also plan to explore online residual nuclei separation possibilities. With future CSNS APEP facility upgrades, supplementary possibilities exist for expanding medical radioisotope variety.

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References:

[1] Radioisotopes in medicine, World nuclear association website (2022).

https://www.world-nuclear.org/information-library/non-power-nuclear-applications/radioisotopes-research/radioisotopes-in-medicine.aspx.
[2] X.D. Tan, X.X. Liu, H.Y. Shao, Healthy China 2030: a vision for health care. Value Health Reg. News. 12, 112–114 (2017). https://doi.org/10.1016/j.vhri.2017.04.001
[3] L.Chen, R.Yan, X.Z. Kang et al., Study on the production characteristics of ^{131}I and ^{90}Sr isotopes molten reactor. Nucl. Tech. (2021). https://doi.org/10.1007/s41365-021-00867-1
[4] C.G. Yu, X.H. Wang, C. Wu et al., Supply of I-131 in a 2MW molten salt reactor with different production methods. Appl. Radiat. Isot. (2020). https://doi.org/10.1016/j.apradiso.2020.109350
[5] C.G. Yu, C.Y. Zou, C. Wu et al., Sustainable supply of ^{99}Mo source in a 2 MW molten salt reactor using low-enriched uranium. Appl. Radiat. Isot. (2020). https://doi.org/10.1016/j.apradiso.2020.109134
[6] N. Liu, J. Gao, Y. Yang et al., The current situation and prospect of accelerator produced medical radioisotopes (in Chinese). Isot. (2022). https://doi.org/10.7538/tws.2022.youxian.015
[7] R. Han, Z. Q. Chen, G. Y. Tian et al., Study of Medical Radioisotopes Production by Accelerator Induced Reactions with FLUKA (in Chinese). Nucl. Phys. Rev. 4, 913-917 (2020). https://doi.org/10.11804/NuclPhysRev.37.2020025
[8] L. Ren, Y.C. Han, J.C. Zhang et al., Neutronics analysis of a stacked structure for a subcritical system with LEU solution driven by a D-T neutron source for ^{99}Mo production. Nucl. Sci. Tech. 32, 123 (2021). https://doi.org/10.1007/s41365-021-00968-x
[9] C. Duchemin, J.P. Ramos, T. Stora et al., CERN-MEDICIS: a review since commissioning in 2017. Front. Med. 8, 693682 (2021). https://doi.org/10.3389/fmed.2021.693682
[10] W. Luo, M. Bobeica, I. Gheorghe et al. Estimates for production of radioisotopes of medical interest at Extreme Light Infrastructure –Nuclear Physics facility. Appl. Phys. B 122, 8 (2016). https://doi.org/10.1007/s00340-015-6292-9
[11] D.E. Fiaccabrino, P. Kunz, V. Radchenko, Potential for production of medical radionuclides with on-line isotope separation at the ISAC facility at TRIUMF and particular discussion of the examples ^{165}Er ^{155}Tb. Nucl. Med. Biol. 94/95, (2021). https://doi.org/10.1016/j.nucmedbio.2021.01.003
[12] T.J. Zhang, Z.G. Li, C.J. Chu, CYCIAE-100, a 100MeV H^- cyclotron for RIB production. Nucl. Instrum. Meth. B 261, 1027-1031 (2007). https://doi.org/10.1016/j.nimb.2007.04.231
[13] T.J. Zhang, Y.L. Lv, S.M. Wei et al., Isotope production by the high current proton beam of CYCIAE-100. Nucl. Instrum. Meth. (2020). https://doi.org/10.1016/j.nimb.2019.07.001
[14] J. Wei, H.S. Chen, Y.W. Chen et al., China Spallation Neutron Source: design, R&D, and outlook. Nucl. Instrum. Meth. A 600, 10–13 (2009). https://doi.org/10.1016/j.nima.2008.11.017
[15] J. Wei, S.N. Fu, J.Y. Tang et al., China Spallation Neutron Source - an overview of application prospects. Chin. Phys. C 33, 1033 (2009). https://doi.org/10.1088/1674-1137/33/11/021

[16] H.S. Chen, X.L. Wang, China' s first pulsed neutron source. Nat. Mater. 15, 689-691 (2016). https://doi.org/10.1038/nmat4655
[17] S. Wang, Y.W. An, S.X. Fang et al., An overview of design for CSNS/RCS and beam transport. Sci. China Phys. Mech. Astron. 54, 239-244 (2011). https://doi.org/10.1007/s11433-011-4564-x
[18] F.W. Wang, T.J. Liang, W. Yin et al., Physical design of target station and neutron instruments for China Spallation Neutron Source. Sci. China Phys. Mech. Astron. 56, 2410–2424 (2013). https://doi.org/10.1007/s11433-013-5345-5
[19] J.Y. Tang, Q. An, J.B. Bai et al., Back-n white neutron source at CSNS and its applications. Nucl. Sci. Tech. 32, 11 (2021). https://doi.org/10.1007/s41365-021-00846-6
[20] Y.Y. Liu, H.T. Jing, L.S. Huang et al., Physical design of the APEP beam line at CSNS. Nucl. Instrum. Meth. A 1042, 167431 (2022). https://doi.org/10.1016/j.nima.2022.167431
[21] G. Beyer, Radioactive ion beams for biomedical research and nuclear medical application. Hyperfine Interact. 129, 529-553 (2000). https://doi.org/10.1023/A:1012670018533
[22] Q.F. Dong, H.T. Jing, W.L. Li et al., Research on the production of ^{99} Tc and ^{99}Mo using multi-layer targets at APEP. Radiat. Phys. Chem. (2024). https://doi.org/10.1016/j.radphyschem.2023.111287
[23] G. Battistoni, F. Cerutti, A. Fasso et al., The FLUKA code: Description and benchmarking. AIP Conf. Proc. Am. Inst. Phys. 896, 31-49 (2007). https://doi.org/10.1063/1.2720455
[24] S. Agostinelli, J. Allison, K. Amako et al., GEANT4 —a simulation toolkit. Nucl. Instrum. Methods Phys. Res. A 506, 250-303 (2003). https://doi.org/10.1016/S0168-9002(03)01368-8
[25] F.H. Garcia, C. Andreoiu, P. Kunz, Calculation of in-target production rates for isotope beam production at TRIUMF. Nucl. Instrum. Meth. (2017). https://doi.org/10.1016/j.nimb.2017.09.023
[26] R. M. S. Augusto, L. Buehler, Z. Lawson et al., CERN-MEDICIS (Medical Isotopes Collected from ISOLDE): A new facility. Appl. (2014). https://doi.org/10.3390/app4020265
[27] P. Kunz, P. Bricault, M. Dombsky et al., Composite uranium carbide targets at TRIUMF: Development and characterization with SEM, XRD, XRF and L-edge densitometry. J. Nucl. Mater. 440, 110-116 (2013). https://doi.org/10.1016/j.jnucmat.2013.04.065
[28] E. Hess, G. Blessing, H.H. Coenen et al., Improved target system for production of high purity [^{18}F]fluorine via the ^{18}O(p, n)^{18}F reaction. Appl. Radiat. Isot. 52, 1431-1440 (2000). https://doi.org/10.1016/S0969-8043(99)00248-1
[29] C. Kratochwil, F. Bruchertseifer, F.L. Giesel et al., ^{225}Ac-PSMA-617 for PSMA-targeted α-radiation therapy of metastatic castration-resistant prostate cancer. J. Nucl. Med. 57, 1941-1944 (2016). https://doi.org/10.2967/jnumed.116.178673
[30] C. Parker, S. Nilsson, D. Heinrich et al., Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J. Med. 369, 213-223 (2013). https://doi.org/10.1056/NEJMoa1213755

[31] J.R. Crawford, P. Kunz, H. Yang et al., ^{211}Rn/^{211}At and ^{209}At production with intense mass separated Fr ion beams for preclinical ^{211}At-based α-therapy research. Appl. Radiat. Isot. 122, 222-228 (2017). https://doi.org/10.1016/j.apradiso.2017.01.035
[32] T. Tiwari, C. Malone, G. Foltz et al., Yttrium-90 radioembolization: current clinical practice review of recent literature. Radiol. Nurs. (2019). https://doi.org/10.1016/j.jradnu.2019.03.004
[33] B.L.R. Kam, J.J.M. Teunissen, E.P. Krenning et al., Lutetium-labelled peptides for therapy of neuroendocrine tumours. J. Nucl. Med. Mol. Imag. (2012). https://doi.org/10.1007/s00259-011-2039-y
[34] M. F. Othman, E. Verger, I. Costa et al., In vitro cytotoxicity of Auger electron-emitting [^{67}Ga]Ga-trastuzumab. Nucl. Biol. (2020). https://doi.org/10.1016/j.nucmedbio.2019.12.004
[35] A.K.H. Robertson, C.F. Ramogida, P. Schaffer et al., Development of ^{225}Ac radiopharmaceuticals: TRIUMF perspectives and experiences. Curr. Radiopharm. 11, 156-172 (2018). https://doi.org/10.2174/1874471011666180416161908
[36] Y.S. Kim, M.W. Brechbiel, An overview of targeted alpha therapy. Tumor Biol. 33, 573-590 (2012). https://doi.org/10.1007/s13277-011-0286-y
[37] A.A. Al Qaaod, V. Gulik, ^{226}Ra irradiation to produce ^{225}Ac and ^{213}Bi in an accelerator-driven system reactor. Nucl. Sci. Tech. 31, 44 (2020). https://doi.org/10.1007/s41365-020-00753-2
[38] B. Jiang, J.L. Han, J. Ren et al., Measurement of ^{232}Th(n, γ) cross section at the CSNS Back-n facility in the unresolved resonance region from 4 keV to 100 keV. Chin. Phys. B 31, 060101 (2022). https://doi.org/10.1088/1674-1056/ac5394
[39] J.C. Wang, J. Ren, W. Jiang et al., Determination of the ^{232}Th(n, γ) cross section from 10 to keV at the Back-n facility at CSNS. Eur. Phys. J. A 59, (2023). https://doi.org/10.1140/epja/s10050-023-01126-0
[40] Experimental Nuclear Reaction Data (EXFOR). https://www-nds.iaea.org/exfor/
[41] J.F. Ziegler, M.D. Ziegler, J.P. Biersack, SRIM–The stopping and range of ions in matter (2010). Nucl. Instrum. Meth. B 268, 1818-1823 (2010). https://doi.org/10.1016/j.nimb.2010.02.091
[42] A. Morgenstern, C. Apostolidis, C. Kratochwil et al., An overview of targeted alpha therapy with ^{225}Actinium and ^{213}Bismuth. Curr. Radiopharm. (2018). https://doi.org/10.2174/1874471011666180502104524
[43] J.G. Jurcic, Targeted alpha-particle immunotherapy with bismuth-213 and actinium-225 for acute myeloid leukemia. Postgrad. Med. Educ. (2013). https://doi.org/10.5005/jp-journals-10028-1051
[44] G. Henriksen, P. Hoff, J. Alstad et al., ^{223}Ra for endoradiotherapeutic applications prepared from an immobilized ^{227}Ac/^{227}Th source. Radiochim. Acta (2001). https://doi.org/10.1524/ract.2001.89.10.661
[45] Ø.S. Bruland, S. Nilsson, D.R. Fisher et al., High-linear energy transfer irradiation targeted to skeletal metastases by the α-emitter ^{223}Ra: adjuvant or alternative to conventional modalities? Clin. Cancer Res. 12, 6250s-6257s (2006). https://doi.org/10.1158/1078-0432.CCR-06-0841
[46] S. Nilsson, R.H. Larsen, S.D. Fossa et al., First clinical experience with

α-emitting radium-223 treatment of skeletal metastases. Clin. Cancer Res. (2005). https://doi.org/10.1158/1078-0432.CCR-04-2244
[47] G. Vaidyanathan, M. Zalutsky, Astatine radiopharmaceuticals: prospects and problems. Curr. Radiopharm. 1, 177-196 (2008). https://doi.org/10.2174/1874471010801030177
[48] J.J. Orozco, T. Bäck, A. Kenoyer et al., Anti-CD45 radioimmunotherapy using ^{211}At with bone marrow transplantation prolongs survival in a disseminated murine leukemia model. Blood 121, 3759-3767 (2013). https://doi.org/10.1182/blood-2012-11-467035
[49] J.R. Crawford, P. Kunz, H. Yang et al., ^{211}Rn/^{211}At and ^{209}At production with intense mass separated Fr ion beams for preclinical ^{211}At-based α-therapy research. Appl. Radiat. Isot. 122, 222-228 (2017). https://doi.org/10.1016/j.apradiso.2017.01.035
[50] R.A. Aliev, S.V. Ermolaev, A.N. Vasiliev et al., Isolation of medicine-applicable Actinium-225 from thorium targets irradiated by medium-energy protons. Solvent Extr. Ion Exch. 32, 468-477 (2014). https://doi.org/10.1080/07366299.2014.896582
[51] J.Y. Chen, Y.L. Lv, F. Wang et al., Production and isolation of actinium-225 with a 100 MeV proton cyclotron and solid-phase extraction. Huaxue Tongbao (2021). 10.14159/j.cnki.0441-3776.2021.11.011
[52] V. Radchenko, J.W. Engle, J.J. Wilson et al., Application of ion exchange and extraction chromatography to the separation of actinium from proton-irradiated thorium metal for analytical purposes. J. Chromatogr. A 1380, 55-63 (2015). https://doi.org/10.1016/j.chroma.2014.12.045

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