

Review

Recent Advances in Separation Strategies for Medical α -Radionuclides

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Abstract: Efficient separation strategies for medical α -radionuclides serve as a critical bridge connecting radionuclide production with biological application. Here, we present a comprehensive review of advanced separation strategies for medical α -radionuclides, systematically summarizing the recent research in the separation of common medical α -radionuclides, including ^{211}At , ^{212}Pb , ^{213}Bi , ^{223}Ra , ^{224}Ra , and ^{225}Ac . A broad spectrum of separation systems is covered, spanning from conventional ion exchange and extraction chromatography to emerging functionalized materials, with detailed elaboration on the underlying principles and practical performance of various strategies. Most importantly, this review aims to provide rational guidance for the design of high-performance separation strategies, thereby facilitating the translation of α -radiopharmaceuticals from laboratory research toward clinical application.

Keywords: medical α -radionuclide; separation; purification; radiochemistry; separation material

1. Introduction

Radiopharmaceuticals incorporating alpha (α)-emitters, which hold significant promise in cancer targeted alpha therapy (TAT), offer a captivating and promising approach for cancer therapy [1,2]. α -Radionuclides release α -particles with extremely high linear energy transfer (LET, $\sim 100 \text{ keV}/\mu\text{m}$), depositing substantial energy within an extremely short path length of $50\sim 100 \mu\text{m}$ [3,4]. This property enables highly efficient induction of DNA double-strand breaks in tumor cells, making α -radionuclides well-suited for TAT of micrometastatic lesions and disseminated disease. In recent years, the approval of $^{223}\text{RaCl}_2$ (Xofigo[®]) [5] has marked a decisive transition of α -radiopharmaceuticals from laboratory research into broad clinical practice, driving a historic leap in global demand for high-quality medical α -radionuclides [6].

In addition to ^{223}Ra , a variety of α -emitting radionuclides have been proposed for TAT, including ^{149}Tb , ^{211}At , ^{212}Pb , ^{213}Bi , ^{224}Ra , ^{225}Ac , ^{227}Th , and ^{230}U (Table 1). However, not all these candidates are equally suited to current radiopharmaceutical practice. For example, ^{149}Tb is too short-lived for the pharmacokinetics of most carriers [7]; ^{230}U not only has a relatively prolonged half-life but also suffers from underdeveloped radiopharmaceutical chemistry, limiting its translation into stable radiopharmaceutical constructs [8]. Notably, neither ^{149}Tb nor ^{230}U has yet advanced into clinical trials. Although ^{227}Th has been investigated in several clinical trials [9], its decay into the long-lived daughter ^{223}Ra complicates dosimetry and radiation safety [10], which has limited its broader adoption. In contrast, ^{211}At , ^{212}Pb , ^{213}Bi , ^{223}Ra , ^{224}Ra , and ^{225}Ac exhibit half-lives compatible with the pharmacokinetics of small molecules, peptides, and antibodies and have already demonstrated clinical feasibility through multiple completed or ongoing trials, thus representing the most mature and promising candidates for TAT.



Table 1. Characteristics and clinical trials of several α -radionuclides suitable for endoradiotherapy.

Nuclide	$T_{1/2}$	α -Radiopharmaceuticals That Have Completed, are Ongoing, or Are Planned to Undergo Clinical Trials ^a
¹⁴⁹ Tb	4.12 h	None
²¹¹ At	7.21 h	²¹¹ At-Girentuximab, ²¹¹ At-BC8-B10, ²¹¹ At-NaAt, ²¹¹ At-PSMA-5, ZA-001
²¹² Pb	10.60 h	²¹² Pb-DOTAM-MAM279, ²¹² Pb-Pentixather, ²¹² Pb-NG001, ²¹² Pb-VMT- α -NET, ²¹² Pb-DOTAMTATE, ²¹² Pb-DOTAM, ²¹² Pb-PSV359, ²¹² Pb-DOTAM-GRPR1, ²¹² Pb-VMT01, AB001
²¹³ Bi	45.59 min	²¹³ Bi-HuM195
²²³ Ra	11.43 d	Xofigo [®]
²²⁴ Ra	3.63 d	²²⁴ Ra-labeled CaCO ₃ microparticles (Radspherin [®])
²²⁵ Ac	9.92 d	²²⁵ Ac-A9-0642, ²²⁵ Ac-AKY-2519, ²²⁵ Ac-anti-CD33, ²²⁵ Ac-rhPSMA-10.1, ²²⁵ Ac-DOTATATE, ²²⁵ Ac-A9-3408, ²²⁵ Ac-ETN029, ²²⁵ Ac-DOTA-SP, RYZ801, ²²⁵ Ac-AKY-1189, ²²⁵ Ac-PSMA-617, ²²⁵ Ac-DOTA-Anti-CD38, ²²⁵ Ac-TR2205, ²²⁵ Ac-LNC1011, ²²⁵ Ac-AZD2284, ²²⁵ Ac-ABD147, ²²⁵ Ac-PSMA-I&T, ²²⁵ Ac-FAPI-XT, ²²⁵ Ac-PSMA-XT, ²²⁵ Ac-DOTATATE, ²²⁵ Ac-FL-020, ²²⁵ Ac-FPI-2068, ²²⁵ Ac-PSMA-62, ²²⁵ Ac-PSMA-Trillium, ²²⁵ Ac-PSMA-R2, ²²⁵ Ac-MTI-201, ²²⁵ Ac-J591
²²⁷ Th	18.70 d	²²⁷ Th-Pelgifatamab, ²²⁷ Th-anetumab corixetan, ²²⁷ Th-anti-HER2, ²²⁷ Th-anti-CD22
²³⁰ U	20.23 d	None

^a Retrieved from clinicaltrials.gov.

The production of medical α -radionuclides relies primarily on three routes: separation from natural U/Th ores, reactor production, and accelerator production (Figure 1) [11,12]. Regardless of the production pathway employed, the target α -radionuclide must undergo efficient separation and purification to remove the impurity radionuclides, thereby achieving the high yield and radionuclidic purity required for downstream applications [13,14]. Taking ²²⁵Ac as an example, commercially supplied ²²⁵Ac typically requires a radionuclidic purity exceeding 99%, which is verified by gamma (γ)-ray spectrometry using high-resolution HPGe detectors [15,16]. To meet this stringent purity standard, a variety of separation strategies have been developed, encompassing ion exchange chromatography, extraction chromatography, liquid-liquid extraction (LLE), solid-phase extraction (SPE), sublimation, and electrochemical separation (Figure 2). Among these, ion exchange chromatography and extraction chromatography have emerged as the most widely adopted approaches, owing to their operational simplicity, tunable selectivity, and compatibility with automated processing [17–19]. Conventional ion exchange resins (e.g., Dowex resin, AG resin) and extraction chromatographic resins (e.g., Diglycolamide (DGA) resin, Uranium/TetraValent Actinide (UTEVA) resin, Lanthanide (LN) resin) have been demonstrated to be versatile in α -radionuclides separation and remain the cornerstone of current practice. However, as separation demands become increasingly stringent, the limitations of these conventional materials have grown more apparent, including restricted adsorption capacity, insufficient selectivity, and diminished stability under highly acidic conditions or intense radiation fields. Lately, a new generation of separation materials has attracted considerable attention [20], including covalent organic frameworks (COFs), functionalized resins, functionalized inorganic materials, and nanocomposite materials, etc. Characterized by high specific surface areas, tunable pore architectures, abundant functional sites, and flexible structural designability, these materials enable highly selectivity and high capacity through precise molecular engineering, offering transformative solutions to overcome the performance bottlenecks inherent in conventional separation strategies.

In recent years, the application of advanced separation strategies to medical α -radionuclides has attracted growing interest from the researchers, yet systematic reviews dedicated to this field remain scarce. In this review, we provide a comprehensive summary of the latest advances in the separation and purification of medical α -radionuclides, across a broad range of separation strategies ranging from conventional ion exchange and extraction chromatography to emerging functionalized materials. We believe that a systematic review of separation strategies for medical α -radionuclides will not only help clarify the current landscape of technological development, but also provide important guidance for advancing high-performance separation materials and processes, while offering valuable reference for the separation of radionuclides intended for other fields.

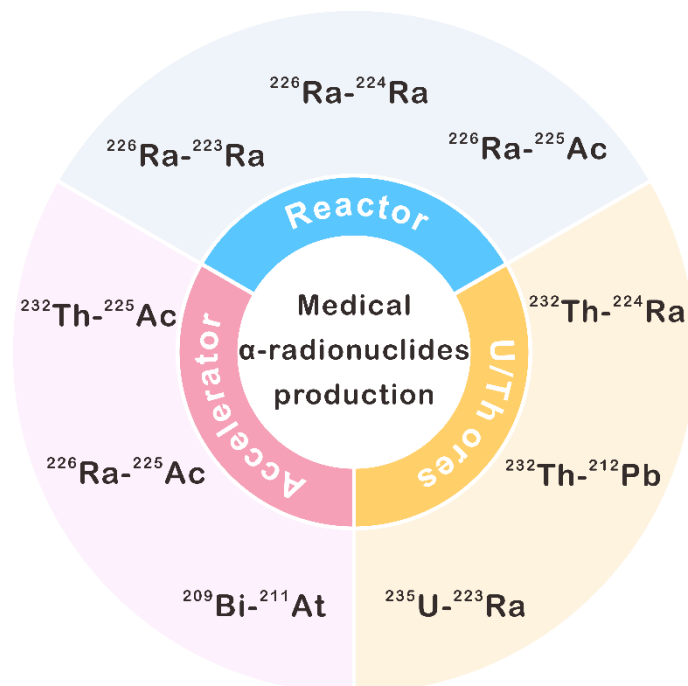


Figure 1. Production routes of medical α -radionuclides suitable for TAT.

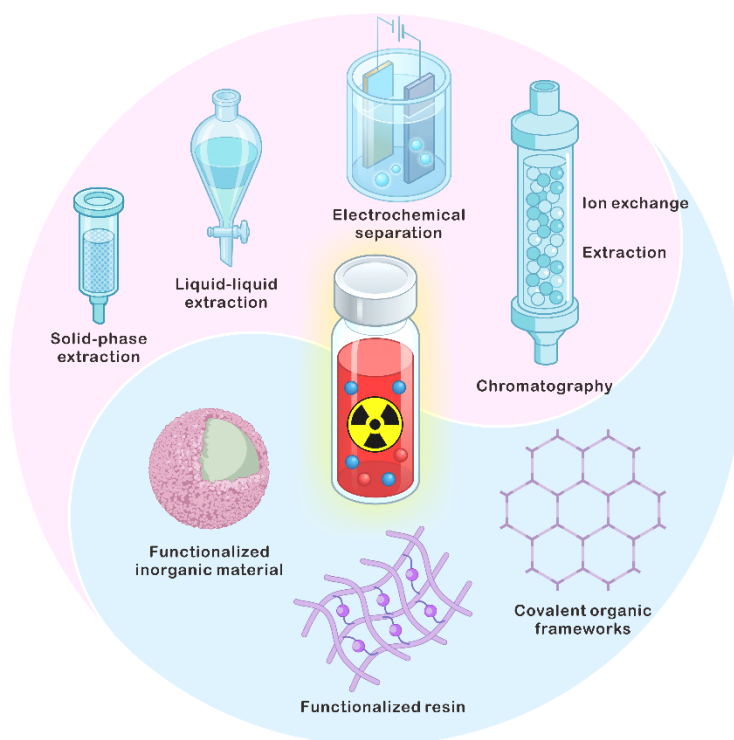


Figure 2. Strategies for the separation of medical α -radionuclides.

2. ^{211}At

^{211}At ($T_{1/2} = 7.21$ h) is widely regarded as one of the most promising α -emitting radionuclides for TAT, owing to its favorable nuclear properties [21–24]. As illustrated in Figure 3, ^{211}At decays to stable ^{207}Pb via two competing branches: through ^{207}Bi ($T_{1/2} = 32.9$ y) via orbital electron capture, and through ^{211}Po ($T_{1/2} = 0.516$ s) via α decay. Although the ^{207}Bi branch produces characteristic X-rays or auger electrons through electron capture, these emissions are of low energy and short range, rendering ^{207}Bi a “relatively stable” daughter radionuclide [25]. Consequently, ^{211}At is generally considered a short decay-chain α radionuclide. However, its short physical half-life demands careful matching of the carrier’s biological half-life [26]. Small molecules such as amino acids, inhibitors, and peptides clear rapidly and thus seem kinetically suited to ^{211}At , but after radioastatination they often exhibit poor tumor targeting, stability, and retention. Monoclonal antibodies provide superior stability and

prolonged tumor retention, yet their long biological half-lives are difficult to reconcile with the half-life of ^{211}At . Currently, ^{211}At is produced in a cyclotron predominantly via $^{209}\text{Bi}(\alpha, n)^{211}\text{At}$ transmutation reaction [27]. Two principal methods have been developed for isolating ^{211}At from irradiated ^{209}Bi targets: dry distillation and wet-chemical separation. These approaches are complementary, each with distinct advantages and limitations, and both continue to undergo active development [26].

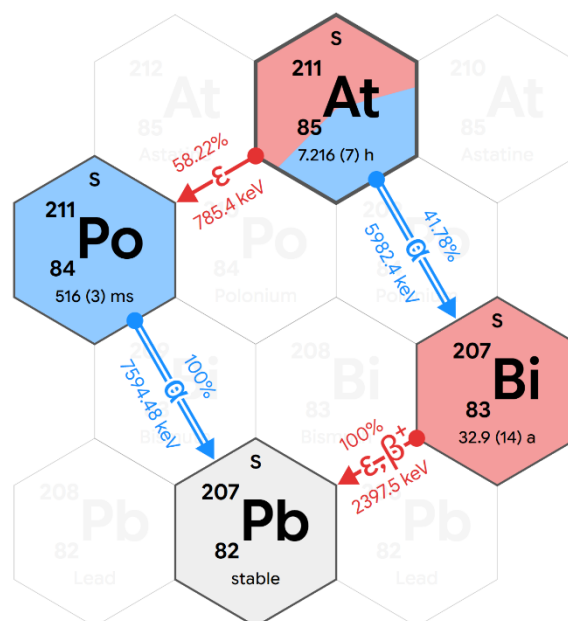


Figure 3. Decay diagram of ^{211}At , drawn from the Laraweb website (<http://www.lnhb.fr/Laraweb/>) (accessed on 1 May 2026).

Dry distillation is currently the most widely employed method for ^{211}At isolation [28]. The underlying principle exploits the large difference in boiling points between At (335 °C) and Bi (1564 °C), enabling selective volatilization of ^{211}At by controlled heating. In a typical procedure, the irradiated Bi target is placed in a furnace connected to a stable carrier gas flow and rapidly heated to 650–800 °C to sublimate ^{211}At [26]. The volatilized ^{211}At is carried by a nitrogen stream into a cold trap maintained under negative pressure, where it condenses and accumulates. The collected ^{211}At is subsequently dissolved using an appropriate solvent, such as chloroform, methanol, or NaOH solution, to yield the final product. The entire process can be completed within 30 min, producing carrier-free ^{211}At without requiring prior dissolution of the irradiated target. Several research groups, including those led by Sture Lindegren [29], Michael R. Zalutsky [30], and Kotaro Nagatsu [31], have explored and refined dry distillation protocols for ^{211}At ; however, the achieved recovery yields remain suboptimal and require further improvement.

To address the drawbacks of low yield and poor process stability in conventional dry distillation, our group [32] developed an optimized semi-automated dry distillation system for ^{211}At production (Figure 4a). By employing iodine dry distillation simulations, we identified the key parameters governing separation performance and established a streamlined, operationally practical protocol. The optimized process achieves a product recovery rate exceeding 98%, a radionuclidic purity greater than 99.9%, and is free from metallic contaminants such as Bi and Cu, with the entire separation completed within 45–60 min. However, conventional dry distillation typically relies on methanol or chloroform as the eluting solvent, both of which carry biological toxicity concerns. To overcome this limitation, Ooe et al. [33] developed a method in which distilled ^{211}At is dissolved directly in pure water, enabling the preparation of $[^{211}\text{At}]\text{NaAt}$ (Figure 4b). In this approach, volatilized ^{211}At is transported through a mixed N_2/O_2 carrier gas containing trace moisture into an ice-water-cooled Teflon tube, then dissolved in 100 μL of pure water. Approximately 80% of ^{211}At is captured within the Teflon tube; however, the recovery of the aqueous dissolution step exhibits considerable variability (35–70%), attributable to fluctuations in the moisture content of the carrier gas. By repeating the dissolution step 2–6 times, a cumulative separation yield of 65–80% can be achieved.

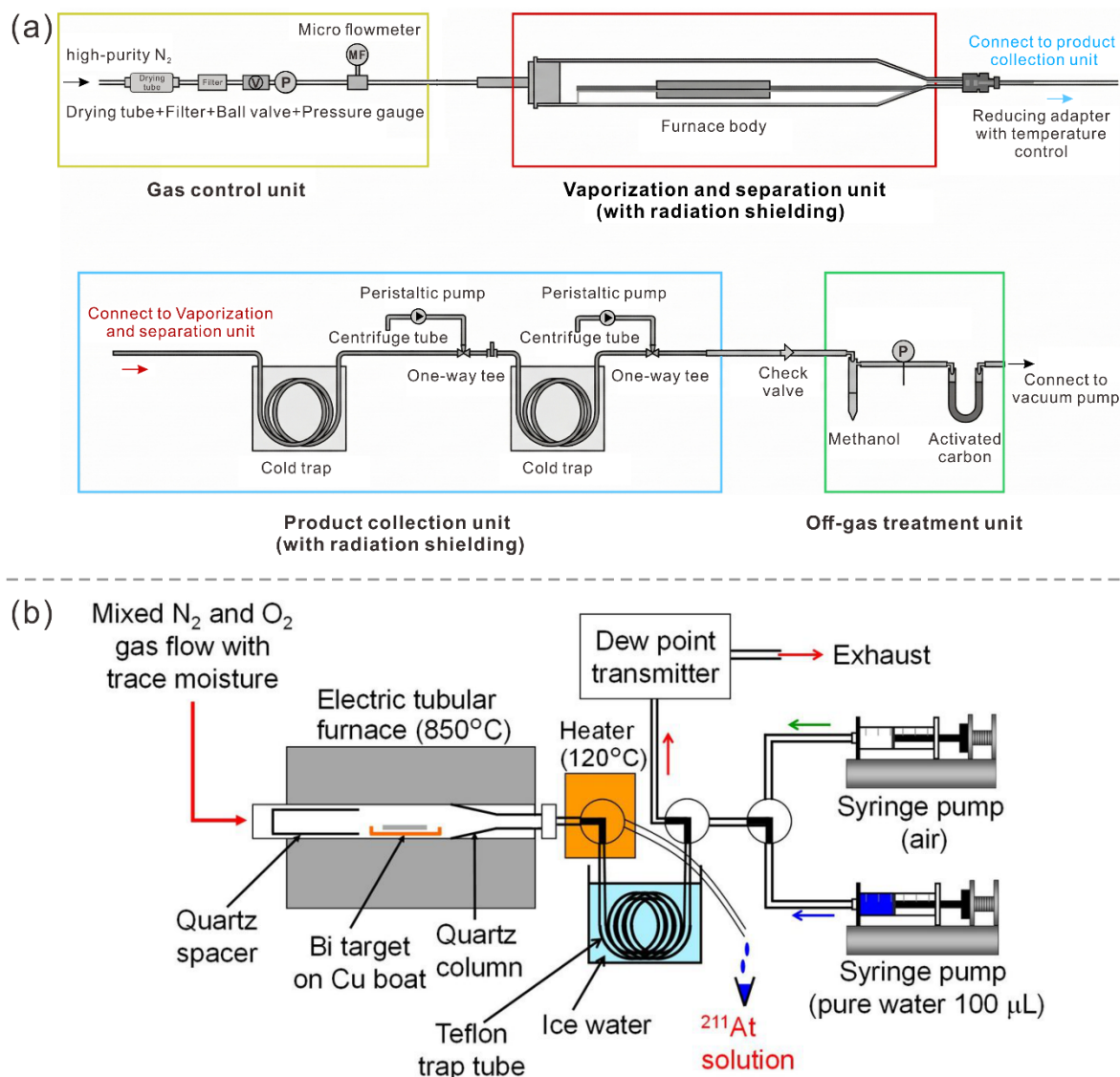


Figure 4. (a) Flow chart of ^{211}At dry distillation process [32]. (b) Preparation of an ^{211}At aqueous solution by dry distillation and dissolution in pure water. Reprinted with permission from Ref. [33]. Copyright 2021, SNMMI.

In recent years, wet-chemical separation strategies for ^{211}At have attracted renewed research interest. Conventional wet methods, based on LLE or SPE, involve initial dissolution of the irradiated target in an acid solution followed by sequential purification. For example, Burns et al. [34] demonstrated that 3-octanone and methyl isobutyl ketone effectively extract ^{211}At from HNO_3 solution while retaining Bi predominantly in the aqueous phase. Furthermore, by loading 3-octanone onto Amberchrom[®] CG300M resin to prepare an impregnated resin, high-performance ^{211}At separation was achieved with a recovery exceeding 90% and a product volume below 1 mL. Woen et al. [35] reported a method using commercial pre-filter resin for ^{211}At recovery, in which Bi impurities were removed by washing with HCl and $\text{NH}_2\text{OH}\cdot\text{HCl}$ solutions of varying concentrations, followed by elution with 2 mol/L (M) NaOH , affording a recovery of 51%. Watanabe et al. [36] investigated anion exchange resin separation of ^{211}At , finding that ^{211}At is retained on the resin when the column is washed with 8 M HCl and HNO_3 , with 75.3~79.1% of the activity subsequently elutable using NaOH or NaOH -ethanol solutions of varying concentrations. The separation times for these wet-chemical approaches range from 20 to 90 min, broadly comparable to dry distillation [36].

Nevertheless, conventional wet-chemical methods are associated with several limitations. First, certain SPE strategies require conversion of the target dissolution medium from HNO_3 to HCl prior to separation, introducing additional processing steps that are particularly disadvantageous for short-lived radionuclides. Second, the use of NaOH as the ^{211}At eluent in most SPE protocols complicates downstream concentration to achieve the high radioactivity concentrations required for radiopharmaceutical applications. Third, for impregnated resins, leaching of the extractant from the support may contaminate the target radionuclide product. To address these challenges, our group [37] proposed a SPE strategy based on chemically functionalized resins for the mild and rapid recovery

of ^{211}At from irradiated Bi targets (Figure 5). A series of resins containing acyl-, thioether-, sulfonate- and phosphonate-groups were synthesized. Among them, the thioether-, sulfonate- and phosphonate-resins were prepared by reacting chloromethyl resin with dodecyl mercaptan, thiourea, and triethyl phosphite, respectively, thereby introducing $-\text{CH}_2\text{SC}_{12}\text{H}_{25}$, $-\text{CH}_2\text{SO}_3\text{H}$, and $-\text{CH}_2\text{PO}(\text{OEt})_2$ groups. The acyl-resin was obtained by reacting polystyrene-divinylbenzene resin (PDVB resin) with acetyl chloride via Friedel-Crafts acylation, introducing $-\text{COCH}_3$ groups onto the resin surface, and demonstrated superior ^{211}At separation performance. An SPE column packed with Acyl-resin enabled direct separation of ^{211}At from the target solution within 20 min, achieving a total recovery of 60.03~79.05%. The resulting ^{211}At product exhibited high radionuclidic and radiochemical purity, suitable for radiopharmaceutical labeling. By modulating the chemical speciation of ^{211}At in HNO_3 medium, this approach enables rapid and efficient isolation, offering a novel SPE platform for ^{211}At separation.

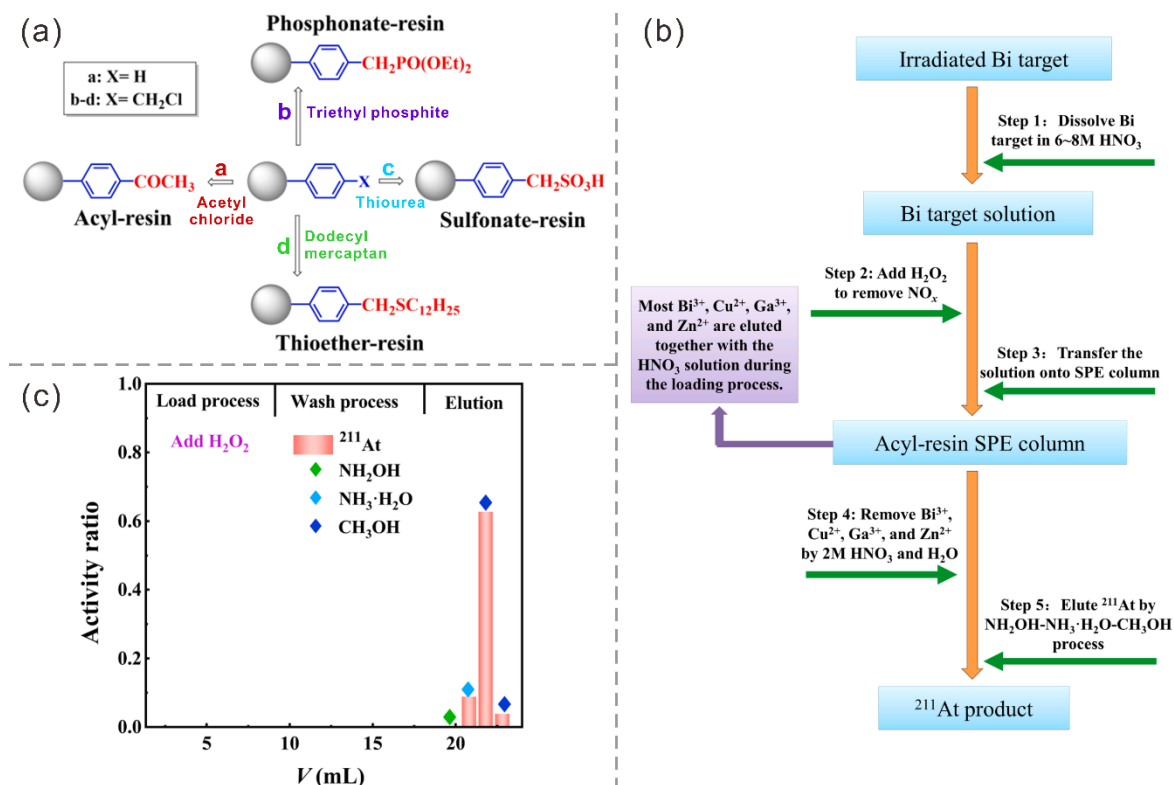


Figure 5. (a) Synthesis scheme of functionalized resins; (b) Flow chart of the Acyl-resin SPE column for separation of ^{211}At ; (c) Column chromatogram of ^{211}At separation from an irradiated Bi target using the Acyl-resin column. Reprinted with permission from Ref. [37]. Copyright 2024, Elsevier.

In summary, wet-chemical separation avoids the use of high-temperature equipment, eliminating concerns over uncontrolled volatilization of ^{211}At , and is more readily amenable to automation and scale-up production. However, it requires time-consuming dissolution of the target material, and residual Bi or co-produced impurities may compromise product quality. Dry distillation and wet-chemical separation are complementary rather than competing approaches, and both continue to evolve, particularly with the emergence of automated separation systems [38,39]. Ultimately, improving the separation efficiency of ^{211}At will be a pivotal factor in advancing either its fundamental radiochemistry or the broader clinical development of ^{211}At -related radiopharmaceuticals.

3. ^{212}Pb

^{212}Pb ($T_{1/2} = 10.6$ h) is a daughter radionuclide of ^{224}Ra . Although ^{212}Pb undergoes β^- decay, it generates two high-energy α -emitting progeny, ^{212}Bi and ^{212}Po (Figure 6), and is therefore considered a highly promising radionuclide for TAT [40–42]. To maximize tumor dose and minimize off-target irradiation, the biological half-life of the vector should be matched to the 10.6 h half-life of ^{212}Pb , favoring vectors with intermediate-to-fast pharmacokinetics such as antibody fragments, peptides, and small molecules [43]. Current strategies for the separation of ^{212}Pb fall into three principal categories: (1) direct separation from natural ^{232}Th ; (2) isolation from a $^{228}\text{Th}/^{224}\text{Ra}/^{212}\text{Pb}$ generator; and (3) isolation from a $^{224}\text{Ra}/^{212}\text{Pb}$ generator.

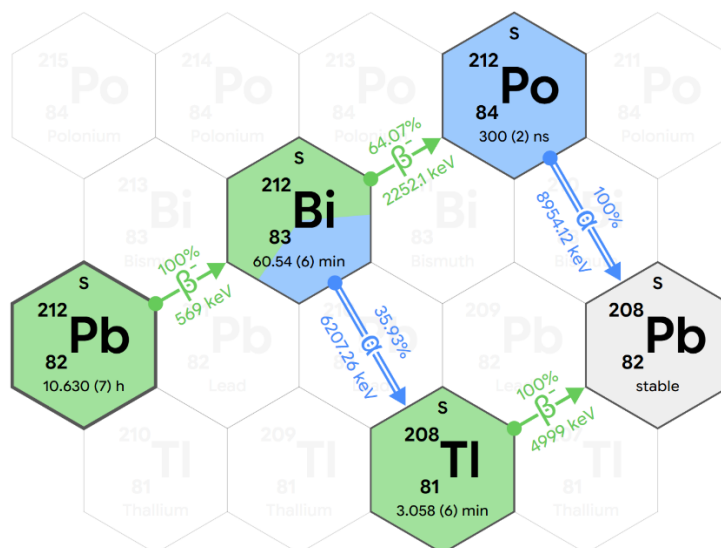


Figure 6. Decay diagram of ^{212}Pb , drawn from the Laraweb website (<http://www.lnhb.fr/Laraweb/> (accessed on 1 May 2026)).

Direct selective extraction of ^{212}Pb from natural ^{232}Th offers several advantages, including broad feedstock availability, low cost, and the potential for complete reuse of the Th solution [44]. However, the enormous concentration disparity between Th and Pb imposes extremely demanding selectivity requirements on the separation material. Chen et al. [45] employed the commercially available Pb-Spec extraction chromatographic resin to directly extract ^{212}Pb from natural Th compounds. The active component of Pb-Spec resin is 4,4',(5')-di-(*t*-butyldicyclohexano)-18-crown-6 immobilized on an inert support, which selectively retains Pb^{2+} while leaving Th, Ra, and Ac unretained. Residual Th^{4+} was removed by washing with 1 M HNO_3 and water, and Pb^{2+} was subsequently eluted with 0.5 M ammonium citrate solution, achieving a ^{212}Pb retention of 85% and a radionuclidic purity over 99.9%. Notably, the Th solution can be subjected to repeated ^{212}Pb separations at 48-h intervals, effectively functioning as a radionuclide generator.

To further advance ^{212}Pb separation from ^{232}Th , researchers have developed a series of novel high-performance separation materials. Chen et al. [46,47] prepared a silica-based quaternary pyridinium-type anion exchange resin (SiPyR-N4) (Figure 7a) that enables the selective separation of ^{212}Pb and ^{212}Bi in HBr medium. In HBr medium, both Pb^{2+} and Bi^{3+} form anionic complexes, predominantly $[\text{PbBr}_3]^-$ and $[\text{BiBr}_5]^{2-}$, respectively, which are retained on the resin, whereas Th^{4+} , Ac^{3+} , and Ra^{2+} remain cationic and are not adsorbed. Using this approach, ^{212}Pb was successfully isolated from ^{232}Th , achieving a record yield of 88.2% and an estimated radionuclidic purity higher than 99.9%. Compared with crown ether-based ^{212}Pb separation methods, SiPyR-N4 resin offers significantly lower cost and superior chemical stability. Jiang et al. [48] developed a series of 2,5-diaminobenzoic acid COF (DBCOF) materials with systematically varied pore sizes and functional groups, namely DBCOF-H, DBCOF-OH, and DBCOF-OMe, based on a “pore sieving-chemical recognition” dual-dimensional synergistic regulation strategy (Figure 7b), revealing a reversed adsorption selectivity between Th^{4+} and Pb^{2+} ions. This reversal arises from the combined effects of chemical coordination and steric pore exclusion, fundamentally overturning the conventional ion capture selectivity governed solely by functional group affinity. The authors further fabricated the powdered COFs into interwoven porous nanofiber membranes via an electrospinning *in situ* growth strategy, constructing a hierarchical membrane separation system capable of high-throughput, high-precision sequential separation of $\text{Th}^{4+}/\text{Pb}^{2+}/\text{Ba}^{2+}$ under dynamic flow conditions. Their work highlights the significant advantages of “chemical-physical” dual-dimensional synergistic effects in radionuclide separation, and provides important insights for the molecular-level rational design and fine-tuning of next-generation functional separation materials.

Isolation of ^{212}Pb from a $^{228}\text{Th}/^{224}\text{Ra}/^{212}\text{Pb}$ generator or a $^{224}\text{Ra}/^{212}\text{Pb}$ generator represents another important technical route. Pruszyński et al. [49] developed a two-stage generator system based on extraction chromatography (Figure 7c). In the first stage, di(2-ethylhexyl)phosphoric acid (HDEHP) extractant is immobilized on polytetrafluoroethylene (PTFE) particles to form an HDEHP-PTFE chromatographic material, which retains ^{228}Th with extremely high affinity. ^{224}Ra could be eluted quantitatively via 0.1 M HNO_3 within 2 min, where the parent radionuclide breakthrough was below 0.005%. In the second stage, the eluted ^{224}Ra is loaded onto a Dowex 50W×12 cation exchange resin column. After ^{224}Ra - ^{212}Pb reach secular equilibrium (~ 3 d), ^{212}Bi and ^{212}Pb are eluted sequentially using 0.75 M and 2.0 M HCl, respectively. Approximately 85% of ^{212}Bi was recovered in the first 1 mL fraction of 0.75 M HCl, and $\sim 90\%$ of

^{212}Pb was recovered in 1 mL of 2.0 M HCl, with no detectable ^{224}Ra breakthrough during repeated elutions. The generator can be milked every 24 h, at which point ^{212}Pb has regenerated to about 80% of its secular equilibrium activity, enabling a continuous supply of ^{212}Pb and ^{212}Bi alike. However, the impact of increasing radioactivity levels on the irradiation stability of the organophosphorus extractant and its support material remains to be evaluated for large-scale implementation. Zhou et al. [50] constructed three COFs with compressed hexagonal pores, namely TAPQ-COF, 2,3-DHTAPQ-COF, and 2,5-DHTAPQ-COF, using a “two-in-one” monomer (2,7-diaminophenanthrene-9,10-dione, PQ), C_2 -symmetric aldehydes (terephthalaldehyde/2,3-dihydroxyterephthalaldehyde/2,5-dihydroxyterephthalaldehyde, TA/2,3-DHTA/2,5-DHTA), and ammonium acetate (NH_4OAc). Among these, 2,3-DHTAPQ-COF, bearing an ortho-hydroxyl configuration, exhibited superior $\text{Ba}^{2+}(\text{Ra}^{2+})/\text{Pb}^{2+}$ separation selectivity, attributed to the additional coordination sites provided by the vicinal hydroxyl groups, which enhance Pb^{2+} binding affinity. Acid stability tests confirmed that both hydroxylated COF materials retain structural integrity below 1 M HCl, and crystallinity and structural stability were maintained following β and γ irradiation.

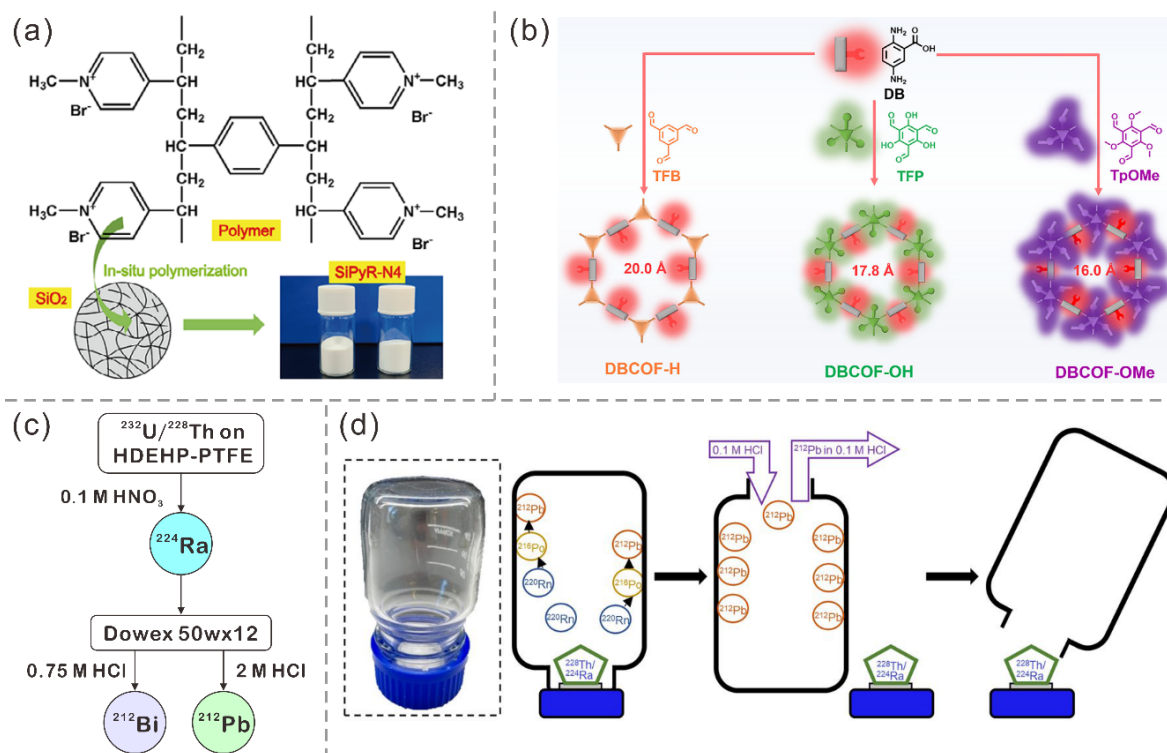


Figure 7. (a) Structure and appearance of SiPyR-N4. Reprinted with permission from Ref. [46]. Copyright 2026, John Wiley and Sons. (b) Schematic diagram of DBCOF monomers and structures. Reprinted with permission from Ref. [48]. Copyright 2025, John Wiley and Sons. (c) Extraction chromatographic procedure for separation of ^{224}Ra , ^{212}Pb , and ^{212}Bi from ^{232}Th or ^{228}Th [49]. (d) Single-chamber ^{212}Pb generator consisting of a glass flask and removable cap containing a ^{228}Th or ^{224}Ra source fixed onto porous quartz wool. Reprinted with permission from Ref. [51]. Copyright 2023, SNMML.

In contrast to the chromatography-based generator systems described above, Li et al. [51] designed a novel and elegantly simple ^{212}Pb generator based on ^{220}Rn emanation (Figure 7d). The device consists of an inverted 100 mL glass flask and a detachable screw cap housing the radioactive source, which was prepared by loading either ^{228}Th or ^{224}Ra dissolved in 0.1–1 M HCl onto approximately 0.2 g of porous quartz wool affixed inside the cap. The operating principle exploits the gaseous nature of ^{220}Rn ($T_{1/2} = 55.6$ s) within the $^{228}\text{Th}/^{224}\text{Ra}$ decay chain: ^{220}Rn emanates from the quartz wool source and, during its brief gas-phase transit, decays to ^{216}Po ($T_{1/2} = 0.145$ s), which in turn rapidly decays to the longer-lived ^{212}Pb . The resulting ^{212}Pb deposits and adsorbs onto the inner wall of the glass flask, achieving physical separation from the parent radionuclides without any chromatographic column, eluent, or complex chemical separation equipment. ^{212}Pb collection requires only replacement of the flask with a clean vessel, followed by gentle rinsing of the inner wall with 0.5–1 mL of 0.1 M HCl for approximately 5 min. The ^{228}Th -based generator delivered stable yields of 67–70% across multiple repeated uses, with ^{228}Th breakthrough of 0.0001–0.005%, average ^{224}Ra breakthrough of 0.02%, and a ^{212}Pb radionuclidic purity exceeding 99.98%. Requiring neither advanced separation instrumentation nor hazardous chemicals, this generator is particularly well-suited as a transportable device for direct use in nuclear medicine departments. Nevertheless, radiation safety

concerns associated with ^{220}Rn emanation (approximately 11% of ^{220}Rn escapes upon opening the cap for 10 s) and the radiation stability of the quartz wool source material at higher activity levels remain engineering challenges to be addressed in future device development, for instance through the integration of shielded sealed-system designs to minimize operator radiation exposure.

4. ^{213}Bi

^{213}Bi ($T_{1/2} = 45.59$ min) is a decay product of ^{225}Ac (Figure 8). Its short half-life requires vectors with similarly short plasma half-lives to achieve a high tumor-to-background ratio [52,53]. Consequently, ^{213}Bi is poorly suited for long-circulating carriers but well matched to small molecules, peptides, and antibody fragments, including nanobodies [53]. Even with such fast-targeting vectors, however, short-lived alpha emitters like ^{213}Bi and ^{211}At remain largely restricted to easily accessible tumors: the targeting agent must reach and accumulate at the tumor site within a narrow time window, and for deep-seated tumors or those needing prolonged drug penetration, the half-lives of these radionuclides are often insufficient for effective therapy [54]. Yet, it is precisely because of this short half-life that ^{213}Bi must be produced on-site at clinical facilities using $^{225}\text{Ac}/^{213}\text{Bi}$ radionuclide generator immediately before use [55]. Over the years, $^{225}\text{Ac}/^{213}\text{Bi}$ generators have been developed based on a variety of separation platforms, including extraction chromatography [56–58], ion exchange [59], and inorganic sorbent systems [60,61]. To meet the growing demands of ^{213}Bi -related TAT drug development, researchers continue to expand the range of generator materials and explore diverse generator configurations.

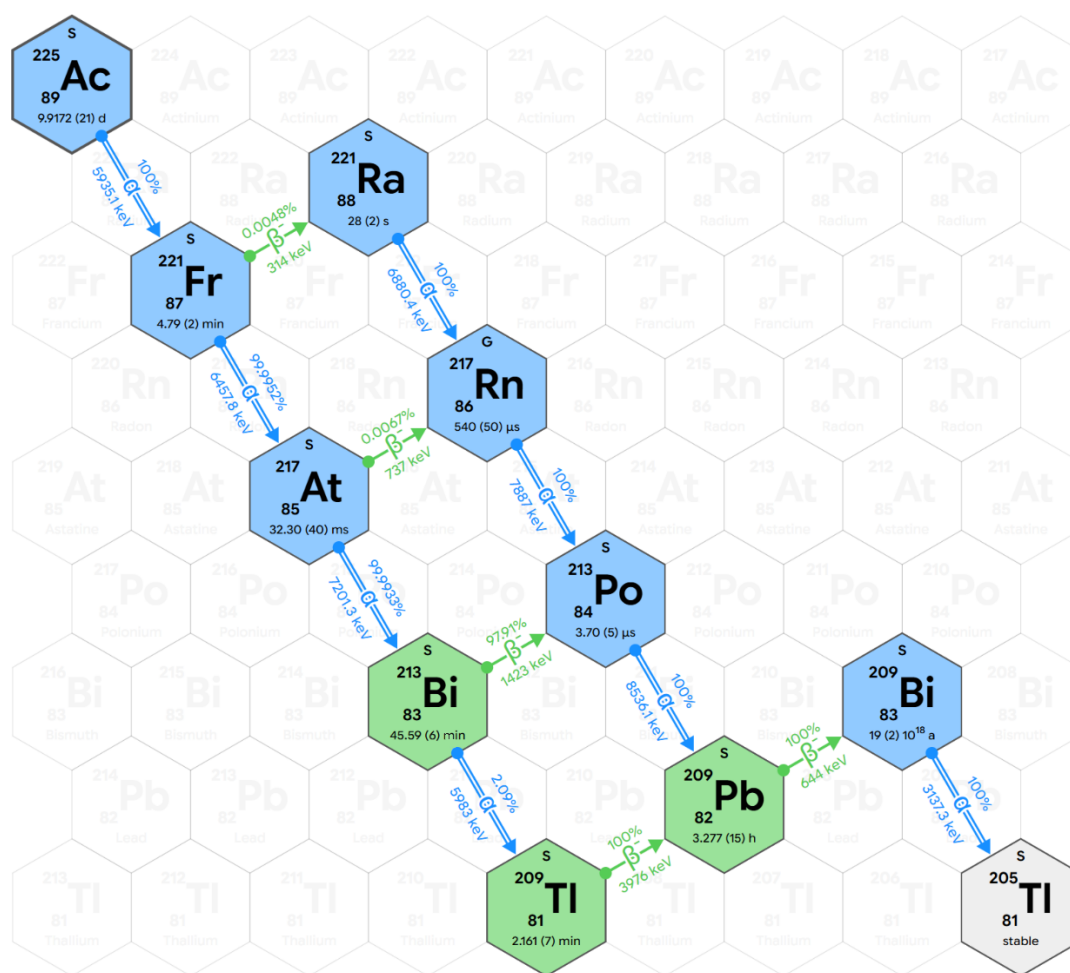


Figure 8. Decay diagram of ^{225}Ac , drawn from the Laraweb website (<http://www.lnhb.fr/Laraweb/> (accessed on 1 May 2026)).

Ondrak et al. [56] developed a $^{225}\text{Ac}/^{213}\text{Bi}$ generator based on an α -ZrP-PAN composite sorbent, in which zirconium(IV) phosphate (ZrP) serves as the active component and polyacrylonitrile (PAN) as the matrix. Elution with a mixed solution of 10 mM diethylenetriaminepentaacetic acid (DTPA) and 5 mM HNO_3 yielded ^{213}Bi recoveries of 77–96%. Over 20 d of continuous operation, ^{225}Ac breakthrough was maintained at the $10^{-3}\%$ level.

However, a progressive increase in ^{225}Ac leakage was observed beyond 20 d, attributed to cumulative radiation damage to the sorbent, indicating that further improvements to the generator design are needed.

Forrester et al. [62] reported an electrochemical $^{225}\text{Ac}/^{213}\text{Bi}$ generator. In this system, ^{213}Bi spontaneously deposits onto a nickel foil from 0.1 M HCl at 70 °C, while the affinity of ^{225}Ac for the nickel surface is negligible (<0.05%). The deposited ^{213}Bi is subsequently recovered by reverse electrolysis (2 V, 6 min) using Ti as the cathode in 0.1 M citrate buffer (pH 4.5), affording a radiochemical purity exceeding 99.8%, an average ^{213}Bi radiochemical yield of $65 \pm 8\%$, and an average ^{225}Ac breakthrough of $0.10 \pm 0.07\%$. Since metallic substrates are inherently more radiation-resistant than organic resins, this approach holds particular promise for accommodating higher ^{225}Ac activity levels, although further optimization and automation are required to improve recovery yields and minimize ^{225}Ac breakthrough.

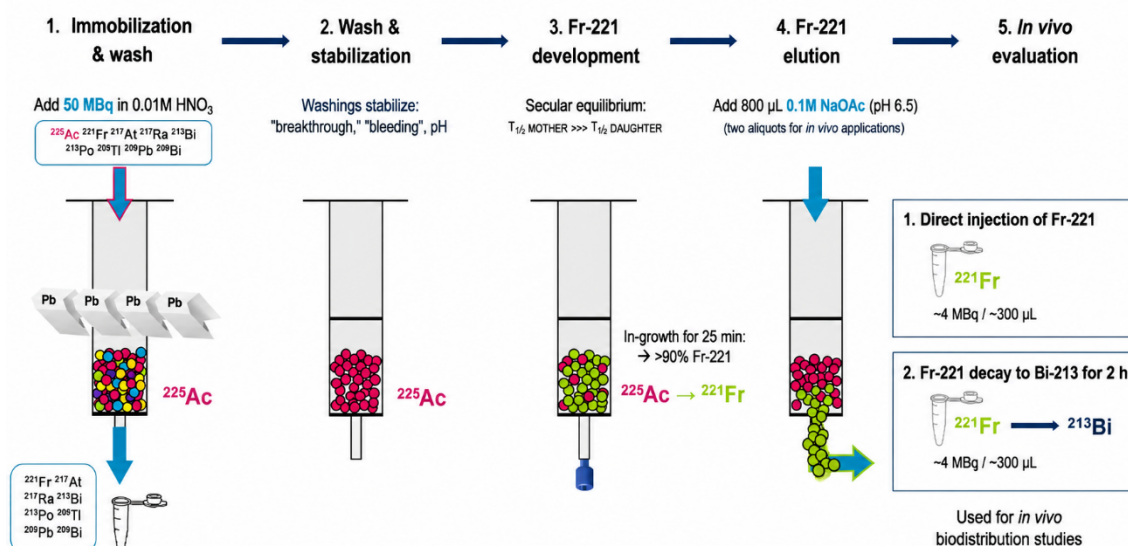


Figure 9. Schematic representation of ^{225}Ac - ^{221}Fr - ^{213}Bi radionuclide generator set-up. Reprinted with permission from Ref. [63]. Copyright 2025, Springer Nature.

Zobnin et al. [64] proposed a gas-chemical $^{225}\text{Ac}/^{213}\text{Bi}$ generator. In this approach, a ^{225}Ac source is heated to high temperature under a H_2 atmosphere, causing volatile ^{213}Bi to be released from the non-volatile Ac matrix and transported by the carrier gas to a Nb collection foil maintained at a lower temperature. The collected ^{213}Bi is subsequently recovered from the foil using a 0.1 M HCl/0.1 M KI solution, with a total chemical recovery of approximately 64%. This method also benefits from inherent radiation resistance, as only inorganic materials are employed. Furthermore, the non-volatility of ^{227}Th and ^{223}Ra under these conditions ensures that decay products of ^{227}Ac do not contaminate the ^{213}Bi product.

While the direct-type $^{225}\text{Ac}/^{213}\text{Bi}$ generators described above focus on the separation of ^{213}Bi itself from the parent radionuclide, an alternative indirect strategy targets the intermediate decay product ^{221}Fr ($T_{1/2} = 4.9$ min) within the ^{225}Ac decay chain, exploiting its rapid decay through ^{217}At ($T_{1/2} = 32.6$ ms) to yield ^{213}Bi . Ermolaev et al. [65] developed a two-column $^{225}\text{Ac}/^{213}\text{Bi}$ generator that achieves accumulation of ^{213}Bi separately from ^{225}Ac via continuous circular separation and decay of the intermediate radionuclide ^{221}Fr . The generator comprises two chromatographic columns connected in a closed loop via an intermediate decay tube: the first column, packed with Ac resin, immobilizes ^{225}Ac , while continuously eluted ^{221}Fr passes through the decay tube, where it decays to ^{213}Bi before being captured on the second column packed with crosslinked dextran gel Sephadex G-25. After approximately 4 h of circulation, equivalent to 5–6 half-lives of ^{213}Bi , ^{213}Bi reaches transient equilibrium with ^{225}Ac on the second column while being spatially isolated from it. Generator performance evaluation demonstrated that contamination by long-lived radionuclidic impurities (^{225}Ac , ^{227}Th , and ^{223}Ra) did not exceed $10^{-6}\%$, while ^{227}Ac impurities arising from the initial $^{227}\text{Ac}/^{225}\text{Ac}$ ratio were even lower, at below $10^{-8}\%$. Zitzmann-Kolbe et al. [63] developed a $^{225}\text{Ac}/^{221}\text{Fr}$ generator (Figure 9) utilizing LN2 resin, specifically a G71m resin loaded with 2-ethylhexylphosphonic acid mono-2-ethylhexyl ester (HEH [EHP]), as a liquid cation exchanger, eluted with 0.1 M sodium acetate (pH 6.5). The LN2 resin exhibits strong retention of ^{225}Ac while effectively releasing monovalent $^{221}\text{Fr}^+$ ions with a yield exceeding 65% and ^{225}Ac contamination below 1%. Given the short half-life of ^{221}Fr , ^{213}Bi is obtained following its complete decay.

5. ^{223}Ra

^{223}Ra ($T_{1/2} = 11.43$ d) was the first α -emitting radionuclide approved by the U.S. Food and Drug Administration (FDA) for medical applications [66,67]. By virtue of its chemical similarity to Ca^{2+} , $^{223}\text{Ra}^{2+}$ selectively accumulates at sites of bone metastasis, underpinning its clinical application in the treatment of bone-metastatic cancers [68]. ^{223}Ra occupies the decay chain ^{227}Ac - ^{227}Th - ^{223}Ra ; accordingly, its production and isolation are contingent upon the availability of the parent radionuclides ^{227}Ac ($T_{1/2} = 21.77$ y) or ^{227}Th ($T_{1/2} = 18.7$ d) [69]. The principal production routes for ^{223}Ra are: (1) separation of $^{227}\text{Ac}/^{227}\text{Th}$ from ^{231}Pa ($T_{1/2} = 32,570$ y) or ^{235}U ($T_{1/2} = 7.04 \times 10^8$ y) (Figure 10); (2) recovery of ^{227}Ac as a by-product of cyclotron-based ^{225}Ac production; and (3) reactor production of ^{227}Ac via the $^{226}\text{Ra}(n, \gamma)^{227}\text{Ra}(\beta^-)^{227}\text{Ac}$ reaction [70].

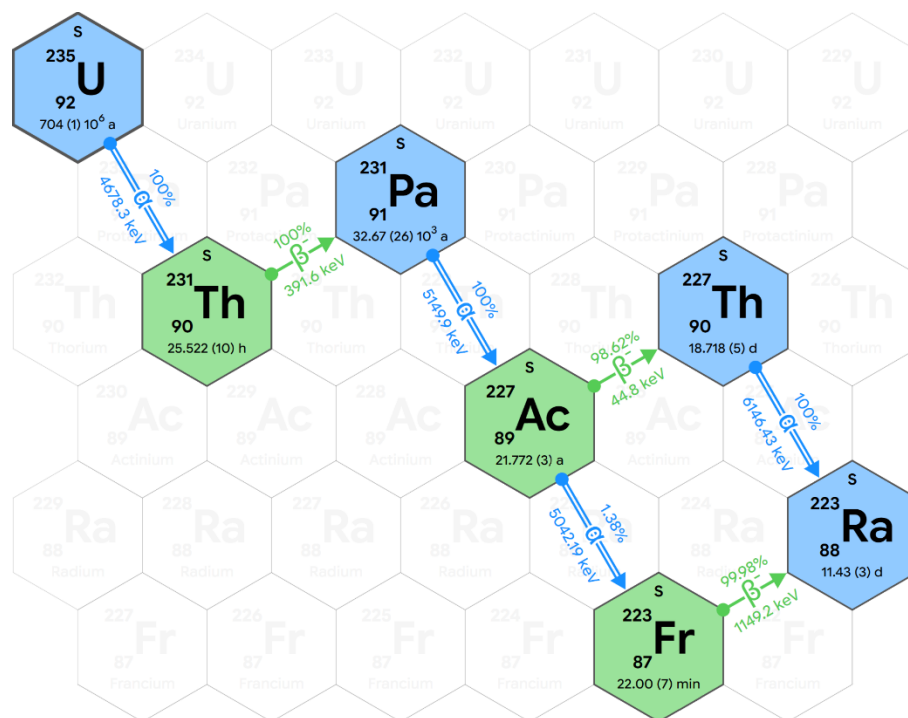


Figure 10. Decay diagram of ^{235}U , drawn from the Laraweb website (<http://www.lnhb.fr/Laraweb/>) (accessed on 1 May 2026).

To isolate ^{223}Ra from ^{231}Pa , Henriksen et al. [71] developed a multi-column separation process employing TRAnsuranic (TRU), P,P'-di(2-ethylhexyl)methanediphosphonic acid on silica (DIPEX-2), and AG50W-X12 resins (Figure 11a). In the first step, ^{227}Ac is selectively isolated from the ^{231}Pa source using TRU extraction chromatographic resin, which retains ^{231}Pa on the column while allowing ^{227}Ac and its progeny to be eluted. The resulting $^{227}\text{Ac}/^{227}\text{Th}$ solution is then loaded onto a ^{223}Ra generator column packed with DIPEX-2 resin, which exhibits high selectivity for the retention of both Ac and Th. ^{223}Ra is subsequently eluted from the generator column using 2–3 mL of 1 M HCl or HNO_3 . A secondary DIPEX-2 column is then employed for further purification, reducing the ^{227}Ac content to below 7×10^{-8} of the ^{223}Ra activity. ^{223}Ra is finally concentrated by an AG50W-X12 cation exchange resin. The generator system demonstrated stable performance over more than 18 consecutive months; ^{223}Ra production typically exceeds 70% during the first three months and subsequently stabilizes at 57–65%.

With advances in cyclotron-based ^{225}Ac production, it has been recognized that approximately 0.3% of the product activity consists of ^{227}Ac as an unavoidable by-product. Abou et al. [72] developed a method for producing high-purity ^{223}Ra at the kBq scale from the ^{227}Ac generated during cyclotron-based ^{225}Ac production (Figure 11b). A solution containing a mixture of ^{225}Ac , ^{227}Ac , ^{227}Th , and ^{223}Ra was loaded onto a Dowex 1×8 anion exchange resin column. Exploiting their different retention on this resin ($^{227}\text{Th} > ^{227}\text{Ac} > ^{223}\text{Ra}$), sequential elution of these radionuclides can be achieved using a mixed solvent of 80% methanol/20% 2 M HNO_3 , where ^{223}Ra was eluted first with a recovery of $71.3 \pm 5.7\%$. ^{227}Ac and ^{227}Th were subsequently recovered using 0.5 M HNO_3 . Quality control analysis showed that in the purified ^{223}Ra fractions, primarily ^{223}Ra was detected without any significant contaminants, demonstrating excellent separation performance.

Reactor neutron irradiation of ^{226}Ra represents an important route for the large-scale production of ^{227}Ac . Irradiation of ^{226}Ra via the (n, γ) reaction produces ^{227}Ra ($T_{1/2} = 42.2$ min), which subsequently undergoes β^- decay to yield ^{227}Ac . Bagheri et al. [73] irradiated approximately 5 μg of ^{226}Ra target material for 24 d at the Tehran

Research Reactor under a thermal neutron density of $5 \times 10^{13} \text{ n} \cdot \text{cm}^{-2} \cdot \text{s}^{-1}$, achieving an ^{227}Ac production yield of 0.103 Ci/g (Figure 11c). Following a cooling period, the irradiated target was subjected to radiochemical separation based on Dowex 1×8 anion exchange resin and Dowex 50W×8 cation exchange resin. The target was first dissolved in 8 M HNO_3 and loaded onto the Dowex 1×8 anion exchange column, where ^{227}Th and ^{228}Th were selectively retained while Ra, Ac, and other radionuclides passed through in the effluent. The collected effluent was evaporated, redissolved in 1 M HNO_3 , and loaded onto the Dowex 50W×8 cation exchange column, on which ^{227}Ac was adsorbed while ^{226}Ra and ^{223}Ra were not retained. The ^{227}Ac -loaded cation exchange column was then stored for approximately one month to allow ingrowth of ^{223}Ra , after which ^{223}Ra was eluted with 1 M HNO_3 . The method achieved a decontamination factor (DF) ($^{223}\text{Ra}/^{227}\text{Th}$) exceeding 10^5 , and no breakthrough of parent radionuclides was detected in the γ spectrum of the final ^{223}Ra eluate.

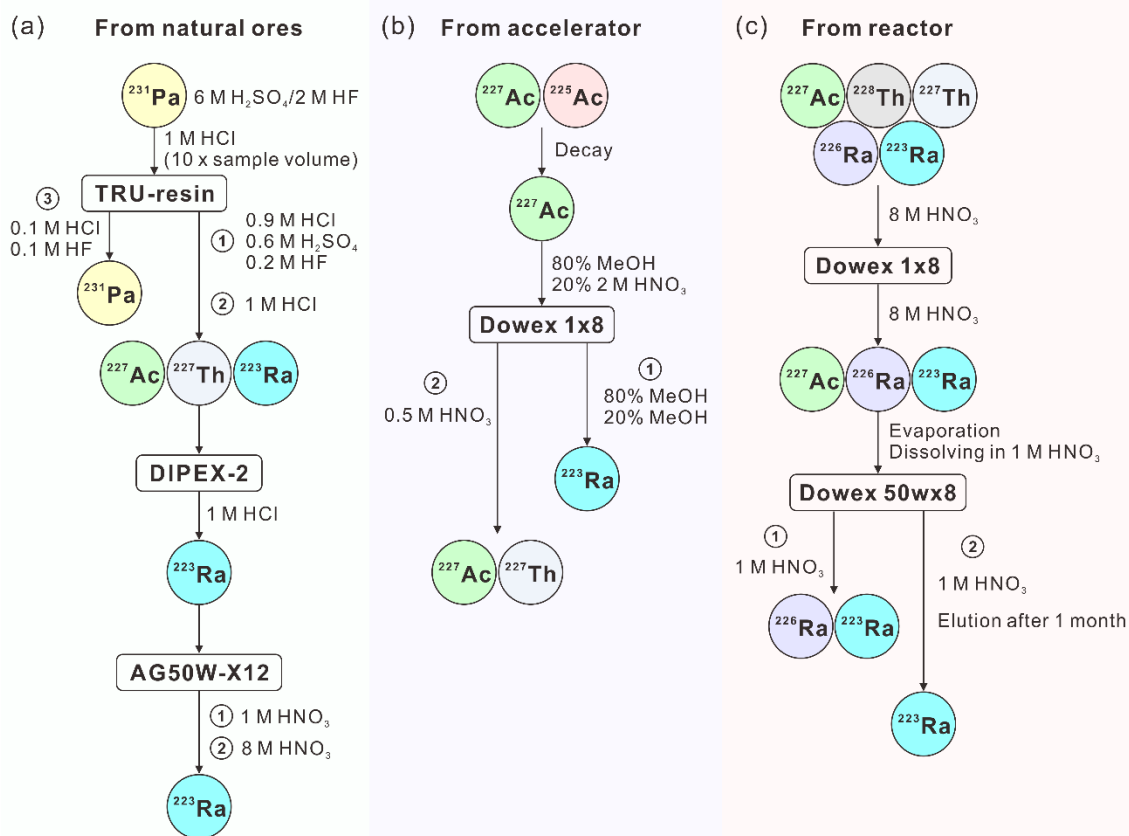


Figure 11. Schematic flow diagrams for the separation of ^{223}Ra from (a) natural ores [71]; (b) $^{227}\text{Ac}/^{225}\text{Ac}$ solutions obtained from accelerator irradiation [72]; and (c) reactor irradiation products of ^{226}Ra [73].

6. ^{224}Ra

In recent years, ^{224}Ra ($T_{1/2} = 3.63 \text{ d}$), a natural isotope of ^{223}Ra , emerges as a particularly noteworthy competitor in terms of its physical properties and production processes [74–76]. Compared with ^{223}Ra , the shorter half-life of ^{224}Ra enables more rapid clearance of radioactivity from the body following administration, thereby reducing the risk of prolonged radiation exposure to normal tissues. Additionally, the 241 keV γ emission associated with ^{224}Ra decay is amenable to single photon emission computed tomography (SPECT) imaging [77], enabling real-time monitoring of the therapeutic process. The decay chain of ^{224}Ra contains multiple α -emitting progeny whose recoil energies exceed 100 keV, far above chemical bond energies ($\sim 5 \text{ eV}$), so that any chelator is inherently unable to prevent daughter release, leading to potential off-target toxicity from freely diffusing daughters [54,78]. To address this, nanocarriers such as liposomes, zeolites, and metal nanoparticles can be employed to physically confine the recoiling daughters and reduce their systemic diffusion. Although the relatively long-lived decay daughters ^{212}Pb and ^{212}Bi ($T_{1/2} = 60.6 \text{ min}$) within the decay chain of ^{224}Ra present a potential risk of secondary *in vivo* redistribution, they also offer the possibility of being harvested independently as α -radionuclides in their own right [79,80]. Current production strategies for ^{224}Ra include: (1) direct separation from the naturally occurring long-lived radionuclide ^{232}Th ($T_{1/2} = 1.40 \times 10^{10} \text{ y}$) (Figure 12); (2) separation of ^{228}Th from the ^{232}Th decay

product ^{228}Ra ($T_{1/2} = 5.75$ y), followed by the generation of ^{224}Ra via a $^{228}\text{Th}/^{224}\text{Ra}$ generator; and (3) reactor neutron irradiation of ^{226}Ra to produce ^{228}Th , followed by the generation of ^{224}Ra via a $^{228}\text{Th}/^{224}\text{Ra}$ generator.

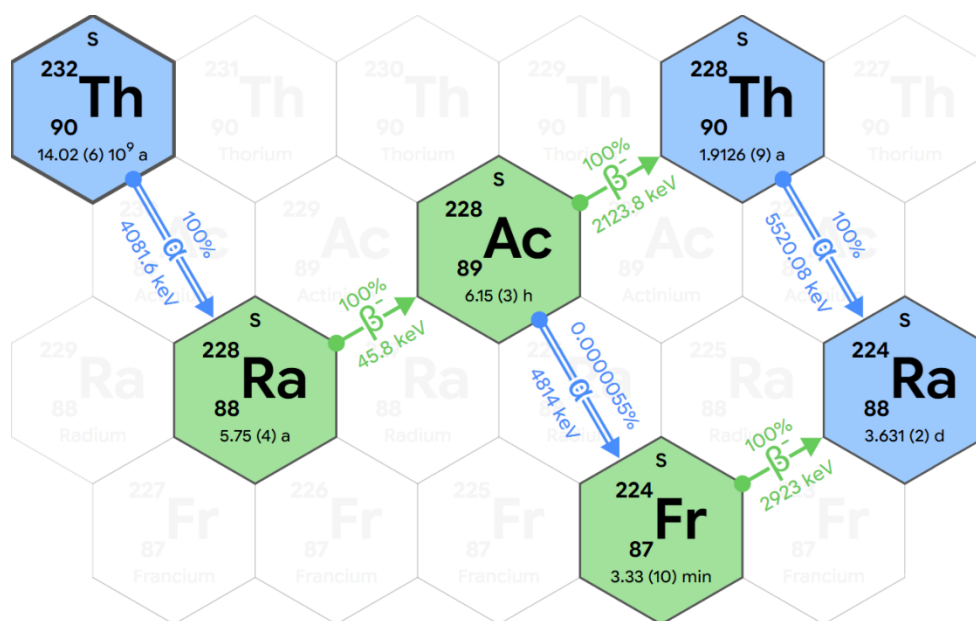


Figure 12. Decay diagram of ^{232}Th , drawn from the Laraweb website (<http://www.lnhb.fr/Laraweb/> (accessed on 1 May 2026)).

^{224}Ra can be generated from ^{232}Th via the sequential decay chain $^{232}\text{Th}(\alpha)^{228}\text{Ra}(\beta^-)^{228}\text{Ac}(\beta^-)^{228}\text{Th}(\alpha)^{224}\text{Ra}$. The abundant natural abundance and low extraction cost of ^{232}Th make it an attractive source material. However, the direct separation of ^{224}Ra from natural Th poses formidable challenges. The Th/Ra mass ratio can reach nine orders of magnitude, imposing extremely stringent requirements on the selectivity of the separation strategy. Available approaches include co-precipitation, LLE, and adsorption-based methods. Narbutt et al. [81] developed a $^{232}\text{Th}/^{224}\text{Ra}$ LLE system in which ^{232}Th is first extracted using HDEHP, and ^{224}Ra is subsequently back-extracted into a 0.1 M HNO_3 solution containing a Ba^{2+} carrier. Although this scheme achieves $^{232}\text{Th}/^{224}\text{Ra}$ separation, it involves extensive manipulation of organic phases, resulting in lengthy processing times, high solvent consumption, and large volumes of secondary radioactive waste. He et al. [82] prepared a porous silica-based composite adsorbent loaded with HDEHP (SiPSf@HDEHP) for the separation of ^{224}Ra from natural Th (Figure 13a). Unlike conventional cation exchange resins that co-adsorb both Th and Ra, this material exhibits highly selective affinity for Th while adsorbing neither Ba nor Ra to any appreciable extent. Batch adsorption experiments demonstrated ultrafast adsorption kinetics and a substantial Th adsorption capacity of 37.87 mg/g. In radiotracers experiments, ^{224}Ra was efficiently separated with a recovery of 96.7% and a Th DF exceeding 10^5 , even when the Th/Ra mass ratio exceeded seven orders of magnitude ($\sim 1.37 \times 10^7$). Spectroscopic analysis indicated that the adsorption mechanism involves coordination of Th^{4+} cations with the oxygen atoms of the P-OH and P=O groups in HDEHP. Cao et al. [83] developed crown ether-based covalent organic polymer microspheres (CE-COPM) for the separation of trace-level Ra from natural Th. This material maintained excellent Ra/Ba adsorption performance ($Q_e = 40.73$ mg/g) under highly acidic conditions, retaining 95% of its initial adsorption capacity after four successive adsorption-regeneration cycles.

When separating ^{224}Ra directly from ^{232}Th , the co-produced isotope ^{228}Ra ($T_{1/2} = 5.75$ y) must also be considered, and its presence severely constrains the practical applicability of the final product [84]. To circumvent the interference of ^{228}Ra impurities, an alternative strategy involves first isolating ^{228}Ra from the Th source, subsequently separating ^{228}Th from the ^{228}Ra decay products, and finally obtaining high-purity ^{224}Ra through a $^{228}\text{Th}/^{224}\text{Ra}$ generator. Zheng et al. [85] developed a quaternary ammonium-functionalized porous silica composite material (QA@SiO_2) to efficiently separate ^{228}Th from ^{228}Ra (Figure 13b). This material was prepared by *in situ* polymerization of quaternary ammonium groups onto a porous silica support. Different from conventional cation exchange resins, it operates through a distinct separation mechanism: in HNO_3 medium, Th^{4+} forms anionic complexes of the form $[\text{Th}(\text{NO}_3)_6]^{2-}$, which are retained on the material via anion exchange interactions with the quaternary ammonium groups, while $\text{Ra}^{2+}/\text{Ba}^{2+}$ remain cationic under the same conditions and are therefore not adsorbed. This separation strategy, based on differences in oxidation state and coordination chemistry, affords highly efficient Th/Ra separation.

Reactor neutron irradiation of ^{226}Ra via the $^{226}\text{Ra}(\text{n}, \gamma)^{227}\text{Ra}(\text{n}, \gamma)^{228}\text{Ra}(\beta^-)^{228}\text{Ac}(\beta^-)^{228}\text{Th}$ reaction represents another important route for large-scale production of ^{228}Th . Our group [86] established a separation process using ion exchange resins to isolate ^{228}Th from the reactor irradiation products (Figure 13c). Initially, the irradiated target was dissolved in 10 mL of 9 M HNO_3 , and the resulting solution was passed through a Dowex 1 $\times$ 8 column. The column was first washed with 20 mL of 9 M HNO_3 to remove ^{226}Ra and ^{227}Ac , while ^{228}Th was retained on the Dowex 1 $\times$ 8 column in the form of $\text{Th}(\text{NO}_3)_6^{2-}$. Subsequently, ^{228}Th was eluted using 80 mL of 0.8 M HNO_3 . The effluent containing ^{226}Ra and ^{227}Ac was collected and evaporated to dryness. The residue was dissolved in 10 mL of 2 M HNO_3 , and this dissolution–evaporation cycle was repeated three additional times. The final residue was re-dissolved in 10 mL of 2 M HNO_3 . This solution was then loaded onto a Dowex 50w $\times$ 8 column, which was eluted with 40 mL of 2 M HNO_3 followed by 50 mL of 9 M HNO_3 . Under the optimized conditions, recovery yields of 92.80%, 99.56%, and 99.20% were achieved for ^{228}Th , ^{226}Ra , and ^{227}Ac , respectively.

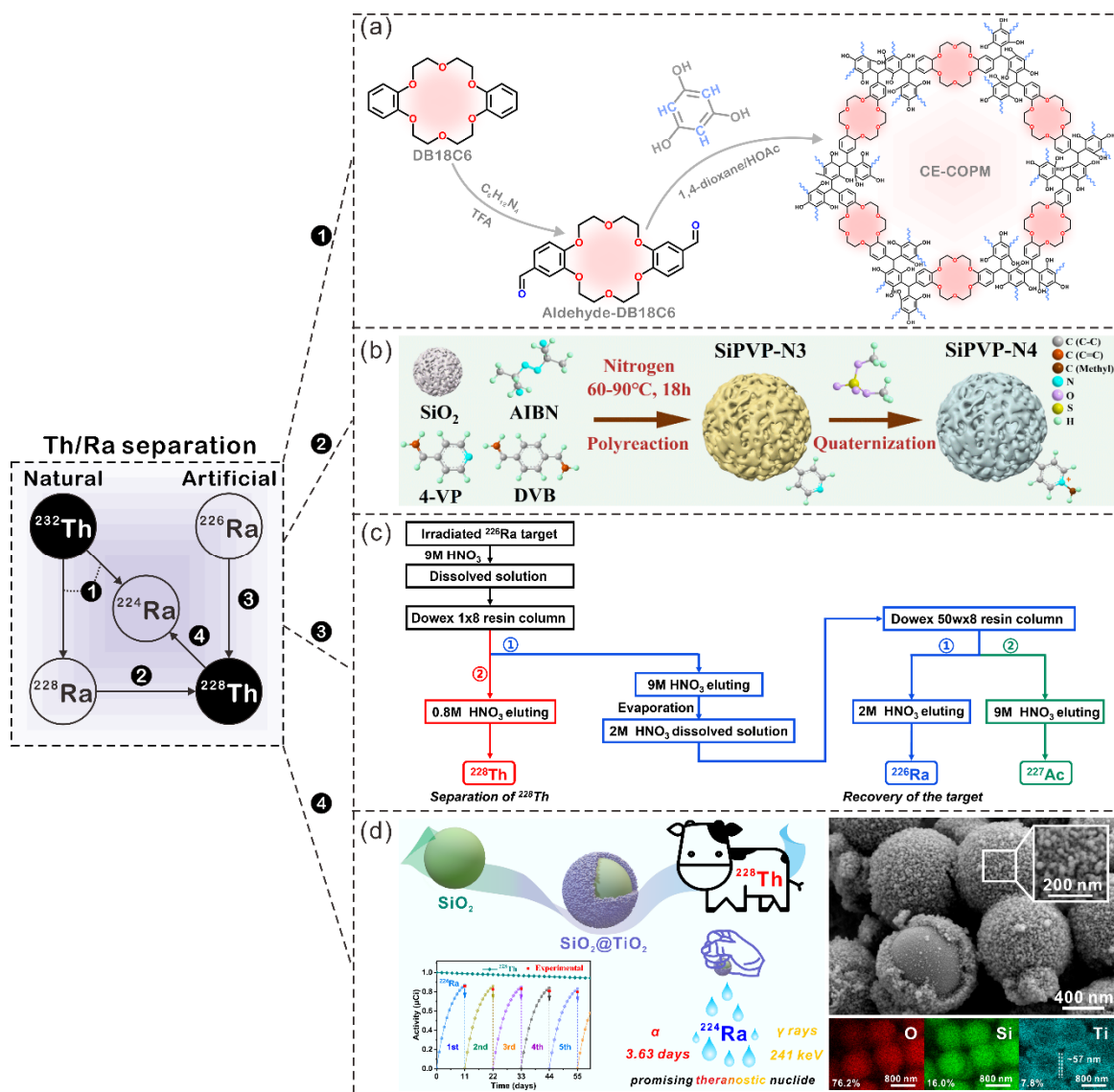


Figure 13. (a) SEM image of HDEHP@SiPS and its dynamic separation of barium from thorium [82]; (b) Schematic illustration of QA@SiO₂ synthesis. Reprinted with permission from Ref. [85]. Copyright 2025, American Chemical Society; (c) Schematic diagram of the radiochemical separation of ^{228}Th and recovery of ^{226}Ra from reactor-irradiated targets [86]; (d) Schematic diagram of the $^{228}\text{Th}/^{224}\text{Ra}$ generator based on SiO₂@TiO₂ core-shell microspheres. Reprinted with permission from Ref. [21]. Copyright 2024, American Chemical Society.

The $^{228}\text{Th}/^{224}\text{Ra}$ generator system is a critical enabling technology for the sustained and reliable supply of ^{224}Ra . Recently, our group [21] developed a $^{228}\text{Th}/^{224}\text{Ra}$ generator based on core-shell SiO₂@TiO₂ microspheres (Figure 13d). Conventional metal oxide supports suffer from limited specific surface areas and consequently suboptimal parent radionuclide loading capacity. The SiO₂@TiO₂ microspheres possess a mesoporous architecture and high specific surface area that substantially increase the ^{228}Th adsorption capacity. In generator elution experiments,

94.04% of ^{224}Ra was eluted using 2 mL of eluent, with a total recovery of 98.72% achieved within 6 mL. γ -energy spectrometric analysis confirmed the absence of ^{228}Th characteristic peaks in the eluate, with only ^{224}Ra peaks observed, demonstrating effective retention of the parent radionuclide.

In summary, whether ^{224}Ra is obtained by direct separation from ^{232}Th , by reactor irradiation of ^{226}Ra , or via a $^{228}\text{Th}/^{224}\text{Ra}$ generator system, the underlying separation chemistry in all cases revolves around the selective fractionation of Th from Ra. As ^{224}Ra -based radiopharmaceuticals and $^{224}\text{Ra}/^{212}\text{Pb}$ generator systems continue to advance toward clinical application, ^{224}Ra separation technologies will undoubtedly attract increasing attention in the future.

7. ^{225}Ac

^{225}Ac ($T_{1/2} = 9.92$ d) is one of the most promising α -emitting radionuclides for future clinical translation [87–89]. Its half-life, over 300-fold longer than that of ^{213}Bi , enables matching with vectors of slow pharmacokinetics such as antibodies [90,91]. Moreover, each decay yields four net α -particles and two γ -emissions, functioning as an *in vivo* generator best paired with long biological half-lives [92]. The remarkable clinical efficacy recently demonstrated by ^{225}Ac -PSMA-617 and some other radiopharmaceuticals in the treatment of metastatic castration-resistant prostate cancer has further intensified global demand for ^{225}Ac [93]. However, the global supply of ^{225}Ac remains critically insufficient, representing the principal bottleneck constraining the broader clinical adoption of TAT. At present, the overwhelming majority of the global ^{225}Ac supply is derived from the decay of ^{229}Th , a daughter radionuclide of ^{233}U (Figure 14). The ^{233}U stockpile was produced by reactor neutron irradiation of ^{232}Th between 1954–1970, after which this production pathway was discontinued under nuclear non-proliferation treaty obligations [94]. The world's existing ^{229}Th inventory is held at three institutions: Oak Ridge National Laboratory (ORNL, Oak Ridge, TN, USA, ~150 mCi), the Institute for Transuranium Elements (ITU, Karlsruhe, Germany, ~46 mCi), and the Institute of Physics and Power Engineering (IPPE, Obninsk, Russia, ~150 mCi), yielding annual ^{225}Ac outputs of approximately 720, 350, and 720 mCi, respectively. Global annual production thus falls well below 2 Ci [95], far short of what large-scale clinical trials and routine patient treatment would demand [96]. To narrow this substantial gap between supply capacity and clinical need, the international radiochemistry community is actively pursuing alternative production routes, principally: (a) spallation of ^{232}Th by high-energy proton irradiation; (b) nuclear reactions on ^{226}Ra via proton irradiation; and (c) reactor thermal neutron irradiation of ^{226}Ra [97]. Each production route presents distinct radiochemical separation challenges, necessitating the development of highly efficient separation strategies.

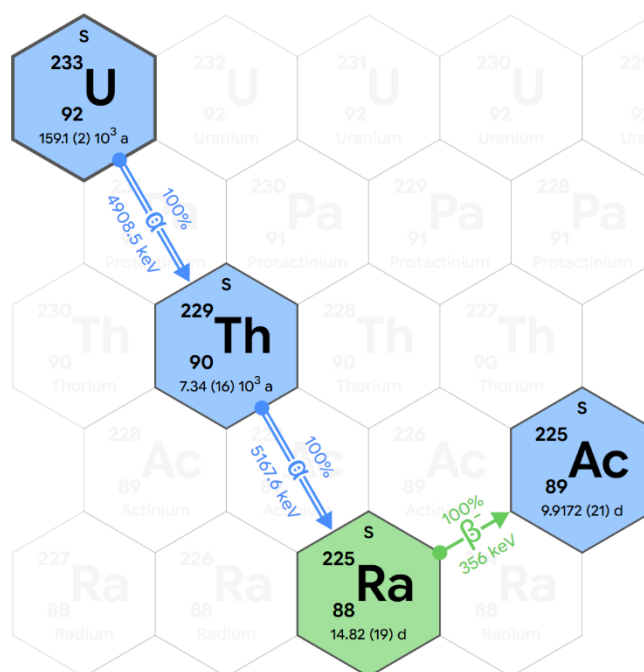


Figure 14. Decay diagram of ^{233}U , drawn from the Laraweb website (<http://www.lnhb.fr/Laraweb/>) (accessed on 1 May 2026).

High-energy proton irradiation of natural ^{232}Th targets via the $^{232}\text{Th}(p, x)^{225}\text{Ac}$ transmutation reaction is one of the most scalable production routes, owing to the low cost and ready availability of the target material. However, this approach confronts formidable radiochemical separation challenges: the irradiated Th target contains nearly

400 radioactive radionuclides spanning the majority of the periodic table [98]. Furthermore, the co-production of long-lived ^{227}Ac and medium-lived ^{226}Ac ($T_{1/2} = 29.37\text{ h}$) is unavoidable; ^{227}Ac activity typically constitutes 0.1~0.3% of the ^{225}Ac activity, increasing the internal radiation dose to patients. An efficient separation process must therefore simultaneously achieve: quantitative recovery of trace-level ^{225}Ac from gram-scale Th matrices; effective removal of hundreds of co-produced fission and spallation products; and maximum suppression of ^{227}Ac impurities.

To address these challenges, researchers have developed several separation strategies. For Th matrix removal, cation exchange chromatography has been widely adopted due to its operational simplicity. McAlister et al. [99] introduced a cation exchange method operating in sulfate medium: Th matrix is dissolved in 8 M H_2SO_4 containing trace HF, then Th^{4+} forms neutral or anionic sulfate complexes, including $[\text{Th}(\text{SO}_4)_3]^{2-}$ and $[\text{Th}(\text{SO}_4)_4]^{4-}$, that are not retained on Dowex 50W×8 cation exchange resin, while Ac^{3+} and Ra^{2+} are selectively adsorbed. This approach requires a column volume only 1/10~1/20 of that needed for anion exchange methods, and eliminates the post-dissolution evaporation and reconcentration steps, substantially streamlining the workflow. Baimukhanova et al. [100] explored trichloroacetic acid as an alternative Th chelating agent, achieving effective partitioning of Th, Ac, and Ra on Dowex 50W×8 resin in 5~6 M CCl_3COOH medium, where the Th distribution coefficient drops below 1 while Ac and Ra remain well-retained. Chen et al. [101] established a citric acid (CA) based cation exchange method in which Th^{4+} is chelated in pH 2 citrate solution to form anionic complexes of the form $\text{Th}(\text{cit})_3^{2-}$, effectively excluding it from adsorption during cation exchange, while Ac^{3+} is first retained on AG50W-X8 resin and subsequently eluted with 6 M HNO_3 at a recovery exceeding 99% (Figure 15a).

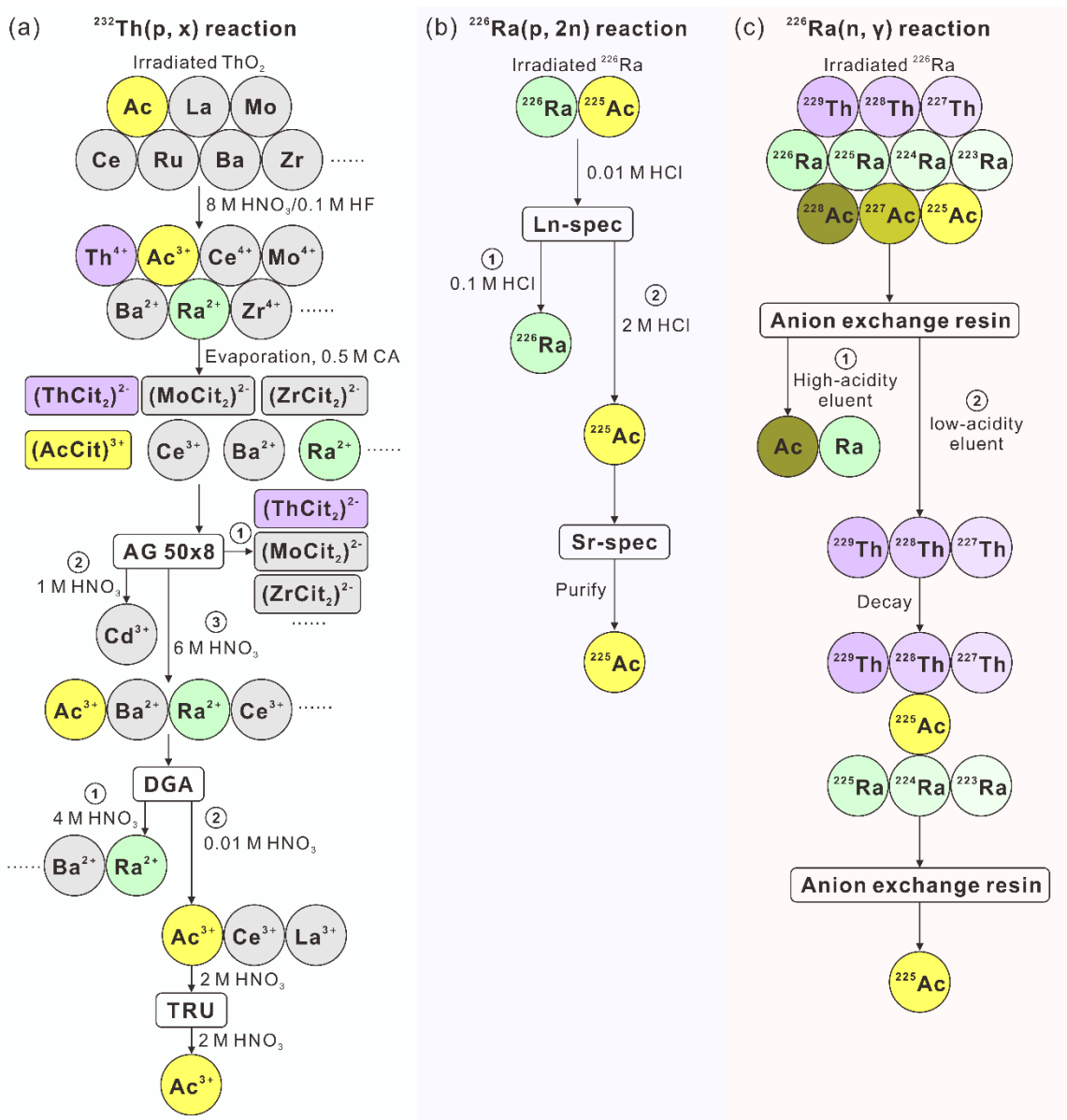


Figure 15. Schematic flow diagrams for the separation of ^{225}Ac from (a) accelerator irradiation products of ^{232}Th [101]; (b) accelerator irradiation products of ^{226}Ra [102]; and (c) reactor irradiation products of ^{226}Ra [103].

Beyond cation exchange resins, DGA extraction resin, which exhibits strong affinity for both Ac^{3+} and lanthanide ions, is frequently employed as a complementary step to further enrich Ac from cation exchange fractions and remove alkali metal impurities [19]. A typical workflow involves loading the 6 M HNO_3 eluate directly onto a DGA column, washing with 4 M HNO_3 to remove impurities, and eluting Ac with dilute HNO_3 or HCl . However, the limited selectivity of DGA resin between Ac and lanthanides necessitates additional separation steps for further Ac purification [99]. Membrane-based sorbent materials for rapid purification have also attracted growing attention. Radhakrishnan et al. [104] fabricated an electrospun membrane sorbent by covalently grafting tetra-2-ethylhexyl-diglycolamide (THDGA) onto poly(vinylbenzyl chloride) (PVBC) fiber surfaces. The resulting material maintains metal ion adsorption trends similar to those of N,N,N',N'-tetraoctyl diglycolamide (TODGA) resin while achieving significantly faster mass transfer kinetics. The THDGA membrane sorbent exhibits a selectivity coefficient of up to 57 for La^{3+} over ^{225}Ac in 10 M HNO_3 , and ^{225}Ac can be rapidly desorbed from the fibers within 20 min. Compared with conventional THDGA extraction chromatographic resin, this membrane sorbent is expected to substantially reduce both elution time and eluent volume.

Minimizing ^{227}Ac impurity content represents another central challenge in the separation of ^{232}Th spallation products. Robertson et al. [93] proposed a strategy where ^{225}Ra ($T_{1/2} = 14.9$ d) is first isolated from the $^{232}\text{Th}(\text{p}, \text{x})$ irradiation products and allowed to decay to generate fresh ^{225}Ac , which is then subjected to a second Ac separation step. This two-stage approach yields a ^{225}Ac product with a ^{227}Ac content below $7.5 \times 10^{-5}\%$, falling below the International Atomic Energy Agency (IAEA) exemption threshold and qualifying as effectively “ ^{227}Ac -free” from a regulatory standpoint. Although the ^{225}Ac yield obtained by this route is approximately 1/5 to 1/6 of that achievable by direct separation of ^{225}Ac from $^{232}\text{Th}(\text{p}, \text{x})$ products, its superior radionuclidic purity makes it more suitable for radiopharmaceutical preparation, while the ^{227}Ac -containing ^{225}Ac fraction can be separately utilized as parent material for $^{225}\text{Ac}/^{213}\text{Bi}$ generator systems.

Cyclotron-based proton irradiation of ^{226}Ra via the $^{226}\text{Ra}(\text{p}, 2\text{n})^{225}\text{Ac}$ transmutation reaction represents another important production route, with the key advantage of generating no long-lived ^{227}Ac impurity. Apostolidis et al. [102] established an extraction chromatography-based purification process for the irradiated products: the dissolved Ra/Ac mixture is loaded onto an Ln-spec column in 0.01 M HCl , Ra is washed through with 0.1 M HCl , and Ac is eluted with 2 M HCl (Figure 15b). The Ac fraction is then directly passed through an Sr-spec column to remove Po and Pb impurities arising from ^{226}Ra decay. α and γ spectrometric analysis of the purified ^{225}Ac product confirmed radiochemical purity comparable to that of material produced via the conventional ^{229}Th route, meeting the quality requirements for TAT clinical research.

Reactor thermal neutron irradiation of ^{226}Ra via the $^{226}\text{Ra}(\text{n}, \gamma)^{227}\text{Ra}(\beta^-)^{227}\text{Ac}(\text{n}, \gamma)^{228}\text{Ac}(\beta^-)^{228}\text{Th}(\text{n}, \gamma)^{229}\text{Th}$ reaction, followed by establishment of a $^{229}\text{Th}/^{225}\text{Ra}/^{225}\text{Ac}$ generator system, represents a potential pathway for the long-term stable supply of ^{225}Ac . However, the extremely high activities of co-produced ^{228}Th and ^{227}Ac contaminants make the separation challenges for this route exceptionally complex. Hogle et al. [105] established a separation process in which Th is separated from Ra and Ac using an anion exchange ($\text{MP-1}/\text{NO}_3^-$) column: in 8 M HNO_3 , Th is strongly retained as the $\text{Th}(\text{NO}_3)_6^{2-}$ complex while Ra passes through, after which Th is eluted with 0.1 M HNO_3 . However, the separated Th fraction contains a mixture of ^{227}Th , ^{228}Th , and ^{229}Th , and the isolation of ^{229}Th from $^{227/228}\text{Th}$ is exceedingly difficult. To address this complex multi-component system, our group [103] proposed an integrated separation scheme: anion exchange resin is first used to separate the $^{227/228/229}\text{Th}$ mixture, followed by cation exchange resin for the recovery of ^{226}Ra and ^{227}Ac , after which ^{225}Ac is periodically harvested from the $^{229}\text{Th}/^{225}\text{Ra}/^{225}\text{Ac}$ generator once secular equilibrium has been established (Figure 15c). The recovered ^{227}Ac can serve not only as the parent radionuclide for a $^{227}\text{Ac}/^{227}\text{Th}/^{223}\text{Ra}$ generator, but also as a highly efficient re-irradiation target for ^{229}Th production, with a ^{229}Th yield approximately 16-fold higher than that of a ^{226}Ra target.

8. Current Challenges

8.1. Purification of Medical Radioactive Wastewater

With the expanding clinical application of therapeutic radiopharmaceuticals, the volume of generated radioactive wastewater is growing substantially, and its safe disposal has emerged as one of the critical challenges confronting the sustainable development of nuclear medicine [106,107]. Following *in vivo* metabolism of radiopharmaceuticals, radionuclides are excreted by patients and enter wastewater systems, generating radionuclide-containing medical effluents. For decades, the globally prevalent strategy for managing such waste has been “storage-to-decay”: radioactive wastewater is held in dedicated decay tanks until more than ten physical half-lives have elapsed before discharge, a process requiring approximately 67 d for ^{177}Lu and approximately 80 d for ^{131}I ($T_{1/2} = 8.04$ d) [26]. The prolonged accumulation of large wastewater volumes places severe pressure on

institutional storage infrastructure. The development of active treatment technologies capable of rapidly and efficiently removing radionuclides from medical wastewater has therefore become an urgent priority.

It is worth noting that the treatment of α -emitting radionuclides wastewater presents challenges far exceeding those of β -emitting radionuclides. α -emitting radionuclides typically possess long decay chains that generate multiple chemically distinct daughter radionuclides, making it difficult for any single sorbent material to achieve complete removal across the entire decay chain [108]. Furthermore, certain decay daughters, such as Rn, are volatile and may form radioactive aerosols, introducing gaseous contamination pathways. Systematic adsorption studies specifically targeting the medical wastewater streams of α -emitting radionuclides remain scarce, and this area warrants dedicated investigation.

8.2. Radiation Stability of Separation Materials

A challenge that cannot be overlooked in the separation of α -radionuclides is the radiation damage inflicted on separation materials by the decay emissions of the radionuclides themselves, which can irreversibly alter separation performance [109,110]. Research in the field of spent nuclear fuel reprocessing has clearly established that extractants and sorbent materials exposed to intense radiation fields inevitably undergo bond cleavage and molecular rearrangement, generating a spectrum of radiolytic degradation products that lead to significant changes in extraction efficiency, selectivity, and even phase separation behavior [111]. Importantly, the different radiation types (α , β , and γ) differ fundamentally in their radiolytic mechanisms and damage modes as a consequence of their differing LET values: α particles, owing to their extremely high LET, deposit energy in a highly localized manner along their tracks, typically causing more severe radiolytic damage than an equivalent absorbed dose of γ radiation [112]. Accordingly, the design of separation materials for medical α -radionuclides should incorporate targeted radiation stability optimization commensurate with the decay characteristics of the target radionuclide, ensuring that reliable separation performance is maintained throughout prolonged contact with highly radioactive species.

8.3. Automated Separation Technologies

Automated separation technology is a critical enabler of both production efficiency and operational safety in radionuclide manufacturing [113,114]. During separation and purification operations involving high radioactivity levels, personnel face substantial radiation exposure risk. Automated systems that execute the entire chemical separation workflow remotely within a hot cell can significantly reduce operator radiation dose while simultaneously improving the reproducibility and process stability of the separation [115]. As an illustrative example, Tan et al. designed an automated multi-column ion exchange system for the continuous separation and purification of ^{225}Ac from accelerator-irradiated natural Th targets [116]. Through a four-step dual-column separation and dual-column purification workflow, the system reproducibly isolated ^{225}Ac with a radionuclidic purity of 92~96% and a recovery of approximately 63% from irradiated solutions containing hundreds of co-produced radionuclidic species, with a total stable impurity content below 2.4 μg . The entire process, encompassing target transfer, dissolution, and final product collection, was completed automatically within approximately 60 h under full remote control within a hot cell, effectively minimizing operator radiation exposure and providing an engineering-scale solution for the large-scale clinical production of ^{225}Ac .

9. Conclusions

In this review, we have systematically summarized the latest advances in separation strategies for medical α -radionuclides, encompassing ^{211}At , ^{223}Ra , ^{224}Ra , ^{212}Pb , ^{225}Ac , and ^{213}Bi . Although commercially available resins with well-established performance continue to dominate the separation of α -radionuclides, persistent efforts are being devoted to exploring novel separation strategies aimed at further optimizing separation efficiency, and considerable progress has already been achieved. With the continued development of novel separation materials, they are anticipated to play a pivotal role in achieving efficient radionuclide separation in the future.

Author Contributions

L.Q.: Conceptualization, methodology, investigation, writing—original draft, visualization; F.L.: supervision, writing—review & editing; J.L.: Project administration; X.C.: Conceptualization, funding acquisition; N.L.: Conceptualization, funding acquisition, project administration, writing—review & editing. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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