^{225}Ac as a Potential Theranostic Radionuclide

Subjects: Radiology, Nuclear Medicine & Medical Imaging

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α radioisotopes can offer a treatment choice to individuals who are not responding to β− or gamma-radiation therapy or chemotherapy drugs. Only a few α-particle emitters are suitable for targeted alpha therapy (TAT) and clinical applications. The majority of available clinical research involves ^{225}Ac and its daughter nuclide ^{213}Bi. Additionally, the ^{225}Ac disintegration cascade generates γ decays that can be used in single-photon emission computed tomography (SPECT) imaging, expanding the potential theranostic applications in nuclear medicine. Despite the growing interest in applying ^{225}Ac, the restricted global accessibility of this radioisotope makes it difficult to conduct extensive clinical trials for many radiopharmaceutical candidates.

targeted alpha therapy 225Ac physical properties production routes theranostic application

1. Introduction

At the end of the 1800s, Pierre and Marie Curie, along with Alexander Graham Bell in the early 1900s, conducted research linked to cancer-targeted α therapy (TAT), which represented one of the earliest non-surgical cancer treatments [1]. Furthermore, α-particle emitters have significant curative effects, particularly in patients with limited therapeutic options and metastatic spread [2][3][4]. They can target very small clusters of metastatic cancer cells.

There are many benefits of using these radioisotopes in cancer therapy over common methods. α particles can selectively destroy tumour cells while preserving adjacent normal tissues due to their narrow extent in human tissue, corresponding to less than 0.1 mm [5]. Meanwhile, highly efficient cell destruction through DNA double-strand and DNA cluster damage is caused by the high energy of α emitters, in addition to the strong linear energy transfer (LET) (80 keV/µm) that goes along with it. These effects are mainly unaffected by the state of the cell cycle and oxygenation [6][7][8]. Thus, α radioisotopes can provide a therapeutic option for patients who are resistant to therapy with β− or gamma radiation or chemotherapeutic medications [9][10][11]. According to research estimations, tens of thousands of β− particles are needed to reach a single-cell killing rate of 99.99%, whereas only a few α decays are needed to accomplish a similar killing potential [4][12].

The high-LET radiation's biological efficacy is explained by its tendency to cause complex multiple clusters and double-strand or single-strand breaks in a target cells' DNA, rendering cellular repair mechanisms ineffective [4][13]. Additionally, reactive oxygen species (ROS), which are produced when emitted particles interact with water, can

react with biomolecules such as proteins, phospholipids, RNA, and DNA, leading to permanent cell deterioration [14]. Moreover, during this type of therapy, the primary tumour and any additional cancerous lesions in the body that the radiation did not directly target may decrease as a result of “the abscopal effect” [14]. It is thought that the immune system is a key player in this process, even though the precise biological mechanisms underlying the phenomenon are as yet unknown [4][15][16] (**Figure 1**).

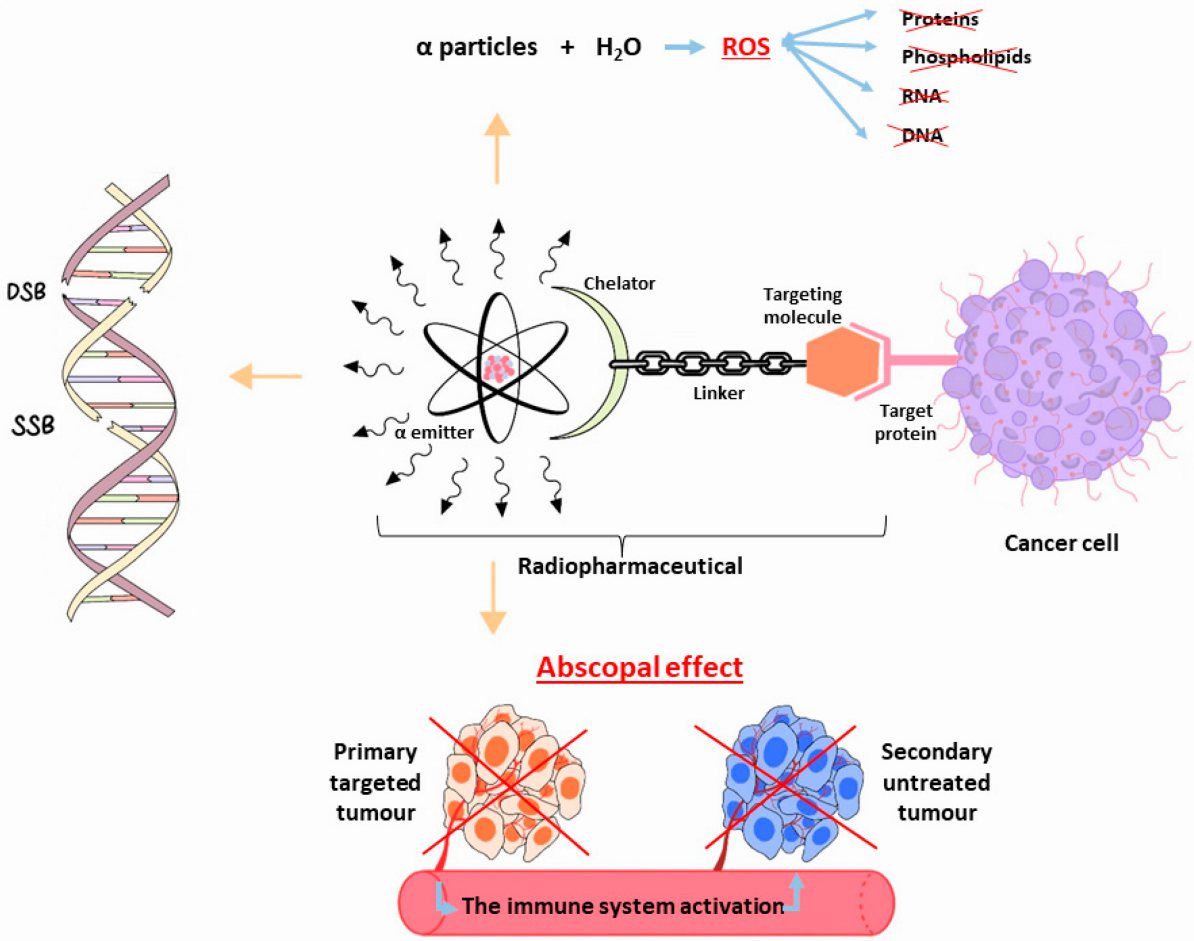

Figure 1. Schematic representation of the biological effects following the use of α-particle emitter radiopharmaceutical for cancer therapy. SSD = Single-Strand Break, DSB = Double-Strand Break, ROS = Reactive Oxygen Species.

Considering the clinical application of TAT, only a limited number of α-particle emitters are appropriate [17]. The use of ^{225}Ac and its short-lived daughter nuclide ^{213}Bi represents the vast majority of available experience in clinical research [5]. Furthermore, applying γ decays, which are produced during the radioactive ^{225}Ac cascade [5] in SPECT imaging, raises the possibility of theranostic nuclear medicine applications.

Although interest in using ^{225}Ac as an α-emitting radiolabel has been steadily increasing [18], substantial clinical investigations of many radiopharmaceutical candidates cannot be supported due to ^{225}Ac’s limited worldwide accessibility [19]. Notwithstanding the significant financial investments made by numerous laboratories to establish production pathways, the widespread use of ^{225}Ac-labeled radiopharmaceuticals in human patients is still not

achievable [19]. This ongoing shortage in ^{225}Ac supply can be explained by the practical production techniques that need difficult logistical tasks, such as using controlled nuclear materials or highly irradiating radioactive accelerator targets [19].

2. ^{225}Ac: Physical Characteristics

Actinium is a radioactive component with atomic number 89 [20]. Only two of its 32 isotopes, ^{228}Ac and ^{227}Ac, are naturally produced as a result of the disintegration of ^{232}Th and ^{235}U, respectively [20][21]. With its long half-life of 21.7 years and predominant β− emissions decay, ^{227}Ac represents the most common actinium isotope. However, ^{228}Ac, which is also a β− emitter, is highly uncommon [20][21].

^{225}Ac is the initial element in the actinide family, and its radioactive parents are parts of the now-extinct “neptunium series” [19][21]. This α-emitter isotope has a long half-life of 9.9 days [5][22].

Starting from ^{225}Ac to reach ^{209}Bi ($T_{1/2}$ = 1.9 × 10^{19} y), the decay series includes six short-lived radionuclide daughters [5][23].

This radioactive cascade is represented by ^{221}Fr ($T_{1/2}$ = 4.8 min; 6.3 MeV α particle and 218 keV γ emission), ^{217}At ($T_{1/2}$ = 32.3 ms; 7.1 MeV α particle), ^{213}Bi ($T_{1/2}$ = 45.6 min; 5.9 MeV α particle, 492 keV β− particle and 440 keV γ emission), ^{213}Po ($T_{1/2}$ = 3.72 µs; 8.4 MeV α particle), ^{209}Tl ($T_{1/2}$ = 2.2 min; 178 keV β− particle), ^{209}Pb ($T_{1/2}$ = 3.23 h; 198 keV β− particle) [24] (**Figure 2**) [14].

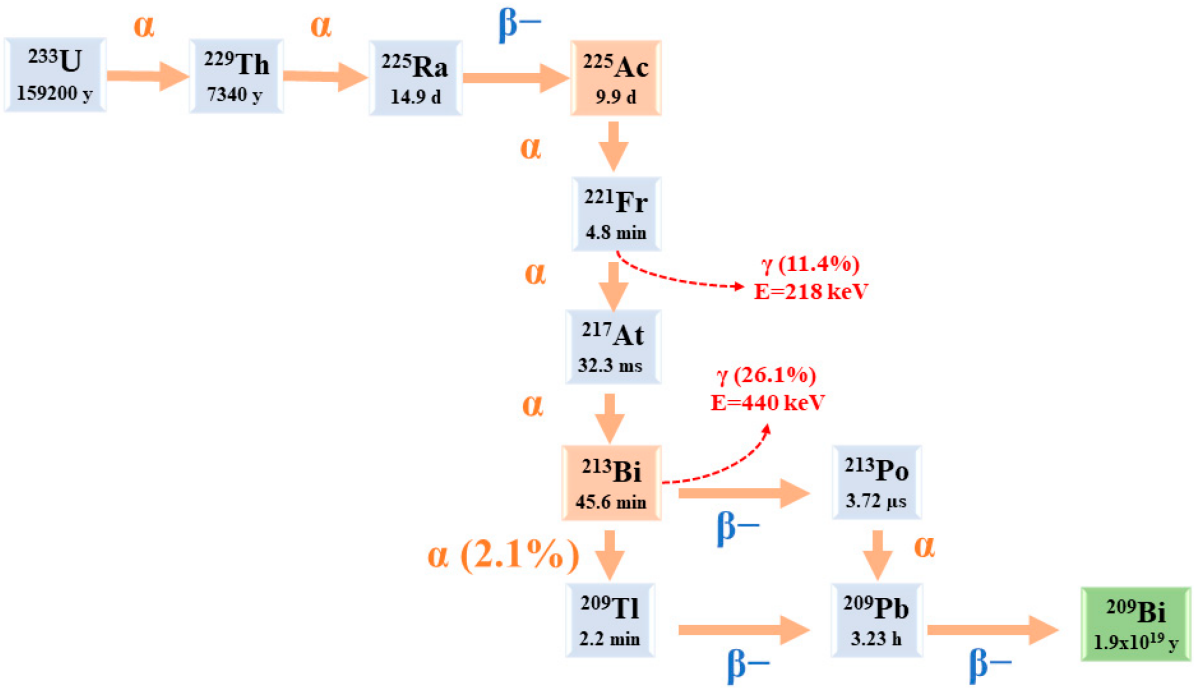

Figure 2. The decay chain of ^{233}U to ^{225}Ac and ^{213}Bi.

3. ^{225}Ac and Its Potential Theranostic Use

^{225}Ac is considered a “nanogenerator”, since one decay of this element produces a total of four α and three β particles, in addition to two γ emissions [24]. Taking into account its α particle emissions, along with the fact that the non-tumour binding activity can be eliminated before most of its dose is deposited in organs, ^{225}Ac is considered an appealing choice for TAT [24][25]. However, it is important to give attention to the notable ^{225}Ac cytotoxicity, including renal toxicity [26], due to its extended half-life and the various α particles produced throughout its decay chain [5].

A theranostic-based approach, characterised by the imaging–therapeutic duality, is the process of obtaining positron emission tomography (PET) and SPECT scans by exchanging the therapeutic α-emitting radionuclide with a positron or gamma diagnostic imaging radionuclide. Significant information on dosimetry and TAT reactions is obtained from these relevant nuclear medicine images.

Chemical characteristics, half-life, radioactive emission type and intensity, related dosimetry, ease and scalability of production, radionuclidic purity, economics, and radionuclide progeny considerations are the factors that determine “the ideal” imaging surrogates for targeted alpha therapy [27][28].

Therapeutic use of ^{225}Ac is often paired with imperfect PET imaging surrogates, such as ^{68}Ga, ^{89}Zr, or ^{111}In, despite significant differences in their half-lives or chelation chemistry [29]. Studies are being conducted to address the limitations of imaging radionuclides by utilising lanthanum (La) as a potential alternative, especially ^{132}La ($T_{1/2}$ = 4.8 h, 42% β+) and ^{133}La ($T_{1/2}$ = 3.9 h, 7% β+) [30][31]. However, the half-lives of these isotopes are much shorter than that of ^{225}Ac, limiting their applicability in PET imaging [29]. In this regard, the production of ^{134}Ce ($T_{1/2}$ = 3.2 d) has recently been started by the U.S. Department of Energy (DOE) Isotope Program [32]. The long ^{134}Ce $T_{1/2}$ and the similar chemical properties of ^{225}Ac and ^{134}Ce were considered potential benefits for monitoring in vivo pharmacokinetics. For PET imaging of the chelate and the antibody trastuzumab, ^{134}Ce has been demonstrated to bind with diethylenetriamine pentaacetate (DTPA) [32] and dodecane tetraacetic acid (DOTA) [33]. On the other hand, greater molar ratios and higher temperatures are needed for isotope combinations with DOTA and DTPA [29]. In contrast, N, N′-bis[(6-carboxy-2-pyridyl)methyl]-4,13-diaza-18-crown-6 (macropa) has shown great stability for nonradioactive cerium and better chelate characteristics for ^{225}Ac [34], indicating that it might be useful for the theranostic development of ^{134}Ce/^{225}Ac [35].

The potential use of γ disintegrations, obtained by the decay of the intermediate ^{221}Fr (218 keV, 11.6% emission probability) and ^{213}Bi (440 keV, 26.1% emission probability) [5], in SPECT in vivo imaging could lead the ^{225}Ac radioactive cascade to a possible theranostic prospective in nuclear medicine applications. Nonetheless, planar SPECT imaging would be challenging because of the effectiveness of ^{225}Ac, which results in modest administered doses (~50–200 kBq/kg [5]), along with low γ emissions [24][25]. As a possible solution to this limitation, we can notice the suitable use of ^{213}Bi, which can be isolated from the ^{225}Ac decay cascades [24]. Nevertheless, it is mandatory to consider the short half-life of ^{213}Bi (45.6 min), which poses difficulties for processing, radiolabelling, and radiopharmaceutical delivery [24]. In addition, it is necessary to point out that these radiations make reaction

monitoring complicated. Moreover, the secular equilibrium must be attained (for at least 6 h) before measuring a trustworthy radiochemical yield (RCY) [21]. Actinium's chemistry lacks advancement because of its restricted availability; all Ac isotopes need specific management and facilities [20].

4. Radiochemistry

During the production of radionuclides, it is mandatory to take into consideration a set of important aspects, such as safety, the co-generation of a few long-lived radionuclidic impurities, and adjustability, to enable delivery through clinical sites [27]. Once the target material has been irradiated, potent chemical purification methods are required to isolate the radioisotope [27][36][37][38]. Furthermore, the alpha particle may radiolytically damage the radiopharmaceutical itself, reducing in vivo targeting and producing more radioactive deposits in nontarget tissue. [27].

Since radiopharmaceuticals are considered typical pharmaceuticals, special manuals have been developed in the *European Pharmacopoeia* to deal with quality control issues [39]. Additionally, optimised protocols for preparing ^{225}Ac agents in therapeutic doses have been established [40] (**Table 1**).

Table 1. Research on ^{225}Ac chemistry. RCY = Radiochemical yield, RCP = Radiochemical purity, TLC = Thin-layer chromatography, ITLC = Instant thin-layer chromatography.

Study	Preparation Method	Radiopharmaceutical	RCY/RCP
Abou. et al., 2022 [41]	❖ The labelling of the DOTA-conjugated peptide was carried out under good manufacturing practice within a shielded hot cell using a multifunctional automated radiosynthesis module (Trasis, AllinOne mini). ❖ 46.6 MBq of the ^{225}Ac source dissolved in 0.2 M HCl was loaded under vacuum in the initial vial for radiolabelling with the DOTA-conjugated precursor (200 µg) on day 5 postsource purification. The source was transferred to the one-pot radiolabelling reactor cassette, in which the reaction occurred in Tris buffer (1 M, pH 7.2) at 85 °C for 70 min in the presence of 20% *v*/*v* L-ascorbic acid at pH 6–8. The radiolabelled peptide was transferred in saline and passed through a 0.2 µm sterilizing filter, resulting in a final volume of 9.7 mL. ❖ The radiolabelled products were characterised using thin-layer chromatography, high-pressure liquid	^{225}Ac-DOTA-conjugated peptide	>99%/>95%

Study	Preparation Method	Radiopharmaceutical	RCY/RCP
	chromatography, gamma counting, and high-energy resolution gamma spectroscopy.		
Dumond. et al., 2022 [42]	❖ PSMA-617 precursor was dissolved in 25 µL metal-free water (0.67 mg/mL) and combined with 500 µL 0.05M Tris buffer, pH 9. ^{225}Ac solution (~65 µCi in 15 µL) was added and the reaction was heated at 120 °C for 40–50 min. The resulting reaction was cooled and 0.6 mL gentisic acid solution (4 mg/mL in 0.2 M NH_4OAc) was added. To formulate the dose for injection, sterile saline (8 mL) was added and the pH was adjusted by the addition of 100 µL 0.05 M Tris buffer (pH 9) to give a final pH of ~7.2. The final solution was filtered using a 0.22 µm GV sterile filter into a sterile dose vial. ❖ Radiochemical purity was determined by radio-TLC (eluent: 50mM sodium citrate, pH 5), and plates were analysed using an AR2000 scanner.	^{225}Ac-PSMA-617	>99%/98 ± 1%
Thakral. et al., 2021 [43]	❖ ^{225}Ac-PSMA-617 was prepared by adding the peptidic precursor-PSMA-617 (molar ratios, ^{225}Ac: PSMA-617 = 30:1) in 1 mL ascorbate buffer to ^{225}Ac and heating the reaction mixture at 90 °C for 25 min. ❖ pH was determined using pH paper. ❖ RCP of ^{225}Ac-PSMA-617 was determined by ITLC.	^{225}Ac-PSMA-617	85–87%/97–99%
Kelly. et al., 2021 [44]	❖ ^{225}Ac (9.25 MBq) was obtained from a thorium generator at Canadian Nuclear Laboratories and supplied as the dried [^{225}Ac]$AcCl_3$ salt. The [^{225}Ac]$AcCl_3$ was dissolved in 1 mL 1 M NH_4OAc, pH 7.0, transferred by pipette to a 50 mL centrifuge tube, and diluted to 45 mL in 1 M NH_4OAc. Stock solution (1 mL), containing approximately 205 kBq [^{225}Ac]$Ac(OAc)_3$, was transferred by pipette to a plastic Eppendorf tube placed	^{225}Ac-PSMA conjugated peptide/ ^{225}Ac-DOTA conjugated peptide/	2.7 ± 0.55%–98.8 ± 0.09%/1.8–99.5%

Study	Preparation Method	Radiopharmaceutical	RCY/RCP
	on a digital TermoMixer heating block. Then, 20 µL of the ligand stock solution (0.01–1 mg/mL of PSMA or DOTA or macropa) was added and the reaction was shaken at 300 rpm at either 25 °C or 95 °C. A 3 µL aliquot of the reaction mixture was withdrawn and deposited on the origin of a silica-gel-60-coated aluminium plate (Sigma Aldrich) after incubating the reaction for 1 min, 5 min, and 15 min. ❖ A TLC method was developed to separate the metal complexed ligand from uncomplexed ^{225}Ac and its daughter radionuclides.	^{225}Ac-macropa conjugated peptide	
Hooijman. et al., 2021 [45]	❖ ^{225}Ac was diluted into 0.1 M HCl. Stock solutions (10 mL) were proceeded in quartz-coated sterile vials. All purchased chemicals were prepared with Milli-Q water. Stock solutions prepared the day before labelling were 1 M HCl (from 37% HCl), 10 M NaOH, and 0.1 M TRIS-buffer pH 9. Two stock solutions were prepared on the day of labelling: First, 20% ascorbic acid was prepared; the ascorbic acid solution was transformed to ascorbate by the addition of 10 M NaOH to a pH 5.8. Secondly, PSMA-I&T (250 µg) was dissolved in 0.1 M TRIS buffer (pH 9) to a concentration of 600 µg/mL. Directly after labelling, 4 mg/mL diethylenetriaminepentaacetic acid (DTPA) was added to the labelling mixture. A solution for injection was prepared by the addition of ascorbate (50% *v*/*v*) and ethanol (6% *v*/*v*, 96%) into saline.	^{225}Ac-PSMA-I&T	>95%/>90% [27]

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Investigations on ^{225}Ac have shown potential in treating neuroendocrine tumours, acute myeloid leukaemia, and metastatic prostate cancer, and more radiopharmaceuticals are being developed for other cancer types [46][47][48][49][50][51][52] (**Table 2**).

Table 2. Clinical research based on ^{225}Ac.

Disease	Study	Radiopharmaceutical
Prostate cancer	Parida et al., 2023 [53]	^{225}Ac-PSMA RLT

Disease	Study	Radiopharmaceutical
	Ma et al., 2022 [54]	^{225}Ac-PSMA-617
	Sanli et al., 2021 [55]	^{225}Ac-PSMA-617
	Sen et al., 2021 [56]	^{225}Ac-PSMA-617
	Zacherl et al., 2021 [50]	^{225}Ac-PSMA-I&T
	Feuerecker et al., 2021 [57]	^{225}Ac-PSMA-617
	Van Der Doelen et al., 2021 [58]	^{225}Ac-PSMA-617
	Sathekge et al., 2020 [51]	^{225}Ac-PSMA-617
	Yadav et al., 2020 [59]	^{225}Ac-PSMA-617
	Satapathy et al., 2020 [60]	^{225}Ac-PSMA-617
	Sathekge et al., 2019 [61]	^{225}Ac-PSMA-617
	Kratochwil et al., 2018 [62]	^{225}Ac-PSMA-617
Neuroendocrine tumours	Ballal et al., 2022 [63]	^{225}Ac-DOTATATE
	Yadav et al., 2022 [48]	^{225}Ac-DOTATATE
	Kratochwil et al., 2021 [64]	^{225}Ac-DOTATATE
	Ballal et al., 2020 [65]	^{225}Ac-DOTATATE

Disease	Study	Radiopharmaceutical
	Kratochwil et al., 2015 [66]	^{225}Ac-DOTATOC
Acute myeloid leukaemia	Rosenblat et al., 2022 [67]	^{225}Ac-lintuzumab
	Jurcic, 2018 [68]	^{225}Ac-lintuzumab
	Jurcic et al., 2016 [69]	^{225}Ac-lintuzumab
	Jurcic et al., 2011 [70]	^{225}Ac-lintuzumab

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clinical production purposes through an automated synthesis platform (cassette-based module—Modular-Lab EAZY, Eckert & Ziegler) [72]. After comparing two purification methods, the researchers obtained ^{225}Ac-labelled peptides in an RCY of 80–90% for tumour therapy in patients [71]. Thus, the whole process was meticulously validated in accordance with the regulations of the German Pharmaceuticals Act §13.2b, knowing that the estimated costs for the automated synthesis of 1 MBq ^{225}Ac is around EUR 300–390, taking into account that the peptides would cost EUR 600–1000, the cassettes would cost EUR 180–200, and the ML EAZY would cost EUR ~30,000 [71].

6. The Production Routes of ^{225}Ac

As already mentioned, ^{225}Ac is part of the ^{237}Np disintegration family that has vanished in nature. This radioactive element could be artificially reproduced [21]. In addition to direct production paths, ^{225}Ac is conveniently reachable at numerous points along the decay chain, in particular via ^{233}U ($T_{1/2}$ =159200 y, 100% α), ^{229}Th ($T_{1/2}$ = 7340 y, 100% α), and ^{225}Ra ($T_{1/2}$ = 14.9 d, 100% β−) [19]. ^{225}Ac possesses many fewer nucleons than other actinide nuclei that are more stable to be employed as production targets, such as ^{232}Th and ^{226}Ra [19]. Thus, production methods should, with rare exceptions, rely on radioactive decay or greater energy bombardments.

The available production routes of ^{225}Ac and its parents are listed below (**Figure 3**) [14]:

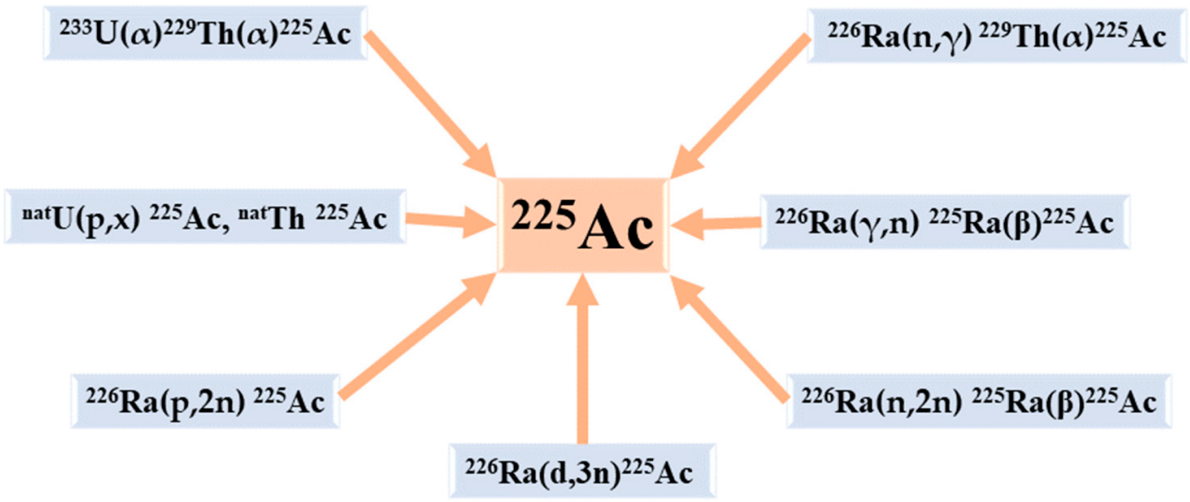

Figure 3. The principal production routes for ^{225}Ac.

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