Acta Biochim Biophys Sin 2025, 57(3): 327–343
https://cstr.cn/32197.14.abbs.2024206
https://doi.org/10.3724/abbs.2024206
Review

Review

Astatine-211 and actinium-225: two promising nuclides in targeted alpha therapy

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Received 11 July 2024 Accepted 22 October 2024 Published 25 November 2024

Abstract

Nuclear medicine therapy offers a promising approach for tumor treatment, as the energy emitted during radionuclide decay causes irreparable damage to tumor cells. Notably, α-decay exhibits an even more significant destructive potential. By conjugating α-nuclides with antibodies or small-molecule inhibitors, targeted alpha therapy (TAT) can enhance tumor destruction while minimizing toxic side effects, making TAT an increasingly attractive antineoplastic strategy. Astatine-211 (^{211}At) and actinium-225 (^{225}Ac) have emerged as highly effective agents in TAT due to their exceptional physicochemical properties and biological effects. In this review, we highlight the applications of ^{211}At-/^{225}Ac-radiopharmaceuticals, particularly in specific tumor targets, such as prostate-specific membrane antigen (PSMA) in prostate cancers, cluster of differentiation (CD) in hematological malignancies, human epidermal growth factor receptor-2 (HER2) in ovarian cancers, and somatostatin receptor (SSTR) in neuroendocrine tumors. We synthesize the progress from preclinical and clinical trials to provide insights into the promising potential of ^{211}At-/^{225}Ac-radiopharmaceuticals for future treatments.

Key words astatine-211, actinium-225, radiopharmaceuticals, cancer, targeted alpha therapy

Introduction

From 1991 to 2021, the cancer mortality rate had a notable reduction of 33%. However, the incidence of cancer continues to increase, with malignant tumors being the second most formidable health threat to humans [1]. Nuclear therapy, particularly radioimmunologic drugs and small-molecule inhibitors, is a promising approach for treating small, diffuse, and micrometastatic tumors. The study of radioactivity originated in 1895 with Roentgen's discovery of X-rays, and groundbreaking discoveries such as the identification of natural radiation, α-rays, and artificial radioactivity laid the foundation for synthesizing and utilizing radionuclides. The use of iodine-131 (^{131}I) marked a pivotal milestone in radiation diagnosis and therapy, and various β-/γ-nuclides, such as fluorine-18 (^{18}F), yttrium-90 (^{90}Y), gallium-68 (^{68}Ga), iodine-125 (^{125}I), iodine-131 (^{131}I) and lutetium-177 (^{177}Lu), have promoted significant advancements in nuclear medicine. Although radium-223 (^{223}Ra) remains the sole α-nuclide approved by the Food and Drug Administration (FDA) for commercial use so far, targeted alpha therapy (TAT) holds immense clinical importance.

Firstly, α-nuclides decay releases energy ranging from 4 to 8 MeV within a limited range of approximately 100 μm, leading to high energy deposition, and the peak relative biological effect (RBE) occurs when the linear energy transfer (LET) approaches ~100 keV/μm [2–4]. Secondly, the average ionization path length of α-particles in cells is closely comparable to the diameter of the deoxyribonucleic acid (DNA) double helix, potentially resulting in irreparable damage to genetic material. Moreover, their cytotoxicity remains unaffected mainly by dose or oxygen level, rendering them highly effective at eliminating hypoxic tumor cells [5].

So α-nuclides are predominantly employed in therapeutic applications, whereas β-particles serve dual roles in diagnosis and treatment. Their energy ranges from 30 keV to 2.3 MeV, with a path length of 0.05 to 12 mm; the low LET of approximately 0.2 keV/μm causes sparse single- and double-strand breaks in DNA. Currently,

the utilization of ^{18}F and ^{68}Ga in imaging diagnostics has reached a relatively advanced stage, while ^{131}I is widely applied for treating thyroid diseases. Additionally, a phase III trial involving 831 patients with metastatic castration-resistant prostate cancer (mCRPC) demonstrated that ^{177}Lu-PSMA-617 significantly prolonged their survival [6].

To increase the enrichment of radiopharmaceuticals in tumors, researchers have coupled α-nuclides with antibodies or small-molecule inhibitors via succinimidyl N-2-(4-^{211}At-phenylethyl) succinamate (SAPS), closo-decaborate (2-) (B10), 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid (DOTA), their derivatives, and other specific chelators (Figure 1). Radiopharmaceuticals exhibit increased potential as our understanding of tumor molecular mechanisms intensifies and novel targeted vectors arise. Astatine-211 (^{211}At), bismuth-212 (^{212}Bi), lead-212 (^{212}Pb), bismuth-213 (^{213}Bi), thorium-227 (^{227}Th), and actinium-225 (^{225}Ac) have been evaluated in preclinical and clinical studies on the basis of the appropriate half-life, minimally toxic decay products, and relatively uncomplicated production circumstances [7]. Herein, we present a brief overview of the targets and indications for ^{211}At-/^{225}Ac-radiopharmaceuticals, review relevant preclinical studies and clinical trials, and delineate advancements in targeted ^{211}At/^{225}Ac complexes over the past decade. Our objective is to serve as a reference for opinions in research on nuclear therapeutics.

Characteristics of ^{211}At and ^{225}Ac

Initially discovered in 1940, astatine encompasses 39 isotopes, among which ^{211}At ($T_{1/2}$ = 7.2 h) is the solitary isotope appropriate for the TAT [8]. ^{211}At decays to stable ^{207}Pb via the emission of an α-particle with a simple dose calculation (Figure 2A). The ability of the thyroid to take up iodine predisposes it to accumulate halogens, indicating that ^{211}At is a suitable candidate for the management of thyroid cancers. Nevertheless, the off-target effects of unstable ^{211}At-radiopharmaceuticals could lead to ^{211}At enrichment in the thyroid. Accordingly, blockers are frequently used to safeguard the thyroid. The ^{211}At employed in studies is predominantly generated in cyclotrons through ^{209}Bi (α, 2n) ^{211}At (20 MeV ≤ $E_α$ ≤ 28.4 MeV) [9,10]. After wet/dry purification, ^{211}At can be labeled with targeted molecules via aryl or B10. Currently, over 30 organizations globally are competent in manufacturing ^{211}At.

^{225}Ac ($T_{1/2}$ = 9.9 d) undergoes a radioactive disintegration, emits 4 high-energy α-particles, ultimately culminating in the stable form of ^{209}Bi, which exhibits substantial clinical potential for use in nuclear therapeutics (Figure 2B). The principal adverse effects of ^{225}Ac arise from the off-target daughter nuclide ^{213}Bi, which is engendered by decay recoil. Presently, the use of ^{225}Ac in clinical

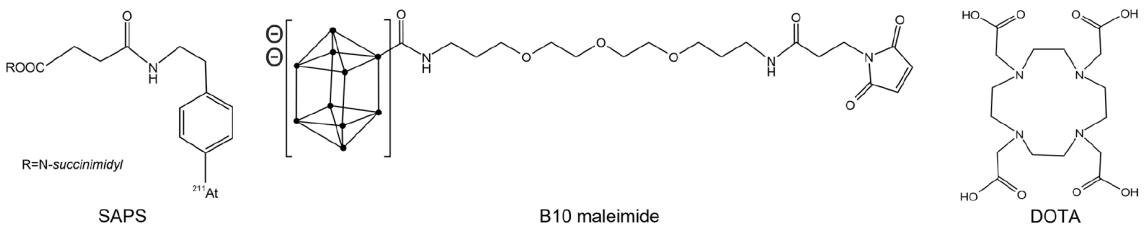

Figure 1. Chemical structures of SAPS, B10 maleimide and DOTA

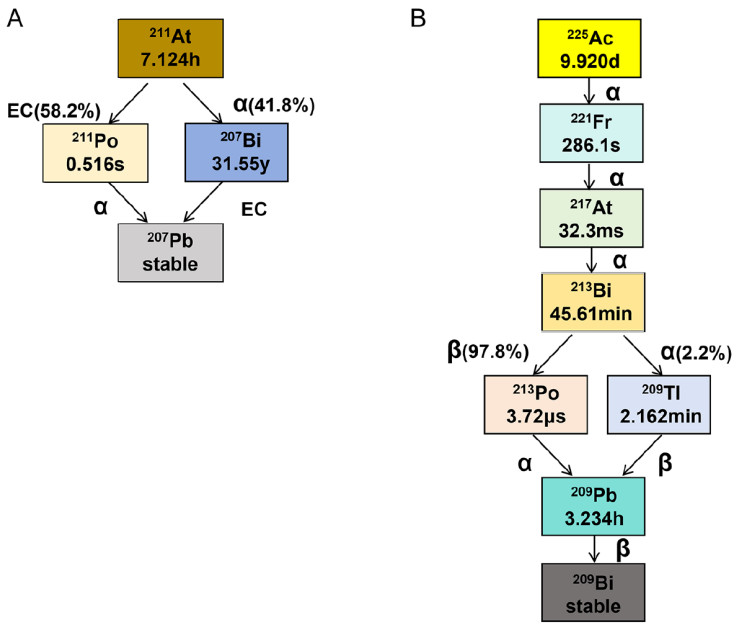

Figure 2. Decay models of ^{211}At (A) and ^{225}Ac (B) The percentage is the probability of decay, and α and β indicate alpha-decay and beta-decay, respectively. EC: electron capture.

research mainly originates from ^{229}Th generators [11]. Oak Ridge National Laboratory (ORNL) in the United States, the Joint Research Centre-Institute for Transuranium Elements (JRC-ITU) in Germany, and the Institute of Physics and Power Engineering (IPPE) in Russia constitute the three cardinal institutions capable of manufacturing medical-grade ^{225}Ac. Regrettably, the global production of ^{225}Ac is less than 2.5 Ci per annum, which is inadequate for satisfying clinical requirements [12].

Preclinical Studies of ^{211}At-/^{225}Ac-radiopharmaceuticals

Preclinical studies on radionuclide-labeled antibodies and small-molecule inhibitors are intended to assess the therapeutic efficacy of their respective targets, chelators, and tumor-homing properties. These endeavors are crucial in ascertaining the suitability of these agents for clinical trials and furnish valuable perspectives for optimizing radiopharmaceuticals. There are several eminent targets in targeted therapy: prostate-specific membrane antigen (PSMA) constitutes a representative target for targeted therapy in prostate cancer (PC), cluster of differentiation (CD) presents novel therapeutic strategies for hematological malignancies, and human epidermal growth factor receptor-2 (HER2) is prominently expressed on the surface of various breast and ovarian cancer cells. Related investigations are being vigorously pursued.

PSMA-targeted radiopharmaceuticals

PSMA is localized on the external surface of PC cells and is particularly conspicuous in instances featuring poor differentiation and metastatic variations. As neoplasms progress, the expression level of PSMA tends to increase, making it an ideal candidate target for diagnosis and treatment. Table 1 summarizes PSMA-targeted radiopharmaceuticals.

Kiess and colleagues [13] reported a significant retardation in the growth of PC xenografts in mice through the administration of (2S)-2-(3-(1-carboxy-5-(4-^{211}At-astatobenzamido)pentyl)ureido)-pentanedioic acid. Furthermore, RPS-027 possesses dual targeting capabilities toward PSMA and albumin, exhibits robust tissue distribution and extends the intratumoral retention time in tumor-bearing mice [14].

The PSMA inhibitor PSMA-769 labeled with ^{211}At has been demonstrated to have relatively low nephrotoxicity and augment the tumor-to-kidney uptake ratio [15]. Li *et al.* [16] subsequently conjugated B10 with streptavidin (SAV) or human serum albumin (HSA), succinylated it to decrease renal uptake, subsequently associated this chelator with polyethylene glycolylated lysine-urea-glutamate (PEGylated LuG, a PSMA-targeting polypeptide) and ultimately radiolabeled it with ^{211}At. The ^{211}At-B10-SAV/HSA-PEGylated LuG exhibited considerable clinical potential in a C4-2B PC xenograft mouse model. While ^{211}At-PSMA5 (Figure 3A,B) demonstrates a pronounced tumor retention of 30.6 ± 17.8 and 40.7 ± 2.6 %ID/g at 3 h and 24 h post-injection respectively, the total excretion (%ID) was 8.26 ± 5.0 %ID at 3 h and increased to 15.33 ± 6.3 %ID at 24 h in the urine and 35.2 ± 9.2 %ID at 24 h in the feces. Moreover, 0.4 MBq of ^{211}At-PSMA5 significantly inhibited LNCaP xenograft growth [18].

For antibodies and micromolecules labeled with ^{225}Ac that are utilized in the therapeutics of PC, RPS-074 can be quantitatively combined with ^{225}Ac, and PSMA-D4 is a targeted derivative of DOTA that manifests considerable therapeutic potency [21,22]. In addition, SibuDAB is an albumin-binding antibody, and the biodistribution revealed that ^{225}Ac-SibuDAB (the structure as shown in Figure 3C) has higher retention in the blood, liver, heart, kidneys, and lungs of PC-3 PIP tumor-bearing mice at 1 h, 4 h, 24 h, and 48 h post-injection. The tumor accumulation reached a maximal value of 80 ± 8 %IA/g at 24 h. Despite the tumor-to-blood/kidney/liver ratios being suboptimal compared with ^{225}Ac-PSMA-617, the tumor uptake of ^{225}Ac-SibuDAB at 48 h is twice that of ^{225}Ac-PSMA-617 (64 ± 11 %IA/g vs 31 ± 3 %IA/g) and significantly inhibited the tumor volume (Figure 3D), indicating that ^{225}Ac-SibuDAB could function as a feasible substitute for ^{225}Ac-PSMA-617 [23].

CD-targeted radiopharmaceuticals

CD family comprises a wide spectrum of proteins that act as distinctive labels on external membranes throughout leukocyte differentiation, maturation, and activation. Investigators have engineered diverse chelators to bind anti-CD antibodies to ^{211}At/

Table 1. PSMA-targeted radiopharmaceuticals

Radiopharmaceuticals	Experimental type (cell lines)	Ref.
(2S)-2-(3-(1-carboxy-5-(4-^{211}At-astatobenzamido)pentyl)ureido)-pentanedioic acid	*in vivo* (PC3 PIP)	[13]
^{211}At-RPS-027	*in vivo* (LNCaP)	[14]
^{211}At-PSMA-769	*in vivo* (PC3 PIP)	[15]
^{211}At-B10-SAV-PEGylated LuG and ^{211}At-B10-HSA-PEGylated LuG	*in vivo* (C4-2B)	[16]
^{211}At-GV-620	*in vivo* (PC3 PIP)	[17]
^{211}At-PSMA5	*in vivo* (LNCaP)	[18]
^{175}Lu(III)(14S,18S)-9-(4-[^{211}At]Astatobenzyl)-2,8,16-trioxo-1-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)-3,9,15,17-tetraazaicosane-14,18,20-tricarboxylic acid	*in vivo* (PC3 PIP)	[19]
[^{211}At]PSAt-3-Ga	*in vivo* (LNCaP)	[20]
^{225}Ac-RPS-074	*in vivo* (LNCaP)	[21]
^{225}Ac-PSMA-D4	*in vivo* (LNCaP)	[22]
^{225}Ac-sibuDAB	*in vivo* (PC3 PIP)	[23]
^{225}Ac-macropa-pelgifatamab	*in vivo* (C4-2)	[24]
[^{225}Ac]Ac-PSMA-NAT-DA1	*in vivo* (LNCaP, PC-3)	[25]
^{225}Ac-L1	*in vivo* (PC3 PIP)	[26]

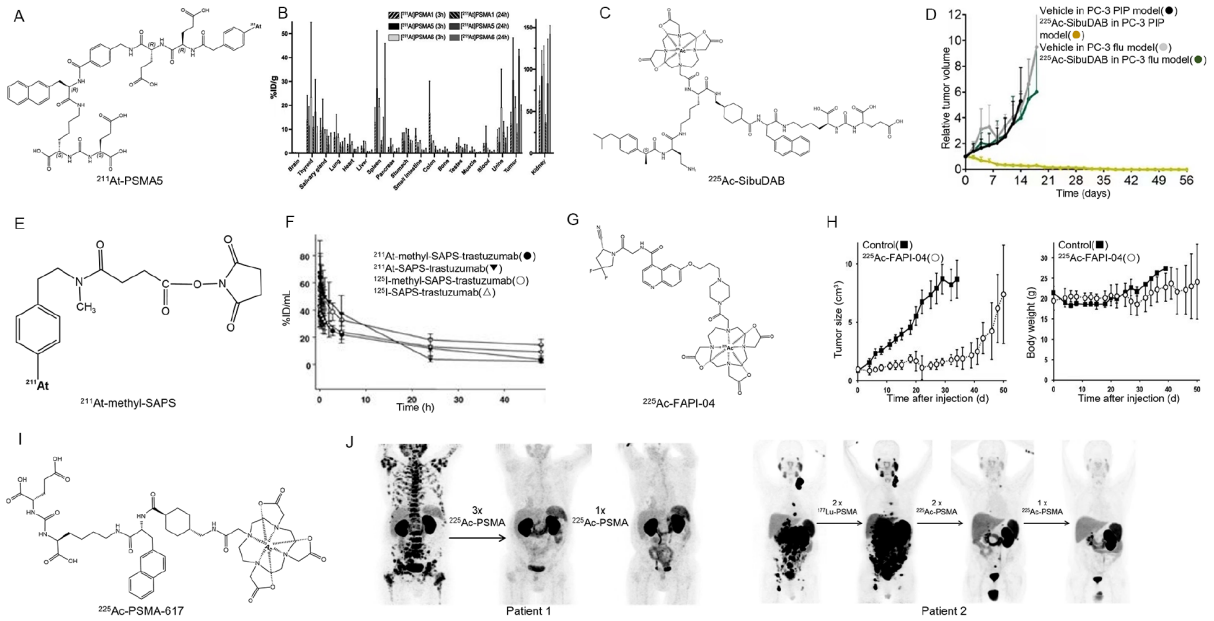

Figure 3. The chemical structures, pharmacokinetic properties and therapeutic effects of representative radiopharmaceuticals (A) Chemical structure of ^{211}At-PSMA5. (B) Whole-body distributions of ^{211}At-PSMA1, ^{211}At-PSMA5 and ^{211}At-PSMA6 at 3 h and 24 h post-injection [18]. (C) Chemical structure of ^{225}Ac-SibuDAB. (D) Relative tumor volume of the vehicle group and ^{225}Ac-SibuDAB group in the PC-3 PIP and PC-3 flu mouse models [23]. (E) Chemical structure of ^{211}At-methyl-SAPS. (F) Pharmacokinetic properties of ^{211}At-methyl-SAPS-trastuzumab, ^{211}At-SAPS-trastuzumab, ^{125}I-methyl-SAPS-trastuzumab, and ^{125}I-SAPS-trastuzumab [48]. (G) Chemical structure of ^{225}Ac-FAPI-04. (H) Tumor volume and body weight of the control group and ^{225}Ac-FAPI-04 group in the PANC-1 mouse model [65]. (I) Chemical structure of ^{225}Ac-PSMA-617. (J) PET/CT images of two CRPC patients after receiving ^{225}Ac-PSMA-617 treatment [66].

^{225}Ac, such as *p*-iso-thiocyanato-phenethyl-*closo*-decaborate (B10-NCS), N-(15-(aminoacyldecaborate)-4,7,10-(trioxatridecanyl)-3-maleimidopropionamide (ADTM), and N-succinimidyl-4-(trimethylstannyl)-benzoate (SPMB). Table 2 summarizes a concise overview of these CD targets and their radiopharmaceuticals.

CD20 is a membrane protein that is prevalent in lymphoid cancers and can be precisely targeted by the FDA-approved therapeutic entity rituximab. Aurlien *et al.* [28] radiolabeled rituximab with ^{211}At, revealing that negligible RAEL cell survival transpired when the radioactivity surpassed 30 kBq/ml *in vitro*. Additionally, the anti-human CD20 single-domain antibody (sdAb) 9079 is amenable to radiolabeling with ^{225}Ac via DOTA, which is substantially inhibited in huCD20 transgenic B16 melanoma xenografts *in vivo* [31].

CD25 is a critical biomarker for evaluating malignant, activated T cells. A total of 10 μg of ^{211}At-labeled 7G7/B6, an anti-CD25 murine monoclonal antibody (mAb), exhibited pronounced therapeutic efficacy against the leukemic MET-1 model *in vitro*. The combination of ^{211}At-7G7/B6 and daclizumab, another CD25-targeted mAb, resulted in an increased lifespan of tumor-bearing mice [33].

CD33, an overexpressed protein in acute myeloid leukemia (AML), serves as a target for ^{225}Ac-lintuzumab. Venetoclax is a novel drug for elderly AML patients or ineligible patients for intensive chemotherapy. Combining ^{225}Ac-lintuzumab with venetoclax demonstrated tumor suppression and resistance reversal in a venetoclax-resistant model [36]. CD123 is another antigen of leukemia. Laszlo *et al.* [46] introduced a dehumanized anti-CD123 mAb named 10C4, which was radiolabeled with ^{211}At via B10 to inhibit MOLM-13 xenografts in mice.

The CD antigens in Table 2 are typically employed in treating hematological disorders, whereas CD44v6 and CD46 are exceptions. CD44v6 is crucial in head and neck squamous cell carcinomas (HNSCCs). The U36 mAb was successfully conjugated with ^{211}At through SPMB, resulting in substantial uptake by SCC-25 cells and consequent induction of cytotoxicity *in vitro* [39]. Compared with PSMA, CD46 is homogeneously expressed in PC cells. Bidkar *et al.* [44] conjugated a humanized YS5 mAb with *p*-SCN-Bn-DOTA and subsequently labeled it with ^{225}Ac. The therapeutic efficiency and targeting efficacy of ^{225}Ac-DOTA-YS5 in 22Rv1 xenografts and toxicity analysis in normal mice yielded promising outcomes.

HER2-targeted radiopharmaceuticals

HER2 is overexpressed on the membrane of breast carcinoma and ovarian cancer cells, rendering it an ideal target for nuclear therapy. Trastuzumab, also known as Herceptin, is a humanized anti-HER2 antibody that has obtained regulatory sanction. ^{211}At-/^{225}Ac-labeled trastuzumab via diverse chelators exhibited considerable potential in treating HER2-positive malignancies (Table 3).

Labeling trastuzumab with ^{211}At via N-succinimidyl 3-[^{211}At] astatobenzoate confirms the therapeutic potential in MCF-7/HER2-18, SKBr-3, and BT-474 cells *in vitro* [47], yet it manifests inadequate stability. Talanov *et al.* [48] incorporated a methyl moiety into SAPS to couple trastuzumab with ^{211}At (Figure 3E,F). Subsequently, they administered approximately 130–220 kBq of ^{211}At-methyl-SAPS-trastuzumab and ^{211}At-SAPS-trastuzumab to athymic mice bearing LS-174T xenografts through the caudal vein. The blood retention rates of ^{211}At-methyl-SAPS-trastuzumab were 26.20 ± 2.49 %ID/g and 16.05 ± 3.59 %ID/g at 2 h and 24 h post-injection, respectively; for the cohort receiving ^{211}At-SAPS-trastuzumab, the values were 23.66 ± 4.10 %ID/g and 11.45 ± 0.86 %ID/g, respectively. The N-methyl-modified SAPS prolonged the plasma

Table 2. CD-targeted radiopharmaceuticals

Targets	Radiopharmaceuticals	Indications	Experimental type (cell lines)	Ref.
CD5	^{211}At-T101	Acute lymphoblastic leukemia	*in vitro* (MOLT-4)	[27]
CD20	^{211}At-rituximab	Lymphoma	*in vitro* (RAEL cells)	[28]
CD20	^{211}At-1F5-B10	Lymphoma	*in vivo* (Ramos cell)	[29]
CD20	^{225}Ac-DOTA-rituximab	Lymphoma	*in vivo* (Raji cells)	[30]
CD20	^{225}Ac-9079	Disseminated tumor	*in vivo* (transgenic B16)	[31]
CD25	^{211}At-labeled HAT	Immunosuppression of heart transplantation	*in vivo* (cynomolgus model)	[32]
CD25	^{211}At-7G7/B6	Leukemia, lymphoma	*in vivo* (MET-1)	[33]
CD30	^{211}At-HeFi-1	Leukemia, lymphoma	*in vivo* (karpas299, SUDHL-1)	[34]
CD33	^{211}At-anti-CD33	Leukemia, lymphoma	*in vivo* (HL-60)	[35]
CD33	^{225}Ac-lintuzumab	Acute myeloid leukemia	*in vivo* (U937, OCI-AML3)	[36]
CD38	^{211}At-OKT10-B10	Multiple myeloma	*in vivo* (NCI-H929)	[37]
CD38	^{225}Ac-DOTA-daratumumab	Multiple myeloma	*in vivo* (MM.1S)	[38]
CD44v6	^{211}At-U36	Head and neck squamous cell carcinoma	*in vitro* (SCC-25)	[39]
CD45	^{211}At-B10-CA12.10C12	Immunosuppression of hematopoietic cell transplantation	*in vivo* (canine model)	[40]
CD45	^{211}At-B10-30F11	Acute myeloid leukemia	*in vivo* (SJL)	[41]
CD45	^{211}At-30F11-ADTM	Acute myeloid leukemia	*in vivo* (normal model)	[42]
CD45	^{211}At-BC8-B10	Lymphoma	*in vitro* (Ramos cell)	[43]
CD46	^{225}Ac-DOTA-YS5	Prostate cancer	*in vivo* (22Rv1)	[44]
CD46	^{225}Ac-DOTA-YS5	Multiple myeloma	*in vivo* (MM.1S)	[45]
CD123	^{211}At-10C4-B10	Acute leukemia	*in vivo* (MOLM-13)	[46]

Table 3. HER2-targeted radiopharmaceuticals

Radiopharmaceuticals	Experimental type (cell lines)	Ref.
^{211}At-trastuzumab	*in vitro* (SKBr-3, BT-474, MCF7/HER2-18)	[47]
^{211}At-methyl-SAPS-trastuzumab	*in vivo* (LS-174T)	[48]
^{211}At-decaborate-trastuzumab	*in vivo* (A431)	[49]
^{211}At-AuNP-PEG-trastuzumab	*in vitro* (SKOV-3)	[50]
^{211}At-trastuzumab	*in vivo* (NCI-N87)	[51]*
^{225}Ac-trastuzumab	*in vivo* (SUM225)	[52]
^{225}Ac-(py4pa-phenyl-trastuzumab)	*in vivo* (SKOV-3)	[53]
^{225}Ac@Fe_3O_4-CEPA-trastuzumab	*in vivo* (SKOV-3)	[54]
^{211}At-B10-$Z_{HER2:342}$-cys	*in vivo* (SKOV-3)	[55]
^{211}At-SAPS-C6.5	*in vivo* (MDA-MB-361/DYT2)	[56]
^{211}At-ABY-025	*in vitro* (SKOV-3, SKBR-3)	[57]
^{211}At-SAGMB-2Rs15d	*in vitro* (SKOV-3)	[58]
Iso-^{211}At-AGMB-PODS-5F7GGC	*in vivo* (BT474)	[59]
^{225}Ac-7.16.4	*in vivo* (N2.5)	[60]
^{225}Ac-DOTA-Nb	*in vivo* (SKOV-3)	[61]
^{225}Ac-2Rs15d	*in vivo* (SKOV3-Luc-IP1, MDA-MB-231Br)	[62]
^{225}Ac-Pr	*in vivo* (BT-474, SKOV-3)	[63,64]

The indications mainly are breast carcinoma and ovarian neoplasms, reference with * means the indication is liver metastatic gastric cancer.

half-lives of radiolabeled trastuzumab compounds, demonstrating increased stability *in vivo*. Fujiki *et al.* [49] moved toward B10 modifications that enhanced *in vivo* stability but failed to meet clinical requirements. In addition, PEG-modified gold nanoparticles (NPs) have been posited as vectors for conjugating ^{211}At and trastuzumab [50], showing efficacious performance against SKOV-3 cells *in vitro*. Recently, the use of ^{211}At-trastuzumab to treat mice with liver metastatic gastric cancer significantly prolonged the survival duration with low toxicity [51].

Studies on ^{225}Ac-trastuzumab have emerged relatively slowly. Yoshida *et al.* [52] undertook experiments on ductal carcinoma *in situ* from the breast in mice. They administered the therapeutic substance through a mammary duct to increase tumor uptake and reduce side effects, resulting in superior efficacy compared with

intravenous administration. Despite DOTA being a prevalently employed chelator for ^{225}Ac, H_4py4pa demonstrates a more robust binding affinity for ^{225}Ac [53]. Each ^{225}Ac@Fe_3O_4 NP could combine with 8–11 mAbs while maintaining high stability and targeting capability via 3-phosphonopropionic acid [54].

In addition to trastuzumab, numerous types of HER2-targeted antibodies exist, such as $Z_{HER2:4}$, C6.5, and ABY-025. These antibodies can be coupled with ^{211}At via SAPS, B10, and their derivatives, indicating their therapeutic potential in preclinical assays [55–62]. Binding 2Rs15d sdAb to ^{211}At via N-succinimidyl 4-(1,2-bis-tert-butoxycarbonyl)guanidino-methyl-3-(trimethylstannyl)benzoate (Boc2-SGMTB) efficaciously inhibited the growth of SKOV-3 cells *in vitro* [58]. Alternatively, ^{225}Ac-labeled p-SCN-Bn-DOTA effectively controlled the SKOV-3 xenograft volume [61], while labeling 7.16.4 mAb with ^{225}Ac prolonged the survival of mice with lung micrometastatic breast cancer for up to 1 year with negligible nephrotoxicity [60].

SSTR-targeted radiopharmaceuticals

Somatostatin receptors (SSTRs) are G protein-coupled receptors featuring multiple transmembrane domains in neuroendocrine tumors (NETs). Octreotide and its analogs have shown considerable efficacy in targeting SSTRs. Table 4 furnishes a compendium of recent preclinical studies concerning SSTR-targeted radiopharmaceuticals.

Vaidyanathan *et al.* [67] synthesized N-(4-guanidinomethyl-3-iodobenzoyl)-Phe^1-octreotate (GMIBO) and radiolabeled it with ^{211}At. They noted substantial liver and kidney accumulation in the D341 Med cell cerebellar medulloblastoma mouse model, rendering it unamenable to intravenous injection. They subsequently formulated N-(1-deoxy-D-fructosyl)-N-(3-O-^{211}At-benzoyl)-Lys^0-octreotate (^{211}At-GABLO) [68], which decreased tumor uptake. Moreover, the radiolabeling of DOTA-phenylalanine 1-tyrosine 3-octreotide (DOTATOC) with ^{225}Ac produced favorable outcomes in a murine model with rat acinar pancreatic AR42J xenografts [69], and ^{211}At-SAB-octreotide might represent a potential therapeutic option for small cell lung cancer [70]. Additionally, King *et al.* [71] developed an 18-membered macrocyclic compound named MACROPA, which could be further modified into MACROPA-octreotate (MACROPATATE), facilitating facile conjugation with ^{225}Ac at room temperature.

FAP-targeted radiopharmaceuticals

Fibroblast activation proteins (FAPs) are remarkable therapeutic targets. They are ubiquitously present in the microenvironments of virtually all epithelial cancers and play crucial roles in tumor growth, invasion, and metastasis. FAP inhibitors (FAPIs) are ideal candidates for cancer diagnosis and treatment because of their superior binding affinity for FAPs (Table 5). ^{225}Ac-FAPI-04 (Figure 3G,H) exhibited effective targeting, a high tumor-to-background ratio, and prompt renal clearance in a pancreatic cancer PANC-1 xenograft model [65]. The urinary distributions at 3 h and 24 h after intravenous administration were 40.66 ± 40.25 %ID/g and 1.34 ± 0.44 %ID/g, the corresponding tumor uptake values were 0.251 ± 0.010 %ID/g and 0.097 ± 0.008 %ID/g, and the blood concentrations were 0.102 ± 0.021 %ID/g and 0.041 ± 0.017 %ID/g over the same temporal intervals. ^{225}Ac-FAPI-04 markedly attenuated the tumor volume compared with that in the control group. Ayaka *et al.* [72] exploited PEG and piperazine (PIP) as connectors in conjunction with FAPI1, FAPI2, FAPI3, FAPI4, and FAPI5. ^{211}At-PEG-FAPI1 exhibited superior cellular uptake, enhanced radionuclide labeling efficacy, and favorable *in vivo* pharmacokinetics. Nevertheless, FAPIs undergo metabolic transformation within a few hours upon cellular ingress; conversely, ^{225}Ac and ^{211}At possess protracted half-lives and may not operate at peak efficiency. Therefore, ^{225}Ac-/^{211}At-FAPI radiopharmaceuticals need prolonged retention in the bloodstream and tumor tissues.

Other targets

Ideal targets for oncological therapeutics should be expressed at high levels on the surface of neoplastic cells while remaining absent in normal cells. However, the majority of promising targets exhibit microexpression in common tissues. As formerly described, we have delineated several targets with substantial clinical potential. Tables 6 and 7 offer a synopsis of some alternative targets.

Table 7 encompasses targets with relatively few preclinical studies, yet their therapeutic potential ought not to be undervalued. Prostate stem cell antigen (PSCA) is hyper-expressed in approximately 90% of primary PCs. The A11 mAb efficaciously targets PSCA and manifests significant tumor suppression in a PC3-PSCA xenograft model [108]. Prostate-specific antigen (PSA) is another helpful target. The PSA-targeting humanized hu5A10 mAb exhibited therapeutic efficacy when conjugated with ^{225}Ac [109]. More-

Table 4. SSTR-targeted radiopharmaceuticals

Radiopharmaceuticals	Indications	Experimental type (cell lines)	Ref.
^{211}At-AGMBO	NET, paraganglioma	*in vivo* (D341 Med)	[67]
^{211}At-GABLO	NET, paraganglioma	*in vivo* (D341 Med)	[68]
^{225}Ac-DOTATOC	NET, paraganglioma	*in vivo* (AR42J)	[69]
^{211}At-SAB-octreotide	Small cell lung cancer	*in vivo* (H446)	[70]
^{225}Ac-MACROPATATE	NET	*in vivo* (U2OS-SSTR2, H69)	[71]

Table 5. FAP-targeted radiopharmaceuticals

Radiopharmaceuticals	Indications	Experimental type (cell lines)	Ref.
^{225}Ac-FAPI-04	Pancreatic cancer	*in vivo* (PANC-1)	[65]
^{225}Ac-FAPI-46	Pancreatic cancer	*in vivo* (PANC-1)	[73]
^{211}At-PEG-FAPI1	Epithelioid cancer	*in vivo* (PANC-1)	[72]
[^{225}Ac]Ac-FAPI-mFS	Fibrosarcoma	*in vivo* (HT-1080-FAP)	[74]

Table 6. Targets more studied in preclinical trials of ^{211}At-/^{225}Ac-radiopharmaceuticals

Targets	Radiopharmaceuticals	Indications	Experimental type (cell lines)	Ref.
Epidermal growth factor receptor (EGFR)	^{211}At-benzoate-EGF	Epithelioid cancer	*in vitro* (A431)	[75]*
	^{211}At-EGF	Epithelioid cancer	*in vitro* (A431)	[76]*
	^{225}Ac-nimotuzumab-SpyTag-ΔN-spyCatcher	Breast cancer	*in vivo* (MDA-MB-468)	[77]
Folate receptor (FR)	FA-HIgG-^{211}At	Lung cancer, breast cancer, *etc.*	*in vivo* (HeLa-S3, OvCar-3, *etc.*)	[78]*
	^{211}At-Mov18	Lung cancer, breast cancer, *etc.*	*in vivo* (OVCAR-3)	[79]*
	^{211}At-farletuzumab	Lung cancer, breast cancer, *etc.*	*in vivo* (OVCAR-3)	[80]
Transferrin receptor (TFR)	^{211}At-BK19.9	Ovarian cancer	*in vivo* (HL60)	[81]*
	^{225}Ac@multifunctional silica nanoconstructs	Malignant tumor	*in vivo* (BT-549)	[82]
Noradrenaline transporter (NET)	^{211}At-AFBG	Neuroblastoma	*in vivo* (SK-N-SH)	[83]*
	^{211}At-MABG	Pheochromocytoma	*in vivo* (PC12)	[84]
	^{211}At-MABG	Neuroblastoma	*in vivo* (NB1691, IMR-05, *etc.*)	[85]
Sodium-dependent phosphate transport protein 2b (NaPi 2b)	^{211}At-MX35 F(ab′)$_2$	Ovarian cancer	*in vivo* (OVCAR-3)	[86]*
	^{211}At-B-PL$_{suc}$	Ovarian cancer	*in vivo* (OVCAR-3)	[87]*
	^{211}At-Rebmab 200	Ovarian cancer	*in vivo* (OVCAR-3)	[88]
L-type amino acid transporter 1 (LAT1)	^{211}At-AAMT	Melanoma, pancreatic cancer, *etc.*	*in vivo* (B16F10, PANC-1)	[89]
	^{211}At -NpGT	Melanoma, pancreatic cancer, *etc.*	*in vivo* (C6)	[90]
Poly(ADP-ribose) polymerase 1 (PARP-1)	^{211}At-MM4	Neuroblastoma	*in vivo* (IMR-05)	[91]
	^{211}At-PTT	Neuroblastoma	*in vivo* (patient-derived model)	[92]
Thrombomodulin	{La$_{0.5}$Gd$_{0.5}$}(^{225}Ac)PO$_4$@4Gd-PO$_4$shell@AuNPs-dPEG-mAb 210b	Lung cancer	*in vivo* (EMT-6)	[93]*
	La(^{225}Ac)PO$_4$-mAb 201b	Lung cancer	*in vivo* (normal model)	[94]*
αvβ3 integrin	Ga-DOTA-[^{211}At]c[RGDf(4-At)K]	Glioblastoma multiforme	*in vivo* (U-87MG)	[95]
	^{225}Ac-DOTA-c(RGDyK)	Glioblastoma multiforme	*in vivo* (U-87MG)	[96]
Glypican-3 (GPC3)	^{225}Ac-hu11B6-IgG1	PC	*in vivo* (LNCaP-AR)	[97]
	^{225}Ac-DOTA-hu11B6	Breast cancer	*in vivo* (BT-474, MFM-223)	[98]
Human kallikrein 2 (hK2)	^{225}Ac-GC33-BZM	Liver cancer	*in vivo* (HepG2)	[99]
	^{225}Ac-Macropa-GC33	Liver cancer	*in vivo* (HepG2)	[100]
Tumor-associated glycoprotein 72 (TAG 72)	^{225}Ac-HEHA-Hu-ΔCH$_2$ CC49	Malignant tumor	*in vivo* (LS-174T)	[101]*
	^{225}AC-DOTA-CC49	Malignant tumor	*in vivo* (OVCAR3)	[102]
Glycoprotein A33 (GPA33)	^{211}At-huA33	Colorectal cancer	*in vivo* (SW1222)	[103]*
	^{225}Ac-Pr	Colorectal cancer	*in vivo* (SW1222)	[63]
Disialoganglioside (GD2)	^{225}Ac-3F8	Neuroblastoma, meningeal carcinoma	*in vivo* (NMB7)	[104]*
	^{225}Ac-Pr	Neuroblastoma, meningeal carcinoma	*in vivo* (IMR-32)	[63]
NK-1R	^{211}At-Rh[16aneS$_4$]-SP$_{5-11}$	Brain glioma	*in vivo* (T98G)	[105]* [106,107]

References with * means they are published in 2014 or earlier.

over, specific agents lack specific targets but can accumulate within tumor cells and play a vital role in the radiolabeling of ^{211}At and ^{225}Ac. For example, L-phenylalanine possesses a high affinity for brain gliomas, spurring the development of radiopharmaceuticals such as 4-[^{211}At]-L-phenylalanine and ^{211}At-AuNPs@mPEG [110,111].

Clinical Trials of ^{211}At-/^{225}Ac-radiopharmaceuticals

α-nuclides have distinctive biophysical attributes, ^{211}At and ^{225}Ac have received great attention in radionuclide therapy, and many potential drugs have been used in clinical trials to verify their indications and efficacy. Table 8 summarizes recent clinical studies

Table 7. Targets less studied in preclinical trials of ^{211}At-/^{225}Ac-radiopharmaceuticals

Targets	Radiopharmaceuticals	Indications	Experimental type (cell lines)	Ref.
PSCA	^{211}At-A11	PC	*in vivo* (PC3-PSCA)	[108]
PSA	^{225}Ac-hu5A10	PC	*in vivo* (LNCaP-AR)	[109]
Insulin growth factor receptor (IGF-1R)	^{225}Ac-cixutumumab	Triple-negative breast cancer	*in vivo* (SUM149PT)	[112]
Vascular endothelial growth factor receptor (VEGFR)	iRGD-C6-lys(^{211}At-ATE)-C6-^{D}A7R	Malignant tumor	*in vivo* (U87MG)	[113]
Gastrin-releasing peptide receptor (GRPR)	^{211}At-AB-3	Prostate cancer	*in vivo* (PC-3)	[114]
Metabotropic glutamate receptor 1 (mGluR1)	^{211}At-AITM	Melanoma, pancreatic cancer, *etc.*	*in vivo* (PANC 1, A375, *etc.*)	[115]
Chemokine(C-X-C motif)receptor 4 (CXCR4)	^{211}At-CXCR4 mAb	Acute myeloid leukemia	*in vivo* (U937)	[116]
σ receptor	^{211}At-pAtV	Malignant tumor	*in vivo* (DU-145)	[117]
Glucose-dependent insulinotropic polypeptide receptor (GIPR)	^{211}At-MeATE-SPN-GIP	Malignant tumor	*in vivo* (CFPAC-1)	[118]
Melanocortin 1 receptor (MC1R)	^{225}Ac-DOTA-MC1RL	Metastatic uveal melanoma	*in vivo* (transgenic A375 cells)	[119]
Cholecystokinin B receptor (CCKBR)	^{225}Ac-PP-F11N	Thyroid cancer, ovarian cancer, *etc.*	*in vivo* (A431/CCKBR)	[120]
Scavenger receptor B type I (SR-BI)	^{225}Ac-rHDL	Ovarian cancer, liver cancer, *etc.*	*in vivo* (HEP-G2, PC-3)	[121]
Interleukin-13 receptor alpha 2 (IL13RA2)	^{225}Ac-Pep-1L	Glioblastoma multiforme	*in vivo* (U251)	[122]
NIS	[^{211}At]NaAt	Thyroid cancer	*in vitro* (transgenic cells)	[123]*
Major histocompatibility complex class I chainrelated protein A and B (MICA/B)	^{211}At-anti-MICA/B	Breast cancer, liver cancer, *etc.*	*in vivo* (HCT116)	[124]
Tenascin	^{211}At-mu81C6	Brain glioma	*in vivo* (D-54MG)	[125]
Delta-like protein 3 (DLL3)	^{225}Ac-DOTA-MMA-huIgG1 ^{225}Ac-DOTA-MMA-SC16.56	Small cell lung cancer	*in vitro* (HEK-293T-oxhSC16)	[126]
Mucoglycoprotein 5AC (MUC5AC)	^{225}Ac-labeled hNd2	Pancreatic cancer	*in vivo* (SW1990)	[127]
Podoplanin	^{225}Ac-labeled NZ-16 ^{225}Ac-labeled NZ-12	Mesothelioma	*in vivo* (H226)	[128]
M-protein	^{225}Ac-anti-5T33 MM sdAb	Multiple myeloma	*in vivo* (5T33MM)	[129]
Vascular endothelial cadherin (VEC)	^{225}Ac-E4G10	Malignant tumor	*in vivo* (LS174T)	[130]*
Oncogenically associated membrane-bound alkaline phosphatase isoenzyme (onco-APase)	6-^{211}At-MNDP	Malignant tumor	*in vivo* (CMT-93)	[131]*
Carbonic anhydrase IX (CAIX)	^{225}Ac-DOTA-hG250	Kidney cancer	*in vivo* (SK-RC-52)	[132]
3H11 antigen	^{211}At-3H11	Stomach cancer	*in vivo* (M85)	[133]*
Osteosarcoma antigen	^{211}At-TP-3	Osteosarcoma	*in vivo* (OHS)	[134]*
Very late antigen 4 (VLA-4)	^{225}Ac-DOTA-anti-VLA-4	Melanoma	*in vivo* (B16-F10)	[135]
Carbohydrate antigen 19.9 (CA19.9)	^{225}Ac-DOTA-PEG7-Tz	Pancreatic ductal adenocarcinoma	*in vivo* (BxPC3)	[136]
Carcinoembryonic antigen (CEA)	^{225}Ac-DOTA-M5A	Breast cancer, colon cancer	*in vivo* (E0771, MC38)	[137]
Glypican-1 (GPC1)	^{211}At -B10-01a33	Pancreatic ductal adenocarcinoma	*in vivo* (PANC-1)	[138]
Lewis Y epitope	^{211}At-BR96	Colon cancer	*in vivo* (BN7005-H1D2, *etc.*)	[139,140]*
Mesothelin	^{211}At-ET210–28 ^{211}At-ET210–6	Pancreatic cancer, lung cancer, *etc.*	*in vitro* (MDA-MB-231)	[141]
Nucleolin	^{225}Ac-DOTA-F3	Peritoneal carcinomatosis	*in vivo* (MDA-MB-435)	[142]*
Melanin	^{211}At-MTB	Melanoma	*in vivo* (HX118, HX34)	[143]*
Acrolein	^{211}At-ADIPA	Lung cancer	*in vivo* (A549)	[144]

References with * means they are published in 2014 or earlier.

Table 8. Clinical ^{211}At-/^{225}Ac-nuclear therapy

Targets	Radiopharmaceuticals	Indications	Clinical stages	Ref.
NIS	[^{211}At]NaAt	Enrichment in thyroid gland	Case reports	[145]
Albumin receptor	^{211}At-labeled human serum albumin microspheres	Tongue cancer	Case reports	[146]
Tenascin	^{211}At-ch81C6	Brain tumors	Phase I	[147]
NaPi 2b	^{211}At-MX35 F(ab′)$_2$	Ovarian cancer	Phase I	[148,149]
PSMA	^{225}Ac-PSMA-617	PC	Case reports	[66]
PSMA	^{225}Ac-PSMA-617	PC	Phase I	[150]
PSMA	^{225}Ac-PSMA-617	PC	Phase II	[151]
PSMA	^{225}Ac-PSMA-617	PC	Phase II	[152]
PSMA	^{225}Ac-PSMA-617	PC	Phase II	[153]
PSMA	^{225}Ac-DOTA-J591	PC	Phase I	[154]
PSMA	^{225}Ac-PSMA-I&T	PC	Phase I	[155]
SSTR	^{225}Ac-DOTATOC	NET	Phase I	[156]
SSTR	^{225}Ac-DOTATOC	Metastatic NET	Phase I	[157]
SSTR	^{225}Ac-DOTATOC	Metastatic hepatic NET	Case reports	[158]
SSTR	^{225}Ac-DOTATOC	Metastatic thymuc NET	Case reports	[159]
SSTR	^{225}Ac-DOTATATE	Gastroenteropancreatic NET	Phase I	[160]
SSTR	^{225}Ac-DOTATATE	Gastric NET	Case reports	[161]
SSTR	^{225}Ac-DOTATATE	Metastatic rectal NET	Case reports	[162]
SSTR	^{225}Ac-DOTATATE	Metastatic paragangliomas	Phase I	[163]
SSTR	^{225}Ac-DOTATATE	Gastroenteropancreatic NET	Phase II	[164]
SSTR	^{225}Ac-DOTATATE	Metastatic NET	Case reports	[165]
SSTR	^{225}Ac-DOTATATE	Metastatic NET	Case reports	[166]
SSTR	^{225}Ac-DOTATATE	Metastatic NET	Case reports	[167]
SSTR	^{225}Ac-DOTATATE	Metastatic NET	Case reports	[168]
SSTR	^{225}Ac-DOTATATE	Metastatic hepatic pancreatic NET	Case reports	[169]
CD33	^{225}Ac-lintuzumab	AML	Phase I	[170]
CD33	^{225}Ac-lintuzumab	AML	Phase I	[171]
CD33	^{225}Ac-lintuzumab	AML	Phase II	[172]
NK-1R	^{225}Ac-DOTA-SP	Glioblastoma	Phase I	[173]

regarding ^{211}At-/^{225}Ac-based nuclear therapeutics.

^{211}At

^{211}At ions demonstrate a predisposition for accumulation in the thyroid gland. Despite their notable benefits in the treatment of thyroid cancer, thyroid blockers and local drug delivery are indispensable for the management of non-thyroid malignancies. A substantial risk of bias persists in ^{211}At-nuclear therapy even though tumor uptake is augmented and the survival period is prolonged.

[^{211}At]NaAt

The sodium/iodide symporter (NIS) is an integral membrane protein located on the basolateral side of thyroid cells that facilitates iodine assimilation and ^{211}At accumulation in a comparable fashion. As early as 1954, 8 patients, including 1 with papillary adenocarcinoma carrying cervical lymph node metastasis, were orally administered 1.85 MBq of ^{211}At [145]. The transfer of the *NIS* gene into cancer cells to augment the localization of [^{211}At]NaAt could offer a therapeutic modality for non-thyroid malignancies [123].

^{211}At-labeled human serum albumin microspheres

Doberenz *et al.* [146] reported a case of recurrent lingual carcinoma. The patient received an injection of 200 MBq of ^{211}At-labeled human serum albumin microspheres through the left lingual artery. The tumor tissue underwent necrosis within a few days, leading to substantial destruction of the tongue. Owing to the patient's death on day 43, no long-term clinical sequelae could be evaluated. We need additional cases for analysis.

^{211}At-ch81C6

Tenogenin is an extracellular matrix glycoprotein with a high expression in malignant glioma. The Ch81C6 mAb can specifically recognize and bind to tenogenin. Zalutsky *et al.* [147] administered 71–347 MBq of ^{211}At-ch81C6 to 19 patients with recurrent brain malignancies through surgically created resection cavities. One patient was excluded, 1 experienced quadrantal blindness, and the remaining subjects presented reversible mild adverse reactions. No dose-limiting toxicity was observed. The median overall survival was 52 weeks.

^{211}At-MX35 F(ab′)$_2$

Sodium-dependent phosphate transport protein 2b (NaPi 2b) is a target recognized by MX35 F(ab′)$_2$ and is detectable in more than 90% of human epithelial ovarian cancers. Andersson *et al.* [148] delivered 1 to 2 liters of ^{211}At-MX35 F(ab′)$_2$ at concentrations ranging from 20 to 215 MBq/L into the abdominal cavities of 12

patients with recurrent ovarian cancer via catheters. The pharmacokinetics and dosimetric results were related to the initial activity concentration (IC); the radioactive activity concentration decreased in the peritoneal fluid to 50% IC at 24 h and increased in the serum to 6% IC at 45 h, and the thyroid blocker significantly reduced enrichment in the thyroid. No dose-limiting toxicity was observed. During a long-term follow-up study [149], 4 patients survived for more than 6 years, including 1 who remained free of relapse. The median survival was 35 months, and the 10-year survival rate was 25%.

^{225}Ac

To identify appropriate chelating agents and targeted molecules, ^{225}Ac has undergone more clinical trials and case reports than ^{211}At. This accumulation of experience has exerted a crucial influence on the evolution and progress of ^{225}Ac-based nuclear therapy.

^{225}Ac-PSMA-617, ^{225}Ac-DOTA-J591, and ^{225}Ac-PSMA-I&T

PSMA-targeted nuclear therapy has emerged as a promising treatment option in clinical trials. A phase I trial of ^{225}Ac-macropa-pelgifatamab has been initiated (NCT06052306) [24]. Two patients with CRPC achieved complete remission after ^{225}Ac-PSMA-617 therapy (Figure 3I,J). Patient 1 received 3 cycles of 100 kBq/kg and an additional 6 MBq of ^{225}Ac-PSMA-617, and the PSA level decreased to less than 0.1 ng/mL. Patient 2 received 2 cycles of 7.4 GBq/cycle ^{177}Lu-PSMA-617; the PSA increased from 294 ng/mL to 419 ng/mL and then changed to 2 + 1 cycle of 100 kBq/kg ^{225}Ac-PSMA-617, and the PSA decreased below 0.1 ng/mL [66]. In another trial [150], 14 patients with advanced CRPC who had undergone prior treatments received ^{225}Ac-PSMA-617 at 50–200 kBq/kg, and 8/14 had a second cycle of the same or reduced radioactivity at 2-/4-month intervals. Notably, severe xerostomia was observed when doses exceeded 100 kBq/kg, while lower doses were devoid of toxicity but yielded inadequate anti-tumor responses. Then, 40 patients with highly advanced mCRPC received 3 cycles (2 months/cycle) of therapy with 100 kBq/kg/cycle ^{225}Ac-PSMA-617 [151]. Two patients passed away before receiving the second cycle. Among the remaining patients, 63% had a more than 50% decrease in PSA. The median tumor control duration was 9.0 months, which was the longest among the current treatments. Similarly, Sathekge *et al.* [152] treated 17 patients with non-previous chemotherapy. The initial dose was 8 MBq, which was then reduced to 7, 6, or 4 MBq in good-response patients (2 months/cycle). PSA declined by more than 90% in 14 patients, 7 in 14 patients had undetectable PSA in the serum, and 11 patients experienced complete regression of all metastases. The comprehensive clinical data of 201 patients with ^{225}Ac-PSMA-617 treatment revealed that 66.1% had a decrease in PSA of more than 50%, and the familiar side effects were xerostomia and anemia [153].

^{225}Ac-DOTA-J591 and ^{225}Ac-PSMA-I&T are emerging PSMA-targeted radiopharmaceuticals. Scott *et al.* [154] examined ^{225}Ac-DOTA-J591 in 22 patients with progressive CRPC; PSA decreased by more than 50% in 9 patients, pain symptoms were present in 11 patients, and 6 patients suffered from xerostomia. Zacherl *et al.* [155] investigated the data of 14 patients with advanced CRPC treated with ^{225}Ac-PSMA-I&T, and the results were highly comparable with those of ^{225}Ac-PSMA-617.

^{225}Ac-DOTATOC and ^{225}Ac-DOTATATE

Compared with octreotide, [Tyr^3]-octreotide has a stronger targeting affinity for SSTRs. The synthesis of ^{225}Ac-DOTATOC, which couples [Tyr^3]-octreotide with ^{225}Ac via DOTA, was administered to 34 patients in 46 cycles [156]. The maximum tolerated dose is 40 MBq. A two-year follow-up of 17 patients revealed no apparent chronic renal toxicity. Zhang *et al.* [159] reported a rare and aggressive case of thymic NETs in which the patient showed significant improvement, without any adverse reactions during treatment or follow-up. DOTATOC can be changed to DOTATATE by using natural Thr to replace the alcohol Thr (ol) at the C-terminus of DOTATOC. ^{225}Ac-DOTATATE was tested by Ballal *et al.* [164] in 91 patients with gastroenteropancreatic neuroendocrine tumors for 453 cycles. The long-term follow-up resulted in a significant prolongation of the median survival time. Among the 79 patients with evaluable disease, 2 patients achieved a complete response, and 38 patients achieved a partial response. Treatment was favorable for patients who were refractory to previous ^{177}Lu-DOTATATE therapy.

^{225}Ac-lintuzumab

Joseph *et al.* [170] conducted a study combining ^{225}Ac-lintuzumab with low-dose cytarabine (LDAC) and reported that a fractionated dose of ^{225}Ac-linutuzumab can be safely administered in combination with LDAC to improve the status of elderly patients with untreated AML. In another trial, 18 patients with relapsed or refractory AML were administered with a single infusion of ^{225}Ac-lintuzumab [171], with radioactivity ranging from 18.5 to 148 kBq/kg. The maximum tolerated dose was 111 kBq/kg, while myelosuppression was the most common side effect. In 10 of the 16 evaluable patients, original peripheral blood cells were eliminated at a dose of 37 kBq/kg. Forty patients participated in a phase II trial [172], 9 patients achieved a complete response, and myelosuppression was observed in all patients.

^{225}Ac-DOTA-SP

Neurokinin-1 receptor (NK-1R), with Substance P (SP) as its ligand, is highly expressed in glioblastomas. ^{225}Ac-DOTA-SP has shown therapeutic efficacy. Twenty-one patients diagnosed with glioblastoma received treatment every 2 months via intracavicular catheter administration at doses of 10, 20, and 30 MBq/cycle. Minor and temporary adverse reactions were primarily observed at the highest dose, and no significant hematological, renal, or hepatic toxicity was detected [173].

Outlooks

This article focuses on the advancement of ^{211}At-/^{225}Ac-radiopharmaceuticals for the treatment of biological entities, with an emphasis on optimizing the targeting accuracy, stability, and efficacy and minimizing toxicity. ^{211}At and ^{225}Ac have garnered significant interest in TAT because of their unparalleled physical, chemical, and biological attributes. Although radiopharmaceuticals possess excellent functionality, there are still numerous challenges, including instability and potential toxicity of radiopharmaceuticals, and supply shortage of nuclides. Advancements in accelerator technology and refinements in manufacturing approaches are anticipated to progressively alleviate the supply predicament.

The half-lives of nuclides need to correspond to the pharmacokinetic half-life of the carrier so that the carrier molecules persist within the tumor for an adequate duration to allow the radionuclides to decay completely and release lethal doses of radiation. Furthermore, the development of superior chelators, antibodies, and small molecule inhibitors is crucial in enhancing the *in vivo* stability of radiopharmaceuticals and increasing their accumulation in tumors. SAPS, B10, DOTA, their derivatives and several novel

chelators are being employed for labeling ^{211}At and ^{225}Ac. Takashima *et al.* [174] reported that sodium ascorbate could increase the *in vivo* stability of ^{211}At-trastuzumab. When L-tyrosine was integrated with neopentyl glycol (NpG), ^{211}At-NpGT showed promising efficacy in a C6 glioma cell mouse model [90]. H_2BZmacropa-NCS could optimize the binding of ^{225}Ac to cotrastuzumab [99]. Recently, Cui *et al.* [74] developed a FAP-targeted covalent radioligand based on the principles of covalent drug theory, which can alleviate reversible interactions between ligands and targets, offering a novel approach to enhancing *in vivo* stability and optimizing tumor uptake.

The potential detrimental effects of radiopharmaceuticals on normal tissues should not be ignored. Pretargeted radioimmunotherapy (PRIT) has emerged as a productive strategy for enhancing clearance and diminishing non-specific toxicity. This therapeutic approach has been corroborated through clinical trial outcomes involving ^{131}I-labeled anti-CEA and anti-diethylenetriaminepentaacetic acid (DPTA) bispecific antibodies in patients with medullary thyroid cancer [175], as well as the trispecific antibodies TF2 and ^{177}Lu-IMP-288 in patients with metastatic colorectal cancer [176]. Cheal *et al.* [63] combined C825 with anti-HER2, huA33, and hu3F8 antibodies and labeled ^{225}Ac via proteus-DOTA (Pr), which increased the survival rates and therapeutic benefits in mouse models harboring breast cancer, colorectal cancer, and glioma. Furthermore, a HER2-targeted ^{225}Ac-PRIT has been validated to improve therapeutic efficacy and mitigate toxicity in epithelial ovarian cancer mouse models [64].

Moreover, nanomaterials and liposomes serve as strategic tools for enhancing the *in vivo* stability and targeting efficacy of radioisotopes. Nanocarriers have high specific surface areas to stow diverse targeting ligands and therapeutic radioisotopes. In addition, size and surface modifications can enhance tumor retention and optimize pharmacokinetic profiles. Gold nanoparticles (AuNPs) are extensively studied; they lack inherent targets and are typically administered via intratumoral injection (*e.g.*, ^{211}At-GNS [177], ^{211}At-AuNPs@mPEG [111] and ^{225}Ac-Au@TADOTAGA [178]). However, $\{La_{0.5}Gd_{0.5}\}(^{225}Ac)PO_4$@4GdPO$_4$shell@AuNPs-dPEG-mAb 210b [93] was engineered to bind with thrombomodulin on lung endothelial cells, yielding favorable results in a mouse model of EMT-6 cell lung cancer. Other inorganic nanocarriers, such as Fe_3O_4 [54] and SiO_2 [82], are also being actively explored as preclinical drugs. Given the limited biodegradability and potential biotoxicity of inorganic nanocarriers, biodegradable organic nanocarriers represent promising alternatives. For example, ^{211}At-MeATE-SPN-GIP [114] targets glucose-dependent insulinotropic polypeptide receptors, has an ideal radiochemical yield and purity, and has high tumor uptake and retention in mouse models of CFPAC-1 cells in pancreatic cancer. Liposomes, as effective encapsulation vehicles, have been employed in drug delivery systems to mitigate the off-target effects of nuclide decay. However, few relevant studies exist. Sofou *et al.* [179] synthesized ^{225}Ac-coated pegylated phosphatidylcholine-cholesterol liposomes and reported that giant liposomes (650 nm) had better nuclide retention.

In addition to their ability to treat tumors, radiopharmaceuticals have also achieved excellent results in nonneoplastic diseases. Jiang *et al.* [180] designed and synthesized 28 kinds of ^{18}F-radiopharmaceuticals that target sphingosine-1-phosphate receptor 1 (S1PR1) for PET images in brain diseases, some of which might hold potential for further study. CD25-targeted ^{211}At-HATs extended the lifespan in heart transplant cynophagous monkey model. And ^{211}At-B10-CA12.10C12, which targets CD45, in combination with whole-body irradiation, successfully abrogated transplant rejection in presensitized canine recipients who had received donor blood transfusions, which potentially represents a groundbreaking strategy for countering transplant rejection in patients subjected to substantial blood transfusions [40]. Furthermore, Emily *et al.* [181] developed and synthesized a novel benzopyrrole derivative that targets amyloid aggregation, which demonstrated robust stability following labeling with ^{211}At (3′-^{211}At-PIB-OMe). Despite the lack of comprehensive biological validation, this study offers a novel perspective for advancing ^{211}At-based therapies for the treatment of Alzheimer's disease.

Despite the increasing diversity and volume of radiopharmaceuticals, substantial impediments have been encountered in the clinic. The integration of numerous disciplines, including radiochemistry, nuclear medicine, oncology, and materials science, is imperative to catalyze the advancement of radiopharmaceuticals. The evolution and translation of radionuclide therapeutics are poised to increase the precision of diagnosis and treatment.

Funding

This work was supported by the grants from the Natural Science Foundation of Gansu Province (Nos. 23JRRA569 and 21JR7RA106), the National Natural Science Foundation of China (No. 12065001), the West Light Foundation of the Chinese Academy of Sciences (No. xbzg-zdsys-201920), the Key Deployment Project of Chinese Academy of Sciences (No. KFZD-SW-222), and the Science and Technology Plan Project of Chengguan District (No. 2022SHFZ0020).

Conflict of Interest

The authors declare that they have no conflict of interest.

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