

From targeted delivery to precision strike: The next-generation innovative radiopharmaceuticals for cancer theranostics

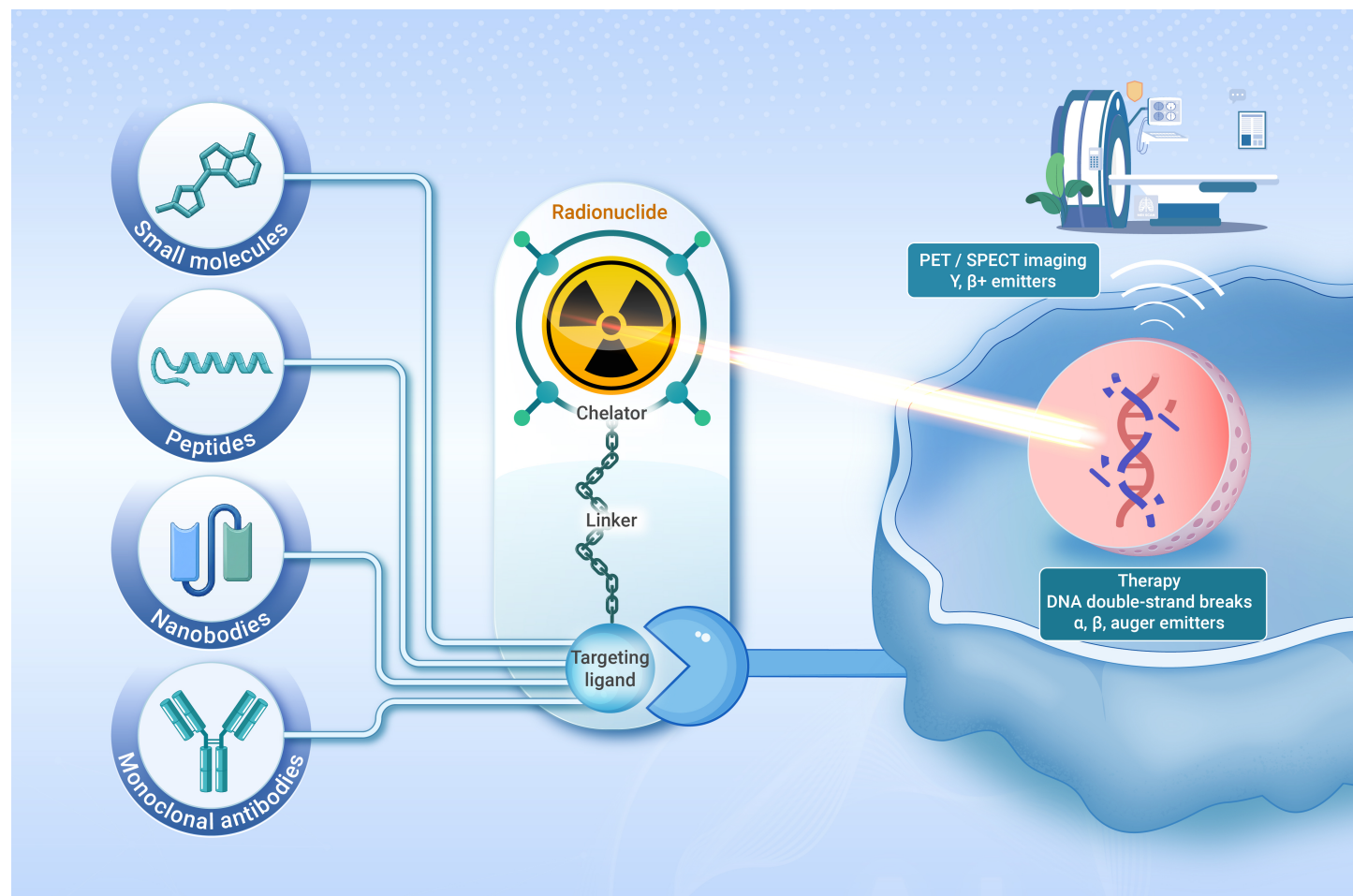
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Radiopharmaceuticals combine tumor-targeting molecules with radiation to image and treat cancer in one step.
- The field is moving from β emitters to potent, precise α emitters.
- Artificial intelligence (AI) and imaging analytics enable personalized, image-guided radiation dosing.
- Wider access now hinges on secure isotope supply chains and coordinated regional production networks.

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This review provides a comprehensive analysis of the evolution of radiopharmaceuticals, tracing their development from fundamental physical chemistry to the global industrial chain. First, the article elucidates the central role of radionuclide decay physics in diagnostic and therapeutic applications, while discussing the decisive impact of coordination chemistry and chelator selection on in vivo stability. Regarding drug design, it analyzes the evolution of targeting vehicles from rapid diffusion small molecules to long-circulating monoclonal antibodies, and the optimization of pharmacokinetics via linkers that modulate polarity. The review further surveys a diverse target landscape, exploring the biological mechanisms of bystander and abscopal effects in overcoming tumor heterogeneity. It emphasizes the critical value of artificial intelligence (AI) and radiomics in achieving personalized biological effective dose predictions. Finally, the article dissects the clinical regulatory frameworks for radiation protection, analyses the challenges of the global nuclide supply chain, and gives a comparative perspective in regional ecosystems.

INTRODUCTION

The landscape of oncology and molecular imaging is undergoing a seismic shift, transitioning from the broad-spectrum approaches of the 20th century toward an era of hyper-individualized precision strikes.^{1,2} At the heart of this revolution lies the field of radiopharmaceuticals that combine the biological specificity of molecular targeting with the physical potency of ionizing radiation. Once confined to nuclear medicine departments at the margins of mainstream oncology, these agents have moved to the center stage of modern pharmacology. The evolution from basic targeted delivery to the sophisticated, integrated paradigm of theranostic represents one of the most significant leaps in clinical medicine, offering a dual-edged sword capable of both visualizing and annihilating disease at the cellular level (Figure 1A).³⁻⁵

For decades, radiopharmaceuticals were primarily synonymous with diagnostic imaging. The introduction of [^{99m}Tc] revolutionized non-invasive visualization, allowing clinicians to map organ function and detect abnormalities with unprecedented clarity.⁶ However, these early tracers were often physiological mimics such as ¹³¹I for thyroid function, rather than engineered molecular hunters. The true paradigm shift began when the focus shifted from metabolic pathways to specific molecular markers.^{4,7} The realization that tumors overexpress distinct cell-surface targets, G-protein-coupled receptors such as the somatostatin receptor (SSTR) in neuroendocrine tumors, or the membrane-bound enzyme prostate-specific membrane antigen (PSMA, glutamate carboxypeptidase II) in prostate cancer, provided the biological zip codes necessary for targeted delivery.^{8,9} This birthed the concept of the magic bullet, a term coined by Paul Ehrlich over a century ago, now finally realized through the marriage of radiochemistry and molecular biology (Figure 1B).¹⁰

Modern radiopharmaceuticals are sophisticated tripartite constructs. At the front end is the targeting ligand which can be a small molecule, a monoclonal antibody, or a peptide, designed to dock with high affinity into a specific biological target.^{3,11} In the middle is the linker, an often-underestimated structural component that must ensure the radioactive payload does not interfere

with the ligand's binding affinity while remaining stable in the complex environment of the human bloodstream. Finally, there is the radionuclide payload with chelator.¹² This is where the transition from targeted delivery to precision strike is most evident. The industry has moved beyond simple β emitters like ¹⁷⁷Lu toward highly potent α emitters like ²²⁵Ac. α particles possess a much higher Linear Energy Transfer (LET), delivering a massive amount of energy over a very short distance.² In principle, this confines the cytotoxic effect to the targeted cell and its immediate microenvironment, sparing the surrounding healthy tissue, which is a clinical goal that traditional external beam radiation struggles to achieve.¹³

Building on this concept, we define the next generation radiopharmaceuticals as agents that depart from the conventional [^{99m}Tc]- and [¹⁸F]- based diagnostic paradigm, and the first generation [¹³¹I]NaI and [¹⁷⁷Lu]Lu-DOTATATE therapeutic paradigm, along four converging axes of innovation. First, at the level of the radioactive payload, the field is transitioning from medium range β^- emitters toward high-LET α emitters such as ²²⁵Ac, ²¹²Pb, and ²¹¹At, and toward Auger electron emitters whose subcellular range demands precise nuclear localization but offers unmatched single cell selectivity. Second, at the level of molecular architecture, the simple chelator-linker-vehicle scaffold is being superseded by programmable platforms. These include pretargeting systems, which temporally decouple the slow biodistribution of a targeting vector from the rapid delivery and clearance of the radionuclide via bioorthogonal ligation in vivo; covalent binders, which convert reversible recognition into irreversible target engagement through proximity-induced bond formation; and click-compatible chelator modules, which integrate radiolabeling, in vivo capture, and pharmacokinetic tuning into a single chemical handle. Third, at the level of biological recognition, the target landscape is expanding beyond the saturated PSMA and SSTR axes into the tumor microenvironment, most notably FAP positive cancer associated fibroblasts and into dual-targeting and multivalent constructs that engage two receptor populations simultaneously to address antigen heterogeneity and emergent resistance. Fourth, at the level of clinical implementation, the shift from fixed-activity prescribing toward personalized, voxel-level dosimetry, enabled by quantitative SPECT/PET and Monte Carlo dose calculation, is being accelerated by artificial intelligence and radiomics, which are beginning to automate organ segmentation and, in early studies, to predict tumor and organ-at-risk absorbed doses from pre-therapy diagnostic imaging. These four axes, new radionuclides, new architectures, new targets, and new computational tools, which together define what we term the next generation of radiopharmaceuticals, and they organize the remainder of this review.

THE PHYSICAL AND CHEMICAL FOUNDATION

Physics of decay: selecting the optimal nuclide

The International Commission on Radiological Protection (ICRP) compilation of radionuclides lists about 1200 radionuclides, but only a smaller subset has been employed long term in clinical practice and biomedical research.^{14,15} Radionuclides vary significantly in their physicochemical properties, such as half-life, decay mode, emission energy and others. Of these basic physical characteristics, the most important factor determining whether a radionu-

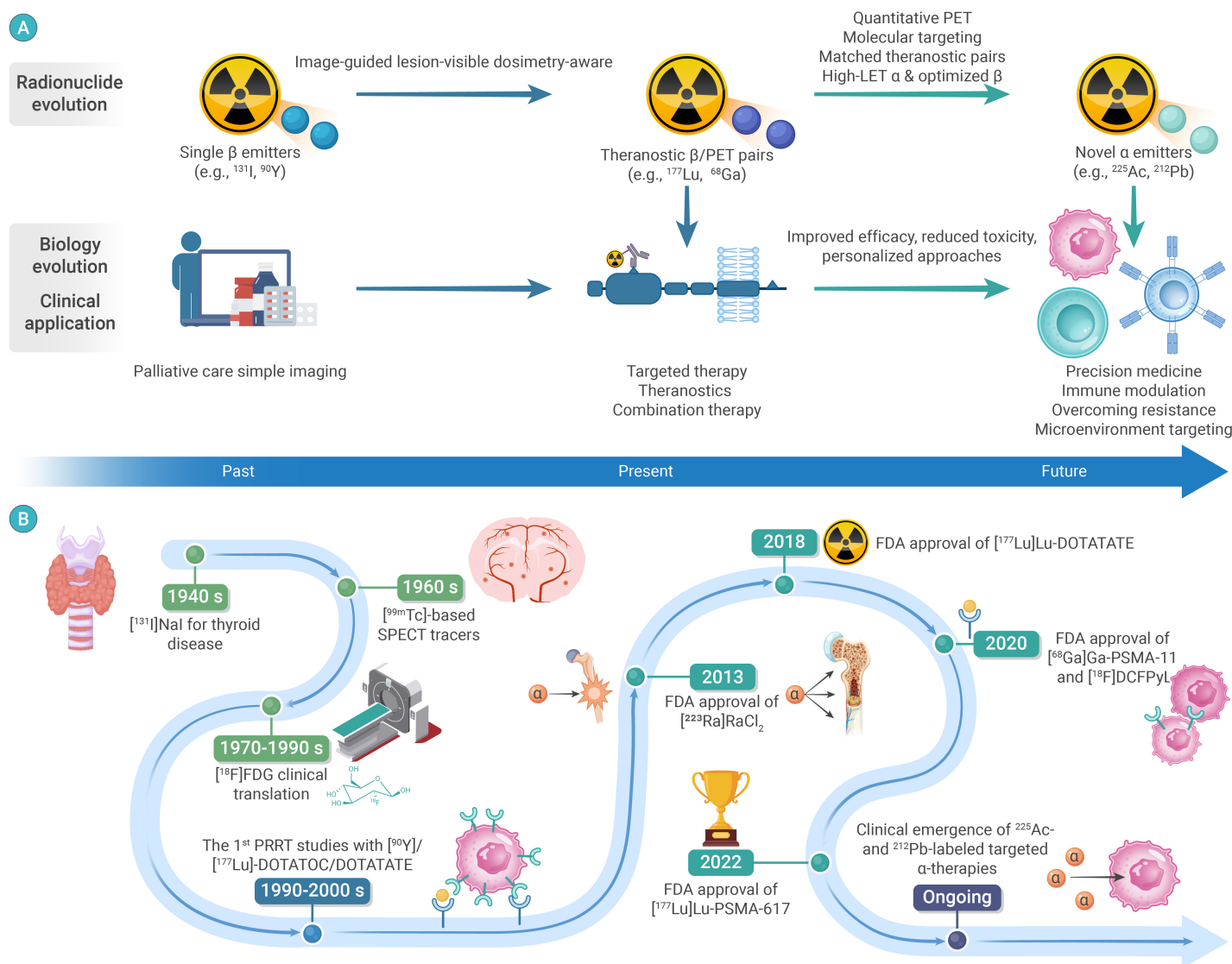


Figure 1. The historical and projected evolution of nuclear medicine

clide is used in nuclear medicine as a diagnostic probe or therapeutic payload is decay physics.^{16–18} Hence, radionuclides are typically classified according to their decay mode into positron emitters, γ emitters, α emitters, β emitters and Auger electron emitters (Figure 2, Table 1).¹⁹ These categories describe the dominant emission relevant to imaging vs therapy, not exclusive decay modes, would preempt referee criticism.

γ emitters and positron emitters. When the nuclei of γ emitters return from the excited state to the ground state, they release the excess energy in the form of γ photons. This process is called γ decay (Figure 2A). The energy of γ photons is moderate, with strong penetrating power, which is sufficient to escape the body. At the same time, its ionization effect is relatively weak, causing minimal damage to the organism. This characteristic makes it an ideal choice for single-photon emission computed tomography (SPECT) imaging, enabling precise localization of lesions, assessment of organ functions, and tracking of drug bio-distribution. Represented by $^{99\text{m}}\text{Tc}$, its physical half life of approximately 6 hours and γ energy of approximately 140 keV are highly compatible with the clinical examination time window and the SPECT detection efficiency.²⁰ γ emission in the clinical nuclear medicine context typically arises from isomeric transition of metastable states rather than from a primary decay mode per se. Noted that many clinically relevant radionuclides exhibit multi-step decay chains in which each daughter contributes distinct LET and range characteristics, with implications for dosimetry and daughter-redistribution effects. Therefore, it has long dominated nuclear medicine

diagnosis. Other commonly used single photon radionuclides include ^{111}In , ^{123}I , ^{67}Ga and others.

Notably, although positron emitters release positrons during decay, these positrons migrate a very short distance within the tissue before undergoing annihilation with surrounding electrons, emitting a pair of γ photons with an energy of 511 keV each, which are emitted in opposite directions. Positron emission tomography (PET) equipment captures these correlated photons to enhance signal-to-noise ratios and data accuracy (Figure 2A). This setup allows for both lesion detection and the precise measurement of metabolic activity or target expression.²¹ Commonly used positron emitters include ^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{68}Ga , ^{64}Cu , ^{89}Zr and so on. Cyclotron production from liquid or solid ^{68}Zn targets has become increasingly important for large-scale, centralized supply of ^{68}Ga Ga-radiopharmaceuticals, complementing the traditional $^{68}\text{Ge}/^{68}\text{Ga}$ generator workflow. In recent years, various PET radiopharmaceuticals based on ^{18}F , ^{68}Ga , and ^{64}Cu have achieved clinical translation and been approved for market launch on key tumor targets.^{22–25} For example, ^{18}F piflufolastat promotes the clinical application of PSMA PET in prostate cancer,²⁶ while ^{64}Cu DOTATATE expands the options for SSTR imaging and demonstrates the advantages of longer half-life nuclides in imaging time windows and logistics.^{27,28}

β emitters. β decay involves interconversion between neutrons and protons within the nucleus with the concomitant emission of a β particle (Figure 2B). Given that β^+ emitters are primarily leveraged for PET imaging,

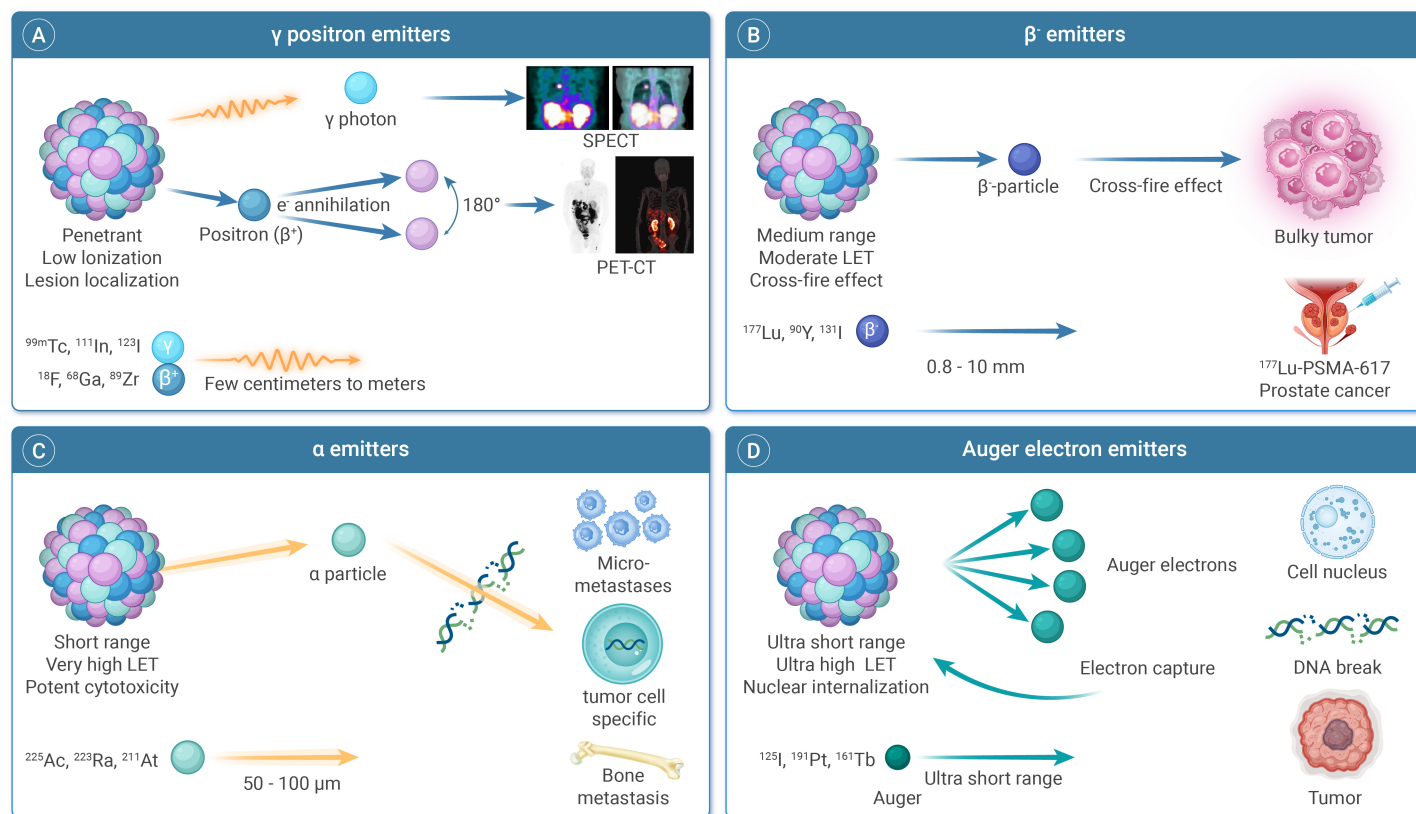


Figure 2. A simplified schematic intended to illustrate the category and characterization of nuclides

therapeutic applications focus predominantly on β^- emitters. The defining physical advantage of β^- particles is their millimeter-scale tissue range coupled with intermediate ionization density and LET.²⁹ This combination enables not only energy deposition within targeted cells but, critically, a crossfire effect that extends cytotoxic dose beyond the cells directly bound by the radiopharmaceutical. Consequently, in bulky or multifocal disease, β^- therapy can partially compensate for non-uniform intratumoral distribution or antigen loss by irradiating and killing neighboring, non drug bound tumor cells, which is an important physical basis for mitigating treatment resistance driven by tumor heterogeneity and hypoperfused regions.^{30,31}

Currently, ^{177}Lu is the most widely used β^- emitter in clinical applications.^{32,33} Its half life matches well with the *in vivo* pharmacokinetics of peptide and small molecule targeting ligands, and the decay process was accompanied by γ rays that can be used for SPECT imaging enables integrated diagnosis and treatment. In 2022, the FDA approved [^{177}Lu]Lu-PSMA-617 for the treatment of PSMA positive metastatic castration-resistant prostate cancer (mCRPC) patients.³⁴ This therapy locates through targeting PSMA and introduces the radionuclide into tumor cells. In clinical trials, the median survival time of the treatment group was 4 months longer than that of the control group.³⁵ Besides ^{177}Lu , commonly used β^- emitters include ^{90}Y and ^{131}I . The former is suitable for the treatment of bulky tumors due to its higher energy and longer range, while the latter has a mature and irreplaceable clinical position in the treatment of thyroid cancer.^{36,37}

α emitters. Although β^- emitters are often effective for bulky disease, their relatively long particle range can disperse energy deposition within tissue, which may limit therapeutic efficiency. α emitters address this limitation. α decay, common in heavy nuclei, releases the α particle characterized by high mass and double positive charge (Figure 2C). In sharp contrast to β^- particles, α particles traverse only a few cell diameters in tissue yet exhibit very high LET.¹⁷

This high LET can directly cause irreparable DNA double-strand breaks in the target cells. This lethal damage has extremely high cytotoxicity and is relatively independent of the cell cycle or the oxygenation status of the tissue. At the same time, its micrometer level precise range ensures that almost all

the energy is deposited in the target area, maximizing the protection of the surrounding healthy tissues.³⁸ Therefore, α emitters are regarded as a beneficial weapon for eliminating small residual lesions, circulating tumor cells, and infiltration of the bone marrow microenvironment.³⁹

In terms of clinical application, [^{223}Ra]RaCl₂ is the first α emitter drug that has revolutionized clinical practice. As a calcium analogue, it can precisely accumulate in areas with active bone metabolism, significantly prolonging the survival period of prostate cancer patients with bone metastasis.³⁴ ^{225}Ac , ^{212}Pb , and ^{211}At , which are α emitters commonly used in targeted radiotherapy, are also leading the new wave of research and development.⁴⁰ Particularly, the [^{225}Ac]Ac-PSMA therapy has demonstrated remarkable efficacy in multiple early clinical studies and is regarded as the next-generation blockbuster radiopharmaceuticals following ^{177}Lu .^{41,42} Although it has great potential, the availability of α emitters and the safety of the treatment remain key factors limiting its wide application. The focus of future research will be on establishing a stable radionuclide production supply chain and developing new chelators and nanocarrier technologies to fully release the clinical efficacy of a therapy while ensuring safety.^{39,43,44}

Auger electrons. Auger electron emitters are often regarded as the third class of therapeutic radionuclides.⁴⁵ They undergo electron capture or internal conversion, generating cascades that emit Auger electrons or conversion electrons (Figure 2D). These electrons have an ultrashort path length, typically on the order of 10 nm, such that their effective range is often smaller than a single cell diameter. Consequently, meaningful cytotoxicity is highly contingent on subcellular localization. Auger electrons can efficiently induce DNA strand damage only when the radiopharmaceutical is internalized and trafficked to the perinuclear or nuclear vicinity.⁴⁶ Compared with β^- emitters, Auger emitters can substantially reduce nonspecific irradiation of surrounding healthy tissue. And compared with α emitters, they may bypass some of the practical challenges associated with chelation stability and control of radioactive decay products. However, these potential advantages come at a cost, carrier molecules must achieve efficient cellular internalization and nuclear trafficking, imposing stringent requirements on ligand design and intracellular delivery strategies.^{16,18,47}

Table 1. Radionuclide properties

Type	Radionuclide	Half-life	Application	Production	Representative radiopharmaceutical
Positron Emitters (β^+ particle)	^{11}C	20.36 min	PET	Accelerator	$[^{11}\text{C}]\text{PiB}$ ⁵²
	^{13}N	9.97 min	PET	Accelerator	$[^{13}\text{N}]\text{Ammonia}$ ⁵³
	^{15}O	2.13 min	PET	Accelerator	$[^{15}\text{O}]\text{H}_2\text{O}$ ⁵⁴
	^{18}F	109.77 min	PET	Accelerator	$[^{18}\text{F}]\text{FDG}$ ⁵⁵
	^{64}Cu	12.70 h	PET, Therapy	Accelerator	$[^{64}\text{Cu}]\text{Cu-ATSM}$ ⁵⁶
	^{68}Ga	67.71 min	PET	Generator/ Accelerator	$[^{68}\text{Ga}]\text{Ga-DOTATATE}$ ⁵⁷
	^{82}Rb	1.26 min	PET	Generator	$[^{82}\text{Rb}]\text{Rb-rubidium chloride}$ ⁵⁸
	^{89}Zr	78.41 h	PET	Accelerator	$[^{89}\text{Zr}]\text{Zr-trastuzumab}$ ⁵⁹
γ Emitters (γ photons)	^{124}I	4.17 d	PET	Accelerator	$[^{124}\text{I}]\text{NaI}$ ⁶⁰
	^{67}Ga	3.26 d	SPECT, therapy	Accelerator	$[^{67}\text{Ga}]\text{Ga-citrate}$ ⁶¹
	$^{99\text{m}}\text{Tc}$	6.00 h	SPECT	Generator	$[^{99\text{m}}\text{Tc}]\text{Tc-tilmanocept}$ ⁶²
	^{111}In	2.89 d	SPECT, therapy	Accelerator	$[^{111}\text{In}]\text{In-oxine}$ ⁶³
β Emitters (β^- particle)	^{123}I	13.22 h	SPECT	Accelerator	$[^{123}\text{I}]\text{ioflupane}$ ⁶⁴
	^{32}P	14.27 d	Therapy	Reactor	$[^{32}\text{P}]\text{chromic phosphate}$ ⁶⁵
	^{47}Sc	3.35 d	SPECT, therapy	Accelerator	$[^{47}\text{Sc}]\text{Sc-PSMA-617}$ ⁶⁶
	^{67}Cu	61.83 h	SPECT, therapy	Accelerator	$[^{67}\text{Cu}]\text{Cu-SARTATE}$ ⁶⁷
	^{90}Y	64.05 h	Therapy	Generator	$[^{90}\text{Y}]\text{Y-microspheres}$ ⁶⁸
	^{153}Sm	46.28 h	SPECT, therapy	Reactor	$[^{153}\text{Sm}]\text{Sm-EDTMP}$ ⁶⁹
	^{131}I	8.03 d	SPECT, therapy	Reactor	$[^{131}\text{I}]\text{MIBG}$
	^{166}Ho	26.82 h	SPECT, therapy	Reactor	$[^{166}\text{Ho}]\text{Ho-microspheres}$ ⁷⁰
	^{177}Lu	6.65 d	SPECT, therapy	Reactor	$[^{177}\text{Lu}]\text{Lu-PSMA-617}$ ³⁵
	^{186}Re	3.72 d	Therapy	Reactor	$[^{186}\text{Re}]\text{Re-HEDP}$ ⁷¹
α Emitters (α particle)	^{188}Re	17.00 h	SPECT, therapy	Generator	$[^{188}\text{Re}]\text{Re-SSS-lipiodol}$ ⁷²
	^{211}At	7.21 h	Therapy	Accelerator	$[^{211}\text{At}]\text{NaAt}$ ⁷³
	^{212}Pb	10.60 h	Therapy	Generator	$[^{212}\text{Pb}]\text{Pb-DOTAMTATE}$ ⁸
	^{212}Bi	60.00 min	Therapy	Generator	$[^{212}\text{Bi}]\text{Bi-MAA}$ ⁷⁴
	^{213}Bi	45.59 min	Therapy	Generator	$[^{213}\text{Bi}]\text{Bi-DOTATOC}$ ⁷⁵
	^{223}Ra	11.43 d	Therapy	Generator	$[^{223}\text{Ra}]\text{RaCl}_2$ ⁷⁶
	^{225}Ac	9.92 d	Therapy	Generator/ Accelerator	$[^{225}\text{Ac}]\text{Ac-lintuzumab}$ ⁷⁷
Auger Electron Emitters	^{227}Th	18.70 d	Therapy	Generator	$[^{227}\text{Th}]\text{Th-MSLN-TTC}$ ⁷⁸
	^{77}Br	57.04 h	Therapy	Accelerator	$[^{77}\text{Br}]\text{BrUdR}$ ¹⁸
	^{125}I	59.41 d	Therapy	Reactor	$[^{125}\text{I}]\text{IUdR}$ ¹⁸
	^{191}Pt	2.83 d	Therapy	Reactor	$[^{191}\text{Pt}]\text{cisplatin}$ ⁷⁹

Although auger electron emitters have great potential in the development of targeted radiopharmaceuticals, no promising candidate compounds with good therapeutic efficacy have emerged yet. The targeted radiopharmaceutical $[^{125}\text{I}]\text{I-mAb 425}$, developed by Bender et al., based on Epidermal Growth Factor Receptor (EGFR) monoclonal antibody, has entered the latest phase II clinical trial (NCT01317888) for the treatment of glioblastoma.⁴⁸ Emrich et al. found that using $[^{125}\text{I}]\text{I-mAb 425}$ in combination with surgery and traditional radiotherapy can significantly improve the median survival time of patients with glioma.⁴⁹ Additionally, $[^{125}\text{I}]\text{IUdR}$ has also been proven to have good targeting properties for colorectal cancer, but its clinical application is still limited by the relatively long half-life of ^{125}I (59.4 days).⁵⁰ Besides ^{125}I , ^{77}Br , ^{111}In and ^{191}Pt are also radionuclides with potential for drug development that emit Auger electrons. Recently, Obata et al. reported a series of ^{191}Pt -labeled trithiol-

hoecht-PSMA conjugates and observed evidence of DNA binding in PSMA-positive tumors.⁵¹ In conclusion, no Auger electron therapies have yet achieved widespread regulatory approval or definitive late stage clinical efficacy. Therefore, the stable labeling of such radionuclides and the development of targeted ligands will become the focus of future research on new targeted radiopharmaceuticals.

Coordination chemistry

Radiometal nuclides need to be stably complexed by bifunctional chelators (BFCs) to evolve from radiation sources into clinically reliable diagnostic and therapeutic agents. If chelation does not suffice, the radiometal nuclides can dechelate and redistribute *in vivo* as a free species to bystander organs leading to unwanted off-target toxicity, ultimately leaving behind degraded

signal-to-noise performance. Thus, coordination chemistry is more than just a technical linkage between radionuclides and targeting vehicles. It is an intrinsic factor that dictates *in vivo* biodistribution and ultimately clinical success.^{80,81}

The framework for evaluating chelator–radionuclide compatibility.

Establishing a scientific evaluation system for chelators is a prerequisite for promoting the clinical application of radiometal nuclides. To determine whether a chelator is suitable for a specific radionuclide, it is not sufficient to rely solely on a single thermodynamic constant. Instead, a comprehensive consideration of the feasibility of radiolabeling, the stability mechanism of the *in vivo* complex, and the overall regulatory effect on the pharmacokinetics of the drug should be taken into account.^{80–82}

In clinical production, an ideal chelation system should possess rapid complexation kinetics and mild reaction conditions. This is not only crucial for matching the time window of short half-life radionuclides, but also a necessary condition to prevent the inactivation of heat-sensitive vehicles such as antibodies. Moreover, whether high molar activity labeling can be achieved at low ligand concentrations will directly affect the imaging sensitivity and therapeutic efficacy of the drug in tumors with low expression of the target.¹⁷

Stability assessment must further distinguish thermodynamic stability from kinetic inertness. Thermodynamic stability constants describe binding at equilibrium and provide a baseline for resisting competition from abundant endogenous metal ions (such as Zn^{2+} and Cu^{2+}). However, because biological systems are open and inherently non-equilibrium, nuclear medicine places greater emphasis on kinetic inertness, which means the ability of a complex to resist dissociation under physiologically relevant, non-equilibrium conditions. Only chelation motifs with high kinetic inertness can effectively suppress *in vivo* dechelation and off-target accumulation of radiometal nuclides.⁸³

Finally, chelators are not merely inert connecting components. Their introduction significantly alters the charge, hydrophobicity, and other properties of the vehicles, thereby exerting a notable impact on pharmacokinetics. An optimized chelation strategy must ensure the stability of the connection while optimizing the excretion pathway by regulating the physicochemical properties of the vehicles. For instance, it can promote renal clearance and reduce hepatic and biliary uptake, thereby maximizing the signal-to-noise ratio between the tumor and the background tissues (Figure 3).^{84,85}

Macrocyclic chelators. Macrocyclic chelators, with their highly rigid cyclic pre-organized structure, can firmly lock the radiometal radionuclides. These chelators usually have extremely high thermodynamic stability and kinetic inertness and are not prone to metal exchange or de-chelation in the body. For this reason, the macrocyclic system is often regarded as the preferred choice for long half-life radionuclides or highly toxic therapeutic radionuclides, in order to minimize the risk of nuclide loss during the longer in-body circulation process.⁸⁶

These benefits are offset by practical limitations. For many macrocyclic chelators, efficient radiolabeling typically requires more forcing conditions, most commonly heating or extended reaction times, to drive complexation to completion. This can be difficult to reconcile with heat-labile biomacromolecules such as antibodies.⁸⁷ Among macrocycles, DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) remains a benchmark scaffold and one of the most widely used chelators. It supports labeling with a range of metallic radionuclides, including ^{177}Lu and has enabled the clinical translation of agents such as [^{177}Lu]Lu-DOTATATE.⁸⁸

More broadly, the field has been shifting from a singular emphasis on stability toward a more pragmatic triad in which stability, labeling kinetics, and bifunctional translatability must be satisfied simultaneously. This trend is particularly evident for the highly promising α emitter ^{225}Ac . Owing to its larger ionic radius and high coordination requirements, conventional DOTA struggles to achieve efficient complexation at room temperature. In response, Macropa developed by Thiele and colleagues, with an expanded cavity and a highly preorganized coordination environment, enables rapid quantitative ^{225}Ac labeling at room temperature while maintaining excellent serum stability, thereby mitigating the sensitivity of antibody conjugates to heating and the associated risk of thermal denaturation.^{89,90} In addition, newer PYTA derivatives, rigid ligands built on a pyridine scaffold, exhibit favorable complexation kinetics and further expand the macrocyclic chelator toolbox

available for α -therapy.⁹¹ In copper radiochemistry, more rigid macrocycles such as cross-bridged cyclams have likewise been used to improve labeling efficiency under mild conditions while preserving *in vivo* inertness.⁹² Collectively, the next generation macrocyclic chelators are being advanced through engineering of preorganization and pendant-arm design to promote room-temperature labeling without substantially compromising *in vivo* stability, thereby providing a stronger chemical foundation for automated and standardized clinical production of radiopharmaceuticals.

Acyclic chelators. Acyclic chelators typically exhibit rapid complexation kinetics and can rapidly capture radiometal ions at room temperature or under mild conditions. This characteristic makes them highly suitable for meeting the core requirements of clinical translation and industrialization. For short-lived radionuclides, the value of acyclic chelators extends beyond laboratory convenience, because shortened preparation times, simplified workflows, and improved batch-to-batch consistency directly translate into clinical accessibility. In the ^{68}Ga setting in particular, mild and fast radiolabeling has enabled kit-based formulations that support on-demand preparation and have become a realistic, implementable clinical approach.⁹³ For instance, the [^{68}Ga]Ga-THP-PSMA supported by the THP chelating system has demonstrated a simplified one-step labeling process, showcasing a transformation paradigm from rapid labeling to clinical accessibility.⁹³

The central debate, however, remains whether acyclic complexes are sufficiently robust *in vivo*. Compared with rigid macrocycles, some acyclic systems are less kinetically inert and are therefore more susceptible to transchelation or dechelation under serum protein competition, endogenous metal ion exchange, or acidic intracellular environments. These liabilities can manifest as off-target organ accumulation and elevated background signal.⁹⁰ Accordingly, recent efforts have shifted from pursuing speed alone toward structural reinforcement that balances rapid labeling with adequate inertness. Key strategies include increasing coordination saturation, optimizing donor atom matching, and imposing conformational constraints to push acyclic platforms toward translatable performance.⁹⁴

In the field of ^{89}Zr immuno-PET, to address the problem of the easy detachment of traditional DFO leading to bone uptake, the new chelators DFO* and 3,4,3-LI (1,2-HOPO) have demonstrated excellent *in vivo* stability in head-to-head comparisons.^{95–97} Meanwhile, modular derivatives such as DFO2K and DFO-Em, while maintaining a similar DFO labeling kinetics, exhibit stronger *in vitro* stability, showing great potential.^{98,99} Additionally, the application of new acyclic chelators like AAZTA in new target molecule Fibroblast Activation Protein Inhibitor (FAPi) and other molecules has further strengthened the new standard of fast labeling, high stability, and convertible process.¹⁰⁰

Multifunctional and bioorthogonal chelation platforms. Overall, the role of chelators is undergoing a marked shift in paradigm. After macrocyclic and acyclic chelators have been iteratively refined through preorganization and scaffold rigidification to approach a three-part target of stability, labeling kinetics, and bifunctional translatability, new research priorities have emerged. The central idea is that chelators are no longer designed only as tight holders for radionuclides. Instead, they are increasingly developed as programmable molecular modules that can incorporate additional functions in a modular manner while maintaining high labeling efficiency and *in vivo* inertness, and while remaining compatible with scalable manufacture and robust batch-to-batch reproducibility. Accordingly, the evaluation focus is moving from a single question of whether the complex is stable enough to a more practical set of combined criteria aligned with clinical translation.⁹⁴

Bioorthogonally functionalized chelators represent a representative platform direction. By introducing bioorthogonal motifs such as tetrazines into efficient chelation scaffolds, it becomes possible to build chelation modules that support rapid radiolabeling and also offer selective reactivity *in vivo*, thereby providing a chemical basis for subsequent pretargeting approaches with slow pharmacokinetic carriers.¹⁰¹ In the case of THP tetrazine, this design preserves the mild and efficient radiolabeling features of ^{68}Ga while integrating the clickable site into a single small-molecule platform, reflecting an integrated concept that combines fast labeling, high stability, and a clickable handle.⁸⁸ In parallel, studies exemplified by HOPO MeTz further suggest that bioorthogonal handles can be compatible with chelation frameworks that demand higher coordination numbers, opening opportunities for clickable chelation platforms that extend across different radionuclides.¹⁰²

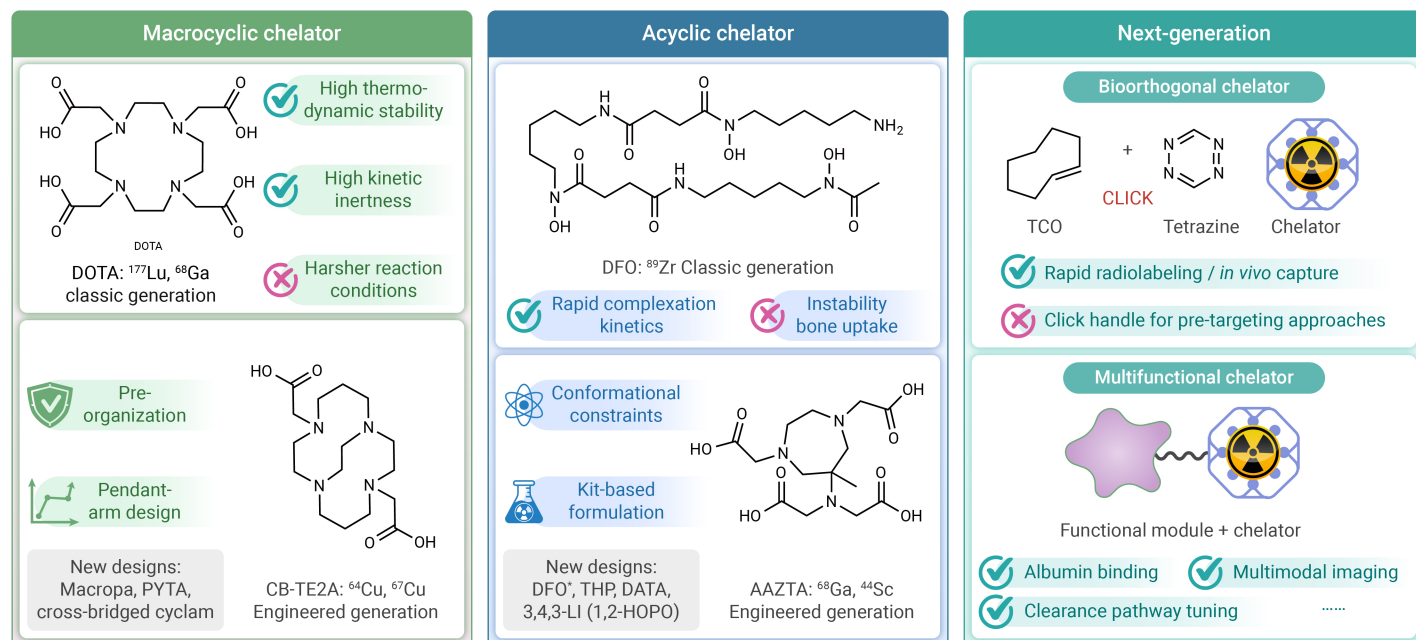


Figure 3. The chelator evaluation and characterization

A further step in this evolution is the development of trifunctional or multifunctional modular platforms. While preserving chelation stability and labeling kinetics, these designs introduce additional elements such as albumin binding, clearance pathway tuning, or multimodal imaging readouts, enabling finer optimization across biodistribution, tumor to background contrast, and so on.¹⁰³ Tsuchihashi et al. incorporated an albumin-binding unit into the effector molecule of a pretargeting system and constructed a new trifunctional chelator, aiming to maintain rapid clearance while mitigating the common limitation of insufficient tumor accumulation.¹⁰⁴ Taken together, the next stage of progress in chelator research is following a clearer trajectory. It moves from addressing whether stability is adequate, to meeting a combined set of requirements spanning stability, kinetics, and bifunctional translatability, and further toward platform-like, programmable multifunctional chelation modules that provide a reproducible and extensible chemical foundation for more advanced strategies.

MOLECULAR DESIGN OF RADIOPHARMACEUTICALS

Targeting vehicles

The choice of targeting vehicle largely determines the *in vivo* distribution, dose–time profile, and toxicity window of the radiopharmaceutical. The same radionuclide, when conjugated to small molecules, peptides and peptidomimetics, nanobodies and diabodies, or macro-molecules, will exhibit markedly different imaging time windows, tumor penetration depth, and normal-organ exposure.¹⁴ Small molecules favor rapid diffusion and early high-contrast imaging; peptides and peptidomimetics are particularly suited to precise recognition of hormone-type receptors and receptor-mediated internalization,¹⁰⁵ nanobodies and diabodies combine high affinity with intermediate tissue penetration; whereas macro-molecules rely on prolonged circulation and high affinity to achieve sustained target engagement.¹⁰⁶ The following sections will examine why each vehicle class has distinct strengths and preferred applications (Figure 4).

Small molecules. Small-molecule radiotracers (<1 kDa) exhibit moderate lipophilicity, facilitating rapid vascular-to-interstitial dispersion and yielding high early-timepoint tumor uptake.^{14,107} These vehicles primarily target cell-surface enzymes and transporters featuring deep binding pockets. Ligand engagement frequently induces rapid receptor-mediated internalization or intracellular trapping of hydrophilic radiometabolites, ensuring sustained intratumoral retention (Figure 4A).¹⁰⁸

The PSMA axis exemplifies this paradigm. The optimized inhibitor [^{177}Lu]Lu-PSMA-617 demonstrates high enzymatic affinity, robust internalization, and

prolonged retention, which translated to significantly extended overall survival in mCRPC (VISION trial).³⁵ Within this ligand class such as PSMA-11, PSMA-I&T, PSMA-617, theranostic utility is delineated by the paired radionuclide. Diagnostic applications with short-lived isotopes (^{68}Ga , ^{18}F) leverage the vehicles' rapid systemic clearance to achieve high-contrast imaging within a narrow temporal window. Conversely, therapeutic applications utilizing ^{177}Lu depend heavily on rapid receptor-mediated internalization and protracted intracellular residence. This mechanism is critical to offset the pharmacokinetic mismatch between the radionuclide's extended physical half-life and the vehicle's rapid biological clearance.¹⁰⁹

Fibroblast activation protein (FAP) targeted ligands illustrate further structural advantages. FAP is heterogeneously expressed on cancer-associated fibroblasts across the tumor stroma and invasive fronts.¹¹⁰ Small molecules such as FAPI-46 and FAP-2286 exploit superior tissue penetrance to enable single-scaffold theranostics across diverse solid tumors. Ultimately, small-molecule vehicles excel in targeting spatially dispersed antigens (e.g., PSMA, FAP) by achieving comprehensive, homogeneous intratumoral distribution within constrained temporal and dosimetric limits.¹¹¹ In contrast, macro-molecular vehicles such as antibodies are frequently restricted to perivascular compartments, limiting uniform therapeutic dose delivery within acceptable toxicity thresholds.

Peptides and peptidomimetics. Peptide and peptidomimetic vehicles (1–3 kDa) serve as intermediate molecular weight radiopharmaceutical carriers derived from endogenous hormone scaffolds.^{112–113} They demonstrate high affinity, selectivity, and efficient receptor-mediated internalization for G protein-coupled receptors (GPCRs), including SSTR2, GLP-1R, and CCK2R.^{114–115} Their compact size enables rapid diffusion into dense tumor interstitium, while predominant renal clearance via glomerular filtration yields a plasma half-life of minutes to hours. This pharmacokinetic profile facilitates rapid target occupancy.¹¹⁶ Following internalization, the radiometal–chelator-loaded peptide complex is retained intracellularly for several days, synergizing temporally with long-lived radionuclides, such as ^{177}Lu and ^{161}Tb , to enable sustained tumor irradiation from a single administration.¹¹⁷ However, their efficacy depends on robust target expression and is dose-limited by proximal tubular reabsorption.¹¹⁸ A more comprehensive discussion regarding peptide and peptidomimetic vehicles is available in the extensive reviews by Xiao et al (Figure 4B).¹¹³

The SSTR2 axis provides robust clinical validation for this paradigm. The agonist [^{177}Lu]Lu-DOTATATE significantly improves survival in gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) and is an established

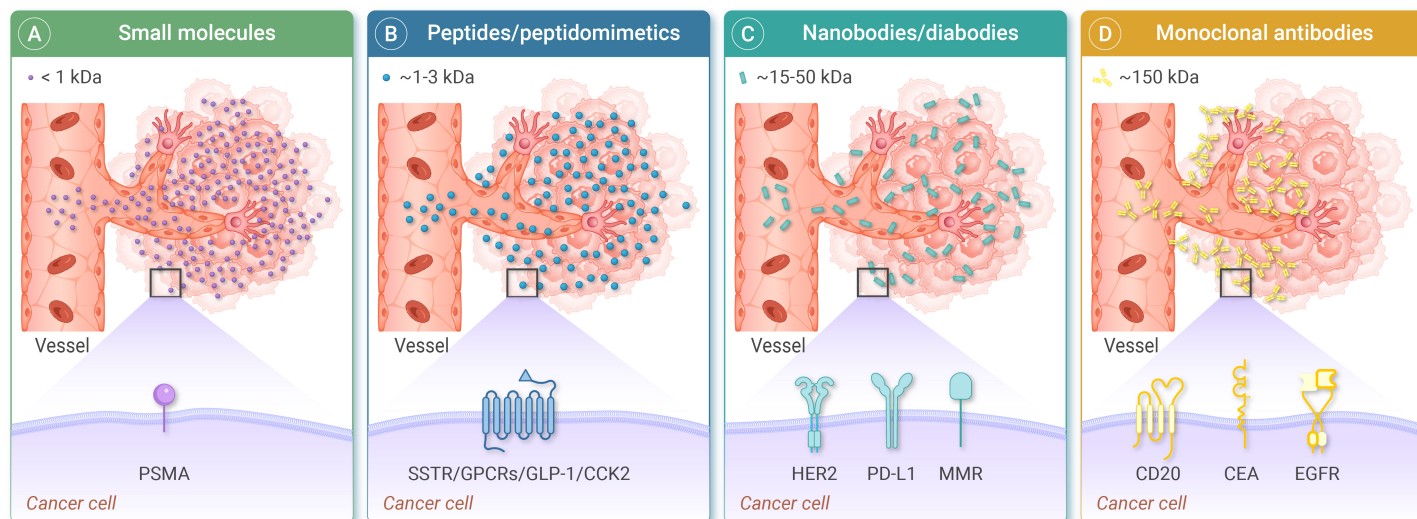


Figure 4. Schematic images of various vehicles

standard of care.^{119–120} Next-generation SSTR2 antagonists, such as [¹⁷⁷Lu]Lu-DOTA-LM3, further enhance tumor uptake and therapeutic indices, particularly when paired with ¹⁶¹Tb, highlighting the dosimetric synergy between internalizing peptides and extended-half-life radionuclides. Similarly, the GLP-1R axis demonstrates the structural utility of these vehicles; the high tumor-to-background contrast of [⁶⁸Ga]Ga-NODAGA-exendin-4 has revolutionized the detection and surgical management of insulinomas.¹²¹

Ultimately, peptides and peptidomimetics overcome the limitations of both small molecules, which often lack sufficient affinity for conformationally sensitive hormone receptors, and antibodies, which suffer from poor tissue penetration and prolonged systemic retention. By balancing precise structural recognition, superior tissue penetrance, and tunable pharmacokinetics, they represent the optimal targeting vehicles for these receptor axes.¹⁰⁵

Nanobodies and diabodies. Since their discovery in camelids, heavy-chain antibodies (HCAbs) and their isolated single variable domains (VHH, or nanobodies; ~15 kDa) have emerged as highly versatile alternatives to conventional monoclonal antibodies (mAbs).^{122–123} Despite lacking a light chain, nanobodies maintain complete antigen-binding functionality. This is primarily facilitated by an elongated CDR3 region that forms a convex, finger-like protrusion, expanding the interaction surface area and enabling deep insertion into antigen molecular clefts. Consequently, nanobodies can efficiently target cryptic epitopes, such as enzyme active sites, that are typically inaccessible to standard mAbs (Figure 4C).^{124–125}

Nanobodies consolidate multiple physicochemical and pharmacokinetic advantages.^{126–131} Their compact dimensions ensure superior diffusion into deep-seated solid tumors and across restrictive physiological boundaries, including the blood-brain barrier, thereby overcoming the heterogeneous intratumoral distribution characteristic of larger mAbs.¹³² Furthermore, their high thermal and chemical stability permits formulation for challenging delivery routes (e.g., oral, inhalation) and withstands harsh microenvironments.^{133–136} Structurally, their single-domain architecture simplifies genetic manipulation, facilitating direct conjugation with therapeutic payloads such as toxins, radionuclides, or nanoparticles.¹³⁷ To mitigate the rapid renal clearance associated with low molecular weight, VHH domains are frequently engineered into tandem configurations or fused with human IgG Fc fragments.¹³⁸ The latter strategy significantly extends *in vivo* half-life while simultaneously introducing effector functions such as antibody-dependent cellular cytotoxicity (ADCC).^{139–144}

In the context of tumor immunotherapy, bispecific nanobody (Nb-BsAb) applications predominantly focus on dual immune checkpoint blockade and T-cell redirection. Dual-targeting constructs directed against synergistic pathways, such as PD-1 and CTLA-4 (e.g., the mRNA-optimized Z15-0-2 Nb-BsAb), demonstrate robust localized antitumor activity.¹⁴⁵ Concurrently, the minimal steric hindrance and high affinity of Nb-BsAbs provide an optimal scaffold for T-cell engagers. By simultaneously binding a tumor-associated

antigen (TAA) and the T-cell CD3ε chain, these constructs forcibly assemble immunological synapses, redirecting potent T-cell cytotoxicity against malignant cells.¹⁴⁶ This T-cell redirection paradigm has been thoroughly validated in the clinic, exemplified by the FDA approval of the BiTE blinatumomab (CD3×CD19) for the treatment of leukemia.¹⁴⁷

Macro-molecules (monoclonal antibodies). Macromolecular vehicles, predominantly intact IgG monoclonal antibodies (mAbs; ~150 kDa), represent a foundational class of targeting agents characterized by exceptional antigen affinity and extended systemic circulation.¹⁴⁸ Their large molecular weight precludes renal filtration; instead, prolonged plasma half-lives ranging from days to weeks are maintained via the neonatal Fc receptor (FcRn) recycling pathway.¹⁴⁹ Beyond target engagement, humanized intact IgGs actively modulate the immune microenvironment by recruiting host effector functions, including ADCC, antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC).^{150–151} The clinical indispensability of this paradigm is evidenced by the enduring efficacy of humanized therapeutics such as trastuzumab (Human Epidermal Growth Factor Receptor 2 (HER2)) and rituximab (Cluster of Differentiation 20 (CD20)), alongside their synergistic integration with immune checkpoint inhibitors (ICIs) (e.g., PD-1/PD-L1 blockade) for advanced solid tumors (Figure 4D).^{152–153}

The evolution of these macromolecules has been heavily reliant on structural engineering. Historically, the transition from murine to humanized scaffolds was imperative to circumvent the human anti-mouse antibody (HAMA) response, which severely compromised efficacy through rapid clearance and immunogenicity.^{154–157} Concurrently, antibody fragmentation technologies have generated derivatives such as antigen-binding fragments (Fab) and single-chain variable fragments (scFv).^{152–153} By excising the Fc domain, these constructs sacrifice effector functions and extended circulation in favor of accelerated systemic clearance and superior tissue penetrance, making them highly suitable for specific diagnostic imaging and drug delivery applications.¹⁵⁸

In the radiopharmaceutical domain, the pharmacokinetic profile of intact mAbs presents distinct challenges. While prolonged circulation drives high absolute tumor uptake—partially mediated by the EPR effect—their slow interstitial diffusion frequently causes peripheral shell loading in large solid tumors. Furthermore, extended blood-pool residence increases radiation toxicity to the bone marrow and highly vascularized organs.¹⁵⁹ To mitigate this pharmacokinetic mismatch, mAbs are conventionally paired with long-lived radionuclides (e.g., ⁸⁹Zr for immuno-PET; ¹⁷⁷Lu, ⁹⁰Y, or ²²⁵Ac for radioimmunotherapy). This approach is exemplified by the clinical success of [⁹⁰Y]ibritumomab tiuxetan in highly radiosensitive lymphomas. To address the diffusion limitations in solid tumors, contemporary research is advancing pre-targeting strategies, which temporally decouple the slow biological distribution of a non-radioactive mAb from the rapid delivery of a subsequently administered radioactive payload. Despite these complexities, macro-

molecules remain the gold standard for non-internalizing targets, offering a robust platform for a emitter therapies where high LET and single-hit cytotoxicity can effectively compensate for heterogeneous intratumoral distribution.¹⁶⁰

Linkers

In radiopharmaceuticals, linkers are not merely passive spacers, but key determinants of the physicochemical properties, *in vivo* stability, intracellular fate and time–dose characteristics of vehicle–radionuclide conjugates.^{161–162} Using the same targeting vehicle and radionuclide, adjusting linker hydrophilicity/hydrophobicity, overall charge, residualizing character, cleavability, or the presence of albumin-binding motifs can produce very different balances between tumor retention and normal-organ clearance, between area under curve (AUC) and peak dose.¹⁶³ In the following, hydrophilic and hydrophobic linkers are used as two main structural axes, into which residual vs non-residual and cleavable vs non-cleavable dimensions are embedded, to illustrate how linkers reshape pharmacokinetics (PK) and dosimetry at the structure–function level (Figure 5).^{14,164}

Hydrophilic linkers. Hydrophilic linkers typically introduce a series of polar or charged groups such as PEG chains, polycarboxylates, polyamines, sulfonates, quaternary ammonium moieties, or short peptides—between the targeting vehicle and the chelator or drug, and together with chelators such as DOTA or HBED-CC, they form a highly hydrophilic aqueous shell with an overall multi-anionic or zwitterionic character. Representative examples include [¹¹¹In]In/[¹⁷⁷Lu]Lu-3BP-227 in NTSR1 targeted applications,¹⁶⁵ [¹⁷⁷Lu]Lu-PS8 in the PSMA setting,¹⁶² and [¹⁸F]FPPRGD2 in integrin $\alpha v \beta 3$ setting (Figure 5A).¹⁶⁶ This design can effectively mask highly hydrophobic drug moieties or aromatic groups, thereby reducing aggregation and nonspecific interactions with lipid membranes; at the same time, electrostatic repulsion and steric hindrance attenuate nonspecific binding to plasma proteins and hepatocyte membranes, thus reshaping the apparent volume of distribution and clearance pathways of the conjugate.¹⁶²

Within the hydrophilic linker framework, residualizing behaviour and cleavability can be further exploited to fine-tune the partitioning between tumor and kidneys. Zhou and colleagues developed an ¹⁸F-labeling strategy for HER2-targeted sdAb 5F7GGC, installing a tetrazine at the C-terminal of GGC, followed by a reaction with ¹⁸F-TCO precursor bearing a kidney brush-border enzyme-cleavable peptide and a PEG₄ segment.¹⁶⁷ The resulting [¹⁸F]5F7GGC generates cationic, hydrophilic residualizing metabolites within tumor cells, prolonging intracellular retention, whereas the cleavable peptide in the linker allows brush-border enzymes in the renal cortex to preferentially cleave the construct and convert the charged radiometabolite into more readily excreted species, thereby accelerating renal clearance. However, the introduction of hydrophilic linkers requires an integrated consideration of target expression patterns, desired clearance routes, and the need for residualizing and cleavable functions.¹⁶⁷

Hydrophobic linkers. In contrast to hydrophilic linkers, hydrophobic linkers incorporate hydrophobic motifs such as aromatic rings, alkyl chains, or fatty acid residues, thereby strengthening the interactions of the conjugate with lipid membranes and serum albumin and reshaping its tissue distribution and *in vivo* circulation time.¹⁰⁸ Moderate hydrophobicity favors membrane partitioning and receptor-mediated endocytosis, leading to increased uptake of the conjugate by tumor cells. However, excessive hydrophobicity often leads to stronger albumin binding and higher hepatic uptake, increasing liver and reticuloendothelial system doses and thus representing a classic double-edged sword.¹⁶⁸

PSMA-617 relies more heavily on hydrophobic linkers that precisely complement deep hydrophobic pockets in the target.¹⁶² An example is [¹⁷⁷Lu]Lu-PSMA-617, which consists of a Glu–urea–Lys inhibitor head, a hydrophobic linker segment containing 2-naphthyl-L-Ala and a cyclohexyl moiety (2NaI–ChX), and a terminal DOTA–Lu-177 chelate (Figure 5B).¹⁶⁹ In its [⁶⁸Ga]Ga-PSMA-617, the reported LogD_{7.4} is around 2.8, clearly more lipophilic than [⁶⁸Ga]Ga-PSMA-11. The VISION phase III trial in mCRPC demonstrated that this agent significantly improves overall survival and radiographic progression-free survival.³⁴ From a structure–function perspective, the 2-naphthyl and cyclohexyl elements of the linker effectively wedge into the hydrophobic channel leading to the enzymatic active site, markedly enhanc-

ing binding affinity and receptor-mediated internalization. The combination of a hydrophobic linker and residualizing chelator thus shapes a pharmacokinetic and dosimetric profile characterized by high AUC and high local dose deposition.³⁵

However, simply increasing lipophilicity does not translate linearly into improved tumor delivery; instead, it readily disrupts the balance between circulation time, elimination routes, and tumor exposure.¹⁷⁰ The NTS₁-targeted peptide tracer [⁶⁸Ga]Ga-UR-LS130 is derived from the C-terminal neurotensin fragment NT (8–13) (Figure 5B).¹⁶⁸ While retaining a DOTA chelation site, a β , β -dimethyl substitution is introduced at the Tyr residue to modestly enhance local hydrophobicity, yet the tracer as a whole remains relatively hydrophilic.¹⁷¹ Systematic modification of the linker region on this scaffold showed that extending or strengthening the lipophilic spacer can shift the clearance pattern from primarily renal excretion to a mixed renal–hepatobiliary route, but these more hydrophobic analogues do not increase tumor uptake and in fact markedly reduce tumor-to-muscle ratios in HT-29 xenografts. By contrast, UR-LS130 combines intermediate hydrophobicity with markedly improved proteolytic stability, achieving efficient NTS₁-mediated tumor uptake while maintaining predominantly renal clearance and a more favourable overall dosimetric profile. This example illustrates that, in the optimization of hydrophobic peptide linkers, what truly requires fine tuning is the coupling among hydrophobicity, *in vivo* stability, and elimination rate, rather than a unidirectional pursuit of higher LogD.¹⁴

Albumin-binding linkers. Albumin-binding linkers introduce motifs between the ligand and chelator that can reversibly bind serum albumin, such as 4-iodophenylbutyric acid, fatty acid analogues, or Evans blue, thereby allowing small molecules or short peptides to borrow the long circulation time of albumin.¹⁷² This strategy endows radiopharmaceuticals with prolonged circulation time, thereby enhancing systemic AUC.¹⁷³

SSTR2-targeted [¹⁷⁷Lu]Lu-DOTA-EB-TATE is among the earliest albumin-binding radiopharmaceuticals with clinical data. A truncated EB-derived azo-aromatic albumin-binding motif is grafted onto the DOTA-TATE scaffold, conferring high-affinity, reversible albumin binding, and first-in-human studies showed roughly a 3–4-fold increase in tumor absorbed dose versus [¹⁷⁷Lu]Lu-DOTATATE at the expense of higher kidney and marrow doses (Figure 5C).¹⁷⁴ A similar EB-based strategy has been applied to PSMA, where [¹⁷⁷Lu]Lu-LNC1003 couples a truncated EB moiety (Figure 5C).¹⁷⁵

For PSMA-targeting radiopharmaceuticals, [¹⁷⁷Lu]Lu-PSMA-ALB-56 and [¹⁷⁷Lu]Lu-SibuDAB achieved optimized pharmacokinetic properties through albumin-binding linkers. [¹⁷⁷Lu]Lu-PSMA-ALB-56 contains 4-(p-iodophenyl)butyrate for albumin binding, and dosimetry studies reveal prolonged plasma retention and elevated tumor doses versus [¹⁷⁷Lu]Lu-PSMA-617 (Figure 5C).¹⁷³ Concurrently, [¹⁷⁷Lu]Lu-SibuDAB employs an ibuprofen-like hydrophobic fragment to provide moderate albumin binding; preclinical and early clinical data suggest that slightly attenuating albumin affinity can preserve much of the gain in tumor AUC (Figure 5C).¹⁷⁶

Modes of construction: conventional/site-specific and click/bioorthogonal approaches. In addition to understanding how linkers reshape the PK and dosimetry of radiopharmaceuticals, an equally important consideration for developing viable drug candidates is how these linkers are introduced. Conventional lysine- or cysteine-based random conjugation is technologically mature, but the resulting heterogeneity in payload-to-antibody ratio and conjugate architecture limits the comparability of different designs on the same scaffold.¹⁶¹ In recent years, site-specific strategies using engineered cysteines, C-terminal GGC tags, and glycoengineering have enabled installation of linker–chelator units at predefined sites and in fixed stoichiometry; for example, C-terminal IEDDA labeling of the HER2-targeted single-domain antibody [¹⁸F]5F7GGC affords more controlled imaging behaviour while maintaining high affinity.¹⁶⁷

In parallel, IEDDA bioorthogonal click chemistry, exemplified by the tetrazine–TCO reaction, has become a broadly applicable conjugation tool for antibody-, nanobody-, and peptide-based Radiopharmaceuticals. due to its high reaction rate, mild conditions, and excellent compatibility with aqueous media. Systematic comparisons of different tetrazine tool compounds indicate that click reactivity and lipophilicity jointly shape the *in vivo* distribution and clearance of pretargeted tracers, providing a platform for establishing linker–PK structure–effect relationships on a given vehicle.^{167,177}

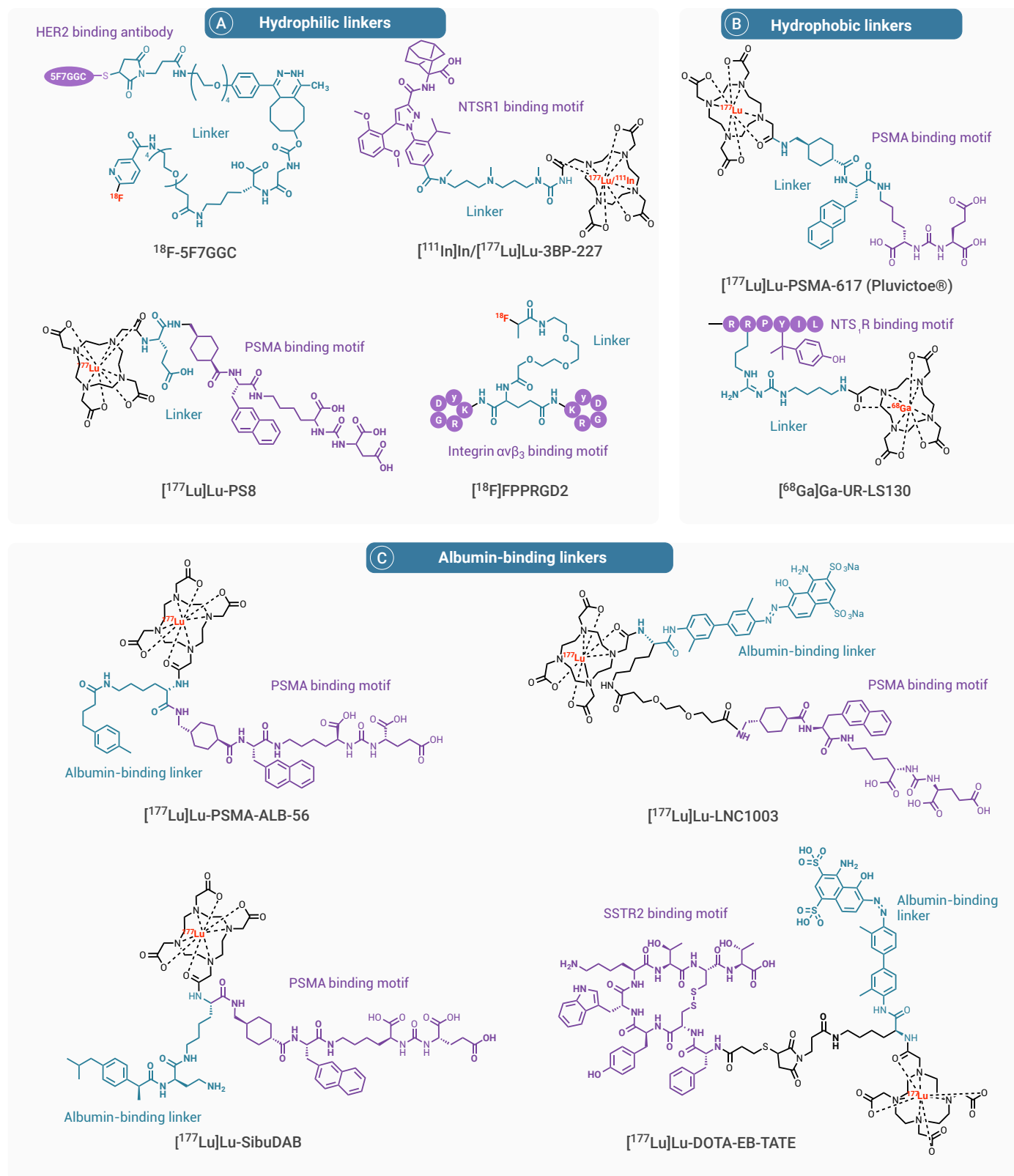


Figure 5. Linkers for radiopharmaceuticals

Pharmacokinetic Modulation of Radiopharmaceuticals

Half-life-PK mismatch and dosimetric constraints. For currently available radiopharmaceuticals, the principal dosimetric constraints arise in the kidneys and bone marrow and are largely driven by a mismatch between the physical half-life of the radionuclide and the pharmacokinetic time scale of

the carrier. Small molecules and peptides typically complete distribution and clearance within a few hours, whereas β or α emitting radionuclides such as ^{177}Lu and ^{225}Ac have physical half-lives on the order of several days. In patients with mCRPC, ^{177}Lu -Lu-PSMA-617 significantly improved overall survival in the VISION trial, yet attempts to further escalate administered

activity are rapidly limited by hematologic and renal toxicity.¹⁰⁹ In SSTR-targeted PRRT, patient-level dosimetric analyses similarly demonstrate that tumor control is bounded by clear upper limits of absorbed dose to the kidneys and bone marrow.¹¹⁸ Consequently, the central objective of PK modulation in radiopharmaceuticals design is, within a fixed radionuclide–target combination, to use structural modification and pharmacologic co-medication to increase tumor AUC while reducing exposure of critical organs.

Albumin–binding–driven modulation of circulation time and tumor AUC. When the intrinsic circulation time of the carrier is clearly shorter than the effective irradiation window of the radionuclide, the introduction of albumin-binding moieties provides a direct chemical solution. For example, [¹⁷⁷Lu]Lu-PSMA-ALB-56 grafted an aromatic acid-type albumin-binding unit onto the PSMA-617 scaffold increases tumor absorbed dose by approximately 2- to 3-fold over [¹⁷⁷Lu]Lu-PSMA-617 in mouse models, while kidney dose rises only moderately.¹⁷³ Therefore, albumin-binding moieties can markedly increase tumor AUC by prolonging circulation, but at the price of elevating overall systemic exposure. Rational design therefore requires integrating information on target expression in normal tissues, radionuclide half-life, and individual bone marrow and renal reserve, and then finely tuning albumin affinity and linker physicochemical properties, rather than only pursuing maximal half-life extension.

Kidney dose mitigation via structural and pharmacologic optimization. For small-molecule and peptide radiopharmaceuticals that are predominantly cleared renally, high cortical kidney doses are mainly driven by proximal tubular endocytosis of cationic and peptide-like structures and subsequent lysosomal retention. Design strategies to reduce renal AUC can be organized along two levels: first, structural modifications that decrease the probability of uptake by proximal tubules; second, measures that, once internalized, favor rapid conversion into readily excretable species.

On the structural level, linker–PK studies of PSMA and SSTR ligands show that introducing additional negative charges and short PEG or sulfonate-containing hydrophilic fragments can substantially reduce cortical kidney uptake while maintaining target affinity, thereby improving tumor-to-kidney and tumor-to-salivary gland ratios.^{178–179} At the level of intrarenal processing, inserting a short peptide linker such as Gly-Phe-Lys (GFK), which is cleavable by brush-border enzymes, between the radiometal chelate and the peptide can promote preferential cleavage in the renal cortex. This releases more hydrophilic low-molecular-weight metabolites that are rapidly excreted. In preclinical models, this design markedly reduced renal retention without materially compromising tumor uptake.¹⁸⁰ Pharmacologic co-medication provides an additional protective layer. In PRRT with [¹⁷⁷Lu]Lu-DOTATATE and related agents, co-infusion of L-lysine and L-arginine has become standard practice; by competitively inhibiting proximal tubular transport of positively charged peptides, this approach can reduce kidney by approximately 30–40% and significantly attenuate long-term decline in estimated glomerular filtration rate (eGFR).¹¹⁸

In the context of radiopharmaceuticals design, albumin binding and kidney protection are best viewed as complementary approaches addressing the same dosimetric challenge at different levels. Albumin-binding units primarily extend circulation time and increase tumor AUC to expand the therapeutic margin, whereas structural optimization and pharmacologic co-medication focus on constraining cortical kidney dose and preventing cumulative renal toxicity. In individual radiopharmaceuticals programs, a commonly adopted strategy is to integrate patient-level dosimetry, jointly adjust the strength of albumin binding, the physicochemical profile of the linker, and the intensity of amino acid–based nephroprotection, and thereby position the dose–time curves for tumor, kidney, and bone marrow within an acceptable region of efficacy and safety.

Innovation of radiopharmaceuticals

Traditional radiopharmaceuticals predominantly rely on reversible, non-covalent interactions. This reversibility frequently results in transient tumor retention, diminishing diagnostic contrast and therapeutic efficacy.¹⁸¹ Furthermore, it exacerbates the inherent pharmacokinetic trade-off between specific tumor uptake and rapid systemic clearance, often leading to dose-limiting off-target toxicity. To address these limitations, targeted covalent

radiopharmaceuticals (CRPs) have emerged. CRPs incorporate engineered reactive groups to achieve irreversible target engagement via a two-step mechanism: initial high-affinity, reversible complexation with the target protein, followed by a proximity-induced reaction with local nucleophilic residues to form a stable covalent bond.^{182–183} This paradigm is exemplified by recent proof-of-concept studies utilizing genetic code expansion to incorporate a proximity-activated reactive amino acid (FSY) into a HER2-targeted nanobody. This covalent modification significantly prolonged tumor retention without altering systemic clearance, thereby maximizing the therapeutic index of conjugated α -emitting radionuclides.¹⁸¹

Parallel to CRPs, pre-targeting strategies have been developed to overcome the dosimetric limitations of conventional monomolecular radiopharmaceuticals, particularly the slow blood clearance of intact antibodies that restricts compatible radionuclides. Pre-targeting decouples target recognition from radionuclide delivery. In this two-step approach, a bioorthogonally tagged targeting vehicle is administered and allowed to accumulate at the tumor site while clearing from systemic circulation.¹⁸⁴ Subsequently, a rapidly clearing, radiolabeled small molecule is administered to selectively bind the pre-localized vehicle *in vivo*. This temporal separation preserves the high binding specificity of macromolecular vehicles while leveraging the favorable pharmacokinetics of small molecules, drastically improving the tumor-to-normal tissue (T/NT) ratio.¹⁸⁵ The feasibility of this strategy has been significantly advanced by bioorthogonal click chemistry, most notably the IEDDA reaction between tetrazine and TCO, which facilitates exceptionally rapid and highly specific *in vivo* covalent conjugation.¹⁸⁶

THE EXPANDING TARGET LANDSCAPE

Radiopharmaceuticals' development is undergoing a paradigm shift toward precision molecular targeting, driven by the identification of novel receptors and the demand for improved specificity, efficacy, and safety in both imaging and radiotherapy.¹⁴ A growing number of molecular targets have been identified and exploited in drug design, and several classes of targeted radiopharmaceuticals have progressed into clinical evaluation. Among these, PSMA and SSTR represent some of the most extensively studied and clinically advanced targets.^{32,108,187–189} For instance, a broad array of PSMA-targeting molecules has been reported, and multiple radiopharmaceuticals have achieved regulatory approval for diagnosis or radiotherapy, such as [⁶⁸Ga]Ga-PSMA-11, [¹⁸F]DCFPyL for diagnosis and [¹⁷⁷Lu]Lu-PSMA-617 for radiotherapy.^{35,190–191} These traditional targets are advantageous because they are highly expressed in malignant tissues yet minimally expressed in normal tissue.^{192–193} This facilitates high tumor uptake and a high tumor-to-background ratio (TBR), both of which are essential for imaging and therapeutic efficacy. However, as the clinical radiopharmaceuticals targeting PSMA, SSTR, and other traditional receptors approach saturation, there remains an unmet need for novel targets that address additional tumor types.¹⁹⁴ Consequently, there is increasing interest in identifying and advancing next generation targeting strategies. In this review, we categorize promising targets into two major groups, including tumor cell-associated receptors and tumor microenvironment (TME)-associated receptors, and further discuss the status and translational prospects of radiopharmaceuticals designed against these targets (Figure 6).

Targeting tumor cell-specific receptors

Gastrin-releasing peptide receptor (GRPR). GRPR is a typical tumor-associated GPCR belonging to the bombesin (BBN) receptor family.¹⁹⁵ It is physiologically activated by gastrin-releasing peptide (GRP), a 27-amino-acid neuropeptide whose C-terminal domain is identical to that of amphibian bombesin.¹⁹⁶ Aberrant GRPR expression has been identified in various cancers, including prostate, breast, pancreatic and lung cancers, as well as certain central nervous system tumors.^{197–199} In contrast, expression in most normal adult tissues is relatively limited.²⁰⁰ GRPR signaling contributes to tumor cell proliferation, migration, and survival, highlighting its crucial role as a diagnostic biomarker and a biologically actionable therapeutic target.

Clinical investigations primarily focused on GRPR agonists. For example, Zhang et al. assessed the imaging performance of the GRP-derived tracer [⁶⁸Ga]Ga-NOTA-Aca-BBN(7–14) in pediatric patients with optic pathway gliomas (Figure 7A). Of the 11 lesions observed in eight patients, all showed

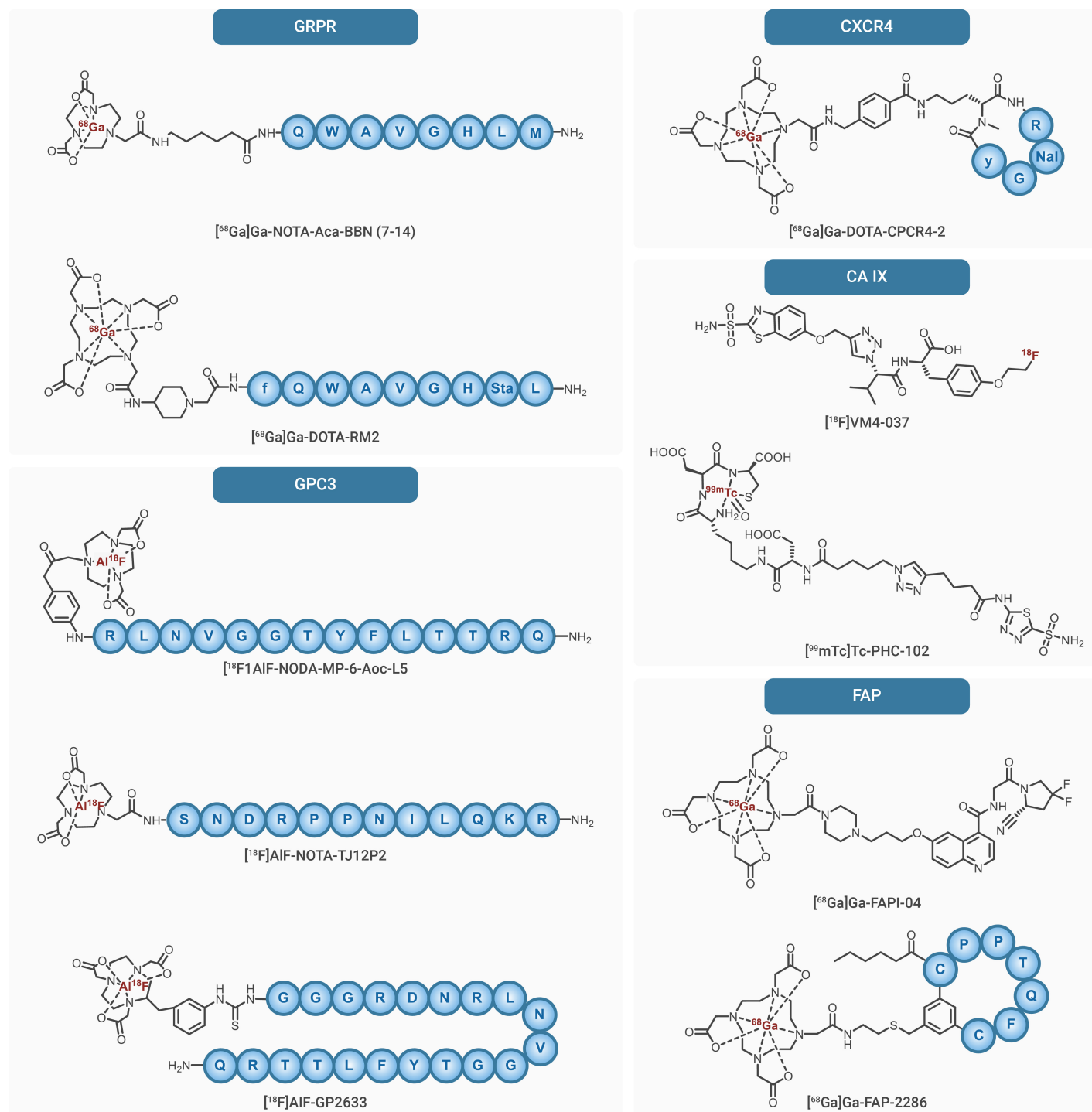


Figure 6. Chemical structures of representative target ligands. Created with ChemDraw

significant tracer uptake with favorable contrast, and the TBR was markedly higher than that of $[^{18}\text{F}]\text{FDG}$ (28.4 ± 5.59 vs. 0.47 ± 0.11).²⁰¹ However, the limitations of agonist-based tracers soon became apparent. In a first-in-human pilot study using the bombesin analogue $[^{99\text{m}}\text{Tc}]\text{Tc-HABBN}$ in prostate cancer patients, the radiopharmaceutical exhibited low metabolic stability *in vivo*, with less than 20% of the intact compound remaining at 30 min post-injection, and no prostate uptake being detected in any patient.²⁰²

These shortcomings prompted a strategic shift towards GRPR antagonists, which demonstrated superior pharmacokinetics and tumor targeting. The antagonist RM2 emerged as a key scaffold, exhibiting high binding affinity and strong tumor uptake. Both $[^{111}\text{In}]\text{In-RM2}$ and $[^{68}\text{Ga}]\text{Ga-RM2}$ showed high and specific accumulation in LNCaP prostate cancer xenografts

(Figure 7A). In a clinical study involving 95 patients with biochemically recurrent prostate cancer, $[^{68}\text{Ga}]\text{Ga-RM2}$ enabled effective tumor detection, although intense physiological uptake was observed in the pancreas, with an average SUV_{max} of 64.9.²⁰³ Therapeutic translation was further explored with $[^{177}\text{Lu}]\text{Lu-RM2}$ in patients with mCRPC and insufficient PSMA expression. High tumor accumulation and rapid clearance from most normal organs were observed, but pancreatic uptake remained the dose-limiting factor.²⁰⁴ To improve metabolic stability and tumor retention, the structure of RM2 was modified to develop AMTG, replacing a metabolically labile peptide bond with α -methyl-L-tryptophan. Compared with $[^{177}\text{Lu}]\text{Lu-RM2}$, $[^{177}\text{Lu}]\text{Lu-AMTG}$ demonstrated improved *in vitro* and *in vivo* stability and achieved a tumor retention of $11.45 \pm 0.43\% \text{ID} \cdot \text{g}^{-1}$ at 24 h post-injection. In a first-in-human

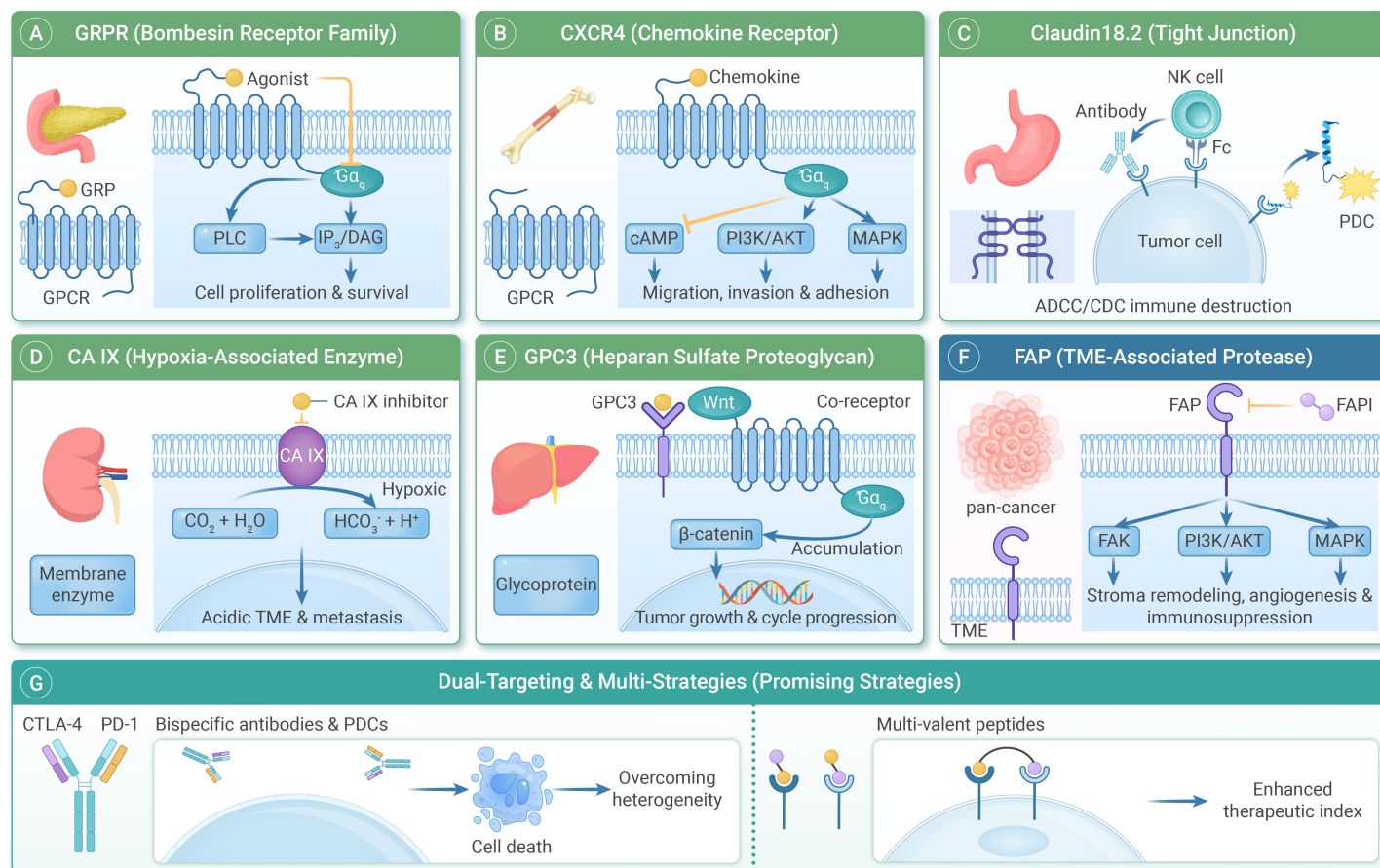


Figure 7. Representative targets for advanced radiopharmaceuticals and enhanced targeting mechanisms

PET/CT study, [^{68}Ga]Ga-AMTG detected multiple lesions with strong focal uptake that were inconspicuous on [^{18}F]PSMA-1007 imaging. More recently, therapeutic studies have suggested that [^{61}Tb]Tb-AMTG may be more effective than its ^{177}Lu -labeled counterpart due to additional Auger electron emission.²⁰⁵

Further advances were achieved with the development of NeoBOMB1, a stabilized GRPR antagonist that incorporates a modified C-terminal dipeptide (Figure 7A). In preclinical PC-3 xenograft models, both [^{68}Ga]Ga-NeoBOMB1 and [^{177}Lu]Lu-NeoBOMB1 exhibited high GRPR-specific tumor uptake exceeding $30\% \text{ID} \cdot \text{g}^{-1}$ at 4 h post-injection, with rapid clearance from non-target organs.²⁰⁶ In a phase I/IIa clinical study, [^{68}Ga]Ga-NeoBOMB1 demonstrated tumor SUV_{max} values ranging from 4.3 to 25.9 at 2 h post-injection; however, the pancreas remained the critical dose-limiting organ.²⁰⁷

Collectively, these studies confirm the clinical relevance of GRPR as a tumor cell target, with the development of antagonist-based radiopharmaceuticals emerging as the dominant approach. Future efforts should focus on optimizing tumor-to-pancreas dose ratios and improving ligand stability further to realize the full therapeutic potential of GRPR-targeted radionuclide therapy.

C-X-C chemokine receptor type 4 (CXCR4). C-X-C chemokine receptor type 4 (CXCR4) is one of the most extensively studied chemokine receptors in oncology and represents a clinically relevant tumor cell-associated target for molecular imaging and radionuclide therapy.^{208–209} Among approximately 50 known chemokines and 20 corresponding receptors, CXCR4 has attracted particular interest due to its widespread overexpression in more than 23 human malignancies, including hematologic cancers and solid tumors.^{210–211} CXCR4 signaling plays a critical role in tumor growth, invasion, angiogenesis, and metastatic dissemination, making it a biologically meaningful and translationally attractive target.^{212–214} CXCR4 is well suited for radiopharmaceutical development because it is a cell surface GPCR with high ligand-binding specificity and relatively stable expression across disease stages. Unlike

targets that primarily reflect tumor differentiation status, CXCR4 expression is closely associated with aggressive tumor behavior and poor prognosis. As a result, CXCR4-directed imaging provides not only anatomical localization, but also functional information related to tumor biology and disease burden, particularly in hematologic malignancies.

The clinical translation of CXCR4-targeting radiopharmaceuticals has been driven largely by peptide-based ligands derived from the cyclic pentapeptide scaffold CPC4. Among these, [^{68}Ga]Ga-DOTA-CPC4-2 (Pentixafor) has emerged as the most widely used diagnostic tracer (Figure 7B).²¹⁵ Pentixafor exhibits high affinity for CXCR4, with an IC_{50} value of $4.99 \pm 0.72 \text{ nM}$. In a large clinical PET/CT study involving 142 patients with histologically confirmed tumors, including 23 solid tumor entities, [^{68}Ga]Ga-Pentixafor demonstrated high imaging contrast, with 67.8% of patients showing CXCR4-positive lesions and a median TBR of 4.4 across 462 detected lesions.²¹¹ Notably, CXCR4 expression can be retained between primary and metastatic lesions in several malignancies, supporting the use of CXCR4 PET imaging for patient stratification across disease sites. In hematologic malignancies, [^{68}Ga]Ga-Pentixafor has shown particular diagnostic value. In patients with advanced multiple myeloma (MM), CXCR4-directed PET/CT identified disease manifestations in 10 of 14 patients, compared with 9 patients detected by [^{18}F]FDG PET/CT, indicating a potential advantage of CXCR4 imaging in this setting.²¹⁶ These findings highlight the complementary role of CXCR4-targeted tracers in malignancies with variable glucose metabolism.

To expand accessibility and reduce costs, SPECT-based CXCR4 tracers have also been developed. By introducing amino acid modifications and an N-terminal $^{99\text{m}}\text{Tc}$ -labeling strategy, PentixaTec was generated as a high-affinity CXCR4 ligand, exhibiting an enhanced binding affinity of $0.6 \pm 0.1 \text{ nM}$. [$^{99\text{m}}\text{Tc}$]Tc-PentixaTec showed high internalization efficiency (approximately 97% of cellular activity within 2 h) and achieved a maximum tumor uptake of $8.6 \pm 1.3\% \text{ID} \cdot \text{g}^{-1}$ at 1 h post-injection.²¹⁷ In a clinical SPECT study of patients with hematologic malignancies, [$^{99\text{m}}\text{Tc}$]Tc-PentixaTec demonstrated favor-

able biodistribution and dosimetry (2.1–3.4 mSv per 500 MBq), as well as high lesion contrast, supporting its use as a cost-effective alternative to PET tracers.

Therapeutic translation of CXCR4-targeting ligands has been explored with Pentixather labeled with β emitting radionuclides. In a first-in-human study, [^{177}Lu]Lu-Pentixather and [^{90}Y]Y-Pentixather were administered to three patients, resulting in a greater than 50% reduction in serum-free light chain differences in two patients.²¹⁸ However, all patients experienced bone marrow ablation, and severe hematologic toxicity was observed, reflecting the high and prolonged uptake of Pentixather in the hematopoietic system. Dosimetry studies confirmed substantial bone marrow accumulation, limiting the maximum safely deliverable dose. These findings suggest that alternative radionuclides, including α emitters, may be more suitable for CXCR4-targeted radionuclide therapy.

Overall, [^{68}Ga]Ga-Pentixafor and [^{177}Lu]Lu-Pentixather represent pioneering agents for CXCR4-targeted imaging and therapy. Future development should focus on improving receptor selectivity, reducing hepatic and renal uptake, and optimizing ligand hydrophilicity to enhance therapeutic index and expand clinical applicability.

Claudin-18 isoform 2 (Claudin18.2). Claudin18.2 (Figure 7C) has emerged as a highly promising target for molecular imaging and radionuclide therapy, attributable to its restricted expression in normal tissues and marked overexpression in gastric cancer and metastatic lesions.^{219–220} A range of antibody-based constructs and derivative radiotracers designed to target claudin18.2 have been developed, encouraging tumor uptake and translational viability in preclinical models. Hu et al. reported three [^{89}Zr]Zr-anti-CLDN18.2 antibodies for immune-PET imaging, identifying [^{89}Zr]Zr-anti-CLDN18.2 VHH-ABD as possessing particularly advantageous pharmacokinetics.²²¹ [^{89}Zr]Zr-anti-CLDN18.2 VHH-ABD achieving tumor uptake of $21.46 \pm 1.78\% \text{ID} \cdot \text{g}^{-1}$ with relatively low liver accumulation ($6.70 \pm 0.74\% \text{ID} \cdot \text{g}^{-1}$). Chen et al. developed a humanized claudin18.2 monoclonal antibody, [^{89}Zr]Zr-DFO-TST001, which exhibited significantly higher tumor uptake in BGC823 claudin18.2 xenografts compared with claudin18.2-negative controls (2.05 ± 0.16 vs $0.69 \pm 0.02\% \text{ID} \cdot \text{g}^{-1}$), with a projected effective dose of $0.0705 \text{ mSv} \cdot \text{MBq}^{-1}$.²²² Beyond diagnostic applications, the therapeutic potential of claudin18.2 targeted radiopharmaceuticals has been substantiated through rigorous preclinical evaluation. Therapeutic evaluation of [^{177}Lu]Lu-DOTA-TST001 revealed a pronounced inhibition of tumor growth in claudin18.2 positive models, with the high-dose group (11.10 MBq) displaying significantly reduced tumor volumes relative to controls and no evident hematological or hepatic toxicity.²²² At the clinical level, Wang et al. conducted a single-center phase 0 study of [^{124}I]I-18B10 (10 L), in 17 patients, demonstrating tumor lesion uptake with SUV_{max} values ranging from 0.4 to 19.5, as well as notable tracer accumulation in metastatic lymph nodes ($\text{SUV}_{\text{max}} = 6.6$).²²³

However, the high production cost, prolonged circulation time, and delayed imaging windows associated with full-length antibodies remain major limitations. To address these challenges, several antibody derivatives and small-molecule ligands have been explored. Wei et al. developed a series of nanobody-based tracers, including [^{68}Ga]Ga/ ^{18}F / ^{64}Cu -labeled hu19V3 variants.²²⁴ While [^{68}Ga]Ga-NOTA-hu19V3T enabled visualization of small claudin18.2-positive lesions, high renal uptake limited imaging contrast. Subsequent [^{64}Cu]Cu-labeled variants demonstrated time-dependent renal clearance ($13.73 \pm 2.16\% \text{ID} \cdot \text{g}^{-1}$ at 1 h decreasing to $0.11 \pm 0.05\% \text{ID} \cdot \text{g}^{-1}$ at 48 h), though sensitivity for disseminated lesions remained suboptimal. An [^{18}F]F-labeled derivative, [^{18}F]hu19V3, achieved improved biodistribution and enabled detection of disseminated claudin18.2 overexpressing lesions ($2.10 \pm 0.53\% \text{ID} \cdot \text{g}^{-1}$).²²⁵

These data highlight claudin18.2 as a compelling next-generation target for both diagnostic imaging and radiopharmaceutical therapy (RPT), while also underscoring the need for optimized ligands, particularly peptides or engineered scaffolds, to enable efficient and scalable theranostic applications.

Carbonic anhydrase isoform IX (CA IX).

CA IX is a hypoxia-associated, membrane-bound enzyme that is highly upregulated in clear cell renal cell carcinoma (ccRCC), making it one of the most clinically validated targets for renal cancer imaging.^{208,226} Antibody-based CA IX radiotracers have demonstrated robust diagnostic performance in advanced clinical studies. Girentuximab (mAb G250), which recognizes an

extracellular conformational epitope of CA IX, was evaluated in a large multicenter phase III trial involving 226 patients using [^{124}I]I-labelled girentuximab. PET/CT imaging achieved a mean sensitivity of 86.2% and specificity of 85.9%, outperforming contrast-enhanced CT for ccRCC lesion detection.²²⁷ Despite its favorable diagnostic accuracy and tolerability, [^{124}I]I-based immunoPET suffers from high radionuclide cost and *in vivo* deiodination, resulting in undesirable thyroid uptake. To address these limitations, [^{89}Zr]Zr-DFO-girentuximab advanced into phase I/II clinical trials.²²⁸ PET-positive lesions detected by [^{89}Zr]Zr-DFO-girentuximab were consistently confirmed as aggressive ccRCC, and additional metastatic lesions were identified beyond conventional imaging. Dosimetry analysis revealed that the liver received the highest absorbed dose ($1.86 \pm 0.40 \text{ mGy} \cdot \text{MBq}^{-1}$), while the median tumor absorbed dose reached $4.03 \text{ mGy} \cdot \text{MBq}^{-1}$, supporting the safety and quantitative reliability of this tracer.²²⁹ The geometric mean SUV_{max} of [^{89}Zr]Zr-DFO-girentuximab-positive lesions ($\text{SUV}=15.5$) was also markedly higher than that of [^{18}F]FDG ($\text{SUV}=4.4$), highlighting its superior sensitivity for ccRCC metastasis detection.²³⁰

In parallel, small-molecule CA IX ligands have gained increasing attention due to their favorable pharmacokinetics and reduced immunogenicity. [^{18}F]VM4-037 was the first small-molecule CA IX PET tracer evaluated clinically (Figure 7D). However, whole-body PET/CT in healthy volunteers revealed high physiological uptake in the kidney and liver (273 ± 31 and $240 \pm 68 \mu\text{Gy} \cdot \text{MBq}^{-1}$, respectively), limiting its utility for primary renal lesion imaging.²³¹ Subsequent phase II studies confirmed poor contrast for intrarenal ccRCC lesions, although extrarenal metastases remained detectable.²³² Acetazolamide-based tracers have shown improved tumor-to-background performance. In a clinical SPECT/CT study, [$^{99\text{m}}\text{Tc}$]Tc-PHC-102 demonstrated significant uptake in primary ccRCC lesions in all five patients, with high tumor-to-background ratios, and enabled the detection of previously occult lung and lymph node metastases (Figure 7D).²³³

To sum up, these results establish CA IX as one of the most clinically mature molecular targets in radiopharmaceutical development for ccRCC. Future efforts focusing on non-renally metabolized ligands, particularly high-affinity cyclic peptides, are expected to further enhance lesion detectability and enable CA IX-directed radionuclide therapy.

Glypican-3 (GPC3). Glypican-3 (GPC3) is a membrane-anchored heparan sulfate proteoglycan that is highly overexpressed in hepatocellular carcinoma (HCC) while being largely absent in normal adult tissues, rendering it a highly specific biomarker for HCC diagnosis and therapy.^{234–236} Among GPC3-targeting radiotracers, antibody-based probes have progressed furthest toward clinical translation. [^{124}I]I-labeled codrituzumab is currently the only GPC3-targeting immuno-PET agent evaluated in clinical trials. In a phase Ib study (NCT00976170), PET imaging was performed in 14 patients, of whom 13 exhibited tumor-positive signals, and 6 patients showed high tracer uptake with SUV values exceeding 9, confirming the feasibility of GPC3-directed PET imaging in HCC.²³⁷

To improve pharmacokinetics and imaging contrast, antibody fragments and engineered antibodies have been explored. [^{89}Zr]Zr-DOTA- $\alpha\text{GPC3-F(ab')}_2$ demonstrated a shortened blood half-life of approximately 11 h, enabling high-quality PET imaging as early as 4 h post-injection, with a peak tumor-to-liver contrast ratio of 23.3.²³⁸ In addition, PET/CT imaging of the bispecific antibody ERY974 revealed that tumor uptake correlated with intratumoral T-cell infiltration, and [^{89}Zr]Zr-labeled ERY974 preferentially accumulated in T-cell-rich tumor regions, supporting its potential utility for immune-engaged tumor characterization.²³⁹ Single-domain antibody (sdAb)-based tracers further improved tumor targeting efficiency and reduced hepatic background.⁶⁸ Ga- and [^{18}F]F-labeled sdAb G2 achieved tumor-to-muscle ratios of 6.58 ± 0.28 and 12.93 ± 3.01 , respectively.²⁴⁰ Similarly, [^{89}Zr]Zr-DFO-ssHN₃ and [^{89}Zr]Zr-DFO-nHN₃ exhibited high tumor uptake (7.2 ± 1.2 and $5.7 \pm 1.8\% \text{ID} \cdot \text{g}^{-1}$ at 1 h post-injection, respectively) with reduced liver accumulation, highlighting the advantages of sdAb scaffolds for GPC3-targeted imaging.²⁴¹ For therapeutic applications, GPC3-directed radionuclide therapy has also been explored. A [^{227}Th]Th-labeled GPC3 antibody conjugated with the Octapa chelator demonstrated potent tumor-killing effects, achieving optimal therapeutic efficacy 23 days after treatment, supporting the feasibility of GPC3-targeted a particle therapy.²⁴² Peptide-based GPC3 ligands have been developed to address the limitations of antibody-based tracers. Peptide tracers, such as [^{18}F]F-labeled L5

derivatives, enabled tumor visualization but exhibited a low tumor-to-liver ratio (0.93 ± 0.16), limiting clinical applicability (Figure 7E).²⁴³ Subsequent screening efforts identified improved peptide ligands. [¹⁸F]AIF-NOTA-TJ12P2 accumulated in HepG2 and SMMC-7721 tumors with uptake values of 1.825 ± 0.296 and 1.575 ± 0.520 ID·g⁻¹, respectively.²⁴⁴ Further structural optimization led to [¹⁸F]AIF-GP2633, which achieved increased tumor uptake (3.37 ± 0.35 ID·g⁻¹) and reduced liver accumulation (1.70 ± 0.26 ID·g⁻¹) at 1 h post-injection.²⁴⁵ In addition, the SPECT tracer [^{99m}Tc]Tc-HPG reached a maximum tumor-to-muscle ratio of 11.55 ± 0.54 at 1 h, indicating favorable imaging contrast.

Overall, GPC3 represents one of the most promising molecular targets for HCC-specific radiopharmaceutical development. Despite encouraging clinical and preclinical results, excessive hepatic uptake remains a major challenge. Continued optimization of ligand structure, particularly the development of high-affinity peptide ligands with subnanomolar binding and improved pharmacokinetics, will be critical for advancing GPC3-targeted imaging and radionuclide therapy toward broader clinical application.

Targeting tumor microenvironment

FAP. FAP has emerged as one of the most compelling targets among TME-targeting radiopharmaceuticals.²⁴⁶ The TME plays a pivotal role in tumor growth, invasion, metastasis, and therapeutic resistance, comprising cancer cells, immune cells, vascular components, extracellular matrix, and cancer-associated fibroblasts (CAFs).^{247–248} FAP is a type II transmembrane serine protease that is highly upregulated in activated CAFs across a wide spectrum of epithelial and mesenchymal malignancies, while its expression remains minimal in most normal adult tissues.²⁴⁹ This distinct expression profile, combined with the abundance and spatial stability of CAFs within solid tumors, makes FAP an attractive and broadly applicable molecular target for diagnostic imaging and radionuclide therapy.^{250–251}

The clinical development of FAP-targeting radiopharmaceuticals has been dominated by small-molecule FAPIs. Quinoline-based tracers such as FAPI-04, have been extensively evaluated in clinical PET/CT studies (Figure 7F). In a cohort of 80 patients with various malignancies, [⁶⁸Ga]Ga-FAPI-04 showed pronounced tumor uptake, with a mean SUV_{mean} of approximately 12 at 1 h post-injection.²⁵² Comparative studies further reported higher detection rates than [¹⁸F]FDG for primary tumors (98.2% vs. 82.1%) and lymph node metastases (86.4% vs. 45.5%).²⁵³ Albumin-binding FAPIs incorporating Evans blue or other moieties significantly prolonged tumor residence time. For example, [¹⁷⁷Lu]Lu-EB-FAPI-B1 maintained high tumor uptake up to 96 h post-injection.²⁵⁴ Dimerization represents an alternative approach: [⁶⁸Ga]Ga-DOTA-2P(FAPI)₂ showed prolonged tumor retention compared with monomeric FAPI-46, and therapeutic FAPI dimers labeled with ¹⁷⁷Lu achieved disease control rates exceeding 90% in small clinical cohorts.²⁵⁵ Beyond small molecules, peptide-based FAP ligands have demonstrated superior tumor retention and target selectivity. FAP-2286, a cyclic peptide selected from a large peptide library, has emerged as a leading clinical candidate (Figure 7F). First-in-human studies of [¹⁷⁷Lu]Lu-FAP-2286 further demonstrated favorable dosimetry, with low absorbed doses to kidneys and red marrow and no dose-limiting toxicities observed.²⁵⁶

FAP-targeted radiopharmaceuticals play a central role in next-generation precision oncology. Beyond these FAP-targeted radiopharmaceuticals, a broad spectrum of next-generation FAP-targeting molecules with optimized targeting and pharmacokinetic profiles has been developed, as comprehensively reviewed in our previous work.²⁴⁶

Dual-targeting & multi-valent radiopharmaceuticals

The inherent spatial and phenotypic heterogeneity of TAA expression poses a critical challenge for single-target radiopharmaceuticals. This often results in false-negative lesion detection when antigen levels fall below the threshold for effective uptake. This can potentially contribute to therapeutic resistance by allowing antigen-negative subpopulations to survive and expand.²⁵⁷ Dual-targeting & multi-valent strategies have therefore emerged as a rational approach to address receptor heterogeneity, enhance tumor retention, and improve the therapeutic index by engaging multiple receptors simultaneously.²⁵⁸ The dual-targeting and multi-valent strategies encompass both bispecific antibodies (bsAbs), which are engineered to recognize two

distinct epitopes, as well as heterodimeric ligands designed for dual-targeting and multi-valent (Figure 7G).²⁵⁹

Among antibody-based platforms, immuno-PET imaging of bsAbs has enabled real-time visualization of target engagement and biodistribution. The anti-PD-1/CTLA-4 bispecific antibody cadonilimab (AK104), radiolabeled as [²⁴¹At]-AK104, demonstrated specific accumulation in PD-1⁺/CTLA-4⁺ tumor-infiltrating lymphocytes within humanized mouse models, achieving superior tumor-to-nontumor ratios compared to monospecific antibody imaging and supporting its potential for patient stratification in immunotherapy.²⁶⁰ Similarly, the PD-L1/4-1BB bispecific antibody ATG-101 was labeled with ⁸⁹Zr for preclinical PET imaging. [⁸⁹Zr]Zr-Df-ATG-101 exhibited PD-L1-dependent tumor uptake in MDA-MB-231 xenografts, with persistent visualization up to 7 days post-injection, confirming the feasibility of monitoring bsAb biodistribution and target engagement *in vivo*.²⁶¹

In parallel, peptide-based heterodimeric radioligands have been extensively investigated to overcome receptor heterogeneity. The combination of RGD motifs (targeting integrin $\alpha_v\beta_3$) with bombesin (targeting GRPR) has yielded tracers such as [^{99m}Tc]Tc-RGD-BBN, which demonstrated enhanced tumor uptake in breast cancer models and was further evaluated clinically, showing superior sensitivity for primary breast tumors and axillary metastases compared to conventional ultrasound.²⁶² More recently, the FAP- and integrin-targeting heterodimer [⁶⁸Ga]Ga-/[¹⁷⁷Lu]Lu-FAPI-RGD has advanced to first-in-human studies; in patients with advanced adenocarcinomas, [¹⁷⁷Lu]Lu-DOTA-FAPI-RGD therapy was well tolerated and achieved a disease control rate of 88.9%, with prolonged tumor retention enabling effective radiation delivery.²⁶³

Multi-valent designs have also been pursued to exploit avidity effects. A tetravalent RGD peptide, [²¹¹At]At-(RGD)₄, retained the capacity for simultaneous binding to multiple integrin $\alpha_v\beta_3$ receptors, exhibiting high and persistent tumor uptake in preclinical models and highlighting the potential of multi-valent scaffolds for targeted α therapy.²⁶⁴ Collectively, these advances underscore that dual-targeting and multi-valent radiopharmaceuticals offer a versatile strategy to address tumor heterogeneity, enhance imaging contrast, and expand the therapeutic window, with ongoing clinical translation poised to redefine precision nuclear medicine.

RADIOBIOLOGY AND INTEGRATION

Radiation-induced effect

One advantage of radionuclide therapy is that it takes advantage of the bystander effect and abscopal effects induced by radiation.²⁶⁵ This enables local treatment to produce broader biological effects and extends them throughout the body. These effects challenge the traditional focus on precise targeting in radionuclide therapy and provide a different conceptual basis for addressing tumor heterogeneity and promoting anti-tumor immunity.²⁶⁶

Bystander effect. The radiation-induced bystander effect (RIBE) describes the phenomenon whereby cells that are not directly traversed by ionizing radiation exhibit biological responses due to signals received from neighboring irradiated cells.²⁶⁷ This non-targeted response is mediated by multiple signaling molecules, including reactive oxygen species (ROS), reactive nitrogen species, nitric oxide (NO), inflammatory cytokines, and mitochondrial-derived factors (Figure 8A).²⁶⁸

In radionuclide therapy, the bystander effect provides an effective way to mitigate the heterogeneity of target expression, which is precisely the main limitation of traditional targeted therapy.²⁶⁹ The spatial extent and intensity of the bystander effect are intrinsically linked to the physical decay properties of the radionuclide used. α emitters (e.g., ²²⁵Ac, ²¹¹At), characterized by their high LET and short path length (typically <100 μ m), confine bystander signaling primarily to gap junction-mediated intercellular communication and short-range exosome transfer.² In contrast, β emitters (e.g., ¹⁷⁷Lu, ⁹⁰Y), with tissue penetration of several millimeters, generate bystander effects largely driven by diffusible soluble mediators, thereby inducing a wider spatial response. Auger electron emitters, often considered to have minimal non-targeted effects due to their subcellular range, can elicit an enhanced bystander response when internalized and localized within the nuclear DNA, mediated by radiation-induced bystander signaling pathways, effectively converting a potential limitation into a therapeutic advantage.²⁷⁰

In recent years, research has increasingly focused on the crucial role of

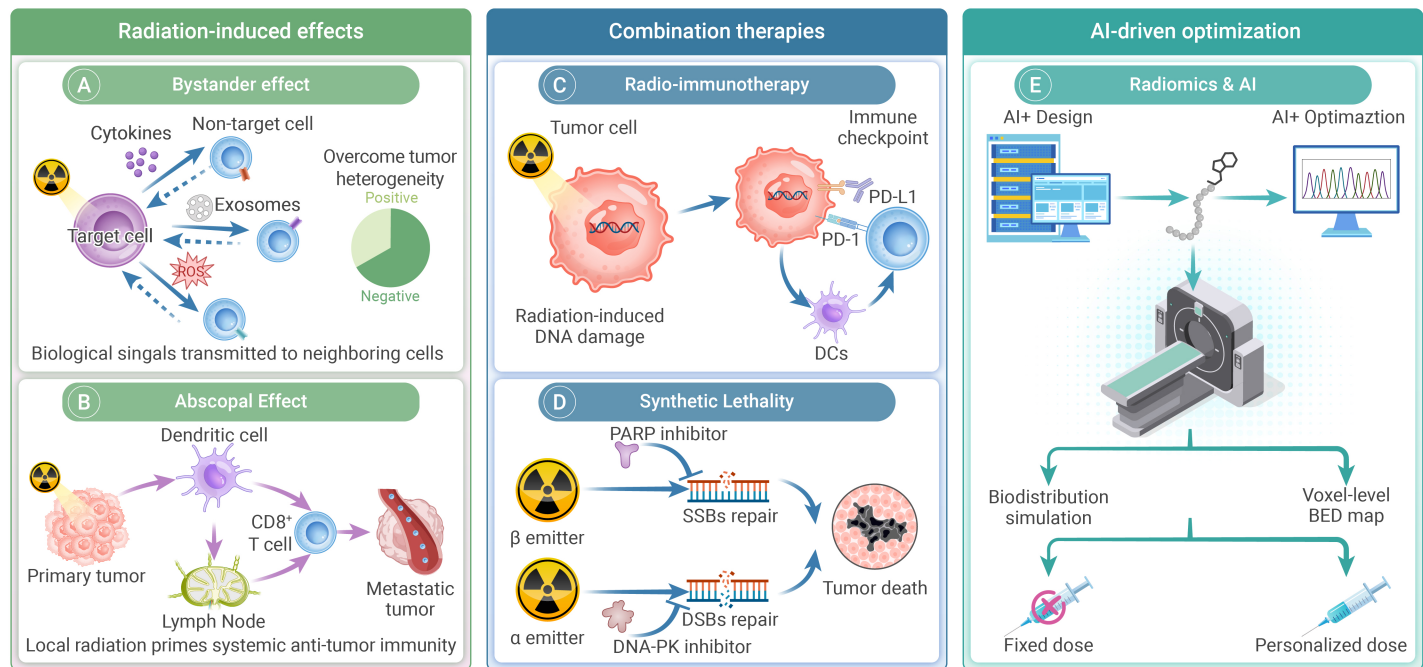


Figure 8. Key mechanisms, therapeutic strategies, and the role of AI in targeted radionuclide therapy

exosomes in mediating bystander signals during radionuclide therapy. After being labeled with radionuclides, tumor cells release a type of exosome that is rich in pro-apoptotic microRNAs and damage-related molecular patterns.²⁷¹ These nanoscale vesicles can then be internalized by neighboring cells that have not been exposed to radiation, exerting an effect by activating the BAX-mediated mitochondrial apoptosis pathway; simultaneously, exosome cargo can activate innate immune signaling axes such as TLR9-MyD88-NF- κ B through recognition of damage-associated molecular patterns, with these pathways cross-regulating to determine bystander cell fate. In experimental models containing antigen-negative tumor cells, this exosome-mediated bystander mechanism makes a significant contribution to overall cytotoxicity and even constitutes a considerable part of the anti-tumor effect. This breakthrough in understanding has elevated the bystander effect from an accidental discovery in radiation biology to a quantifiable and strategically modulable therapeutic variable.^{271–272}

Abscopal effect. The abscopal effect is defined as the phenomenon where distant metastatic lesions that were not exposed to radiation undergo regression after local radiotherapy. This is an immune-mediated response.²⁷³ The potential cascade process usually begins with radiation-induced immunogenic cell death. These dying tumor cells release damage-associated molecular patterns (DAMPs) and TAA, which are subsequently captured by dendritic cells. Through cross-presentation, CD8⁺ cytotoxic T lymphocytes (CD8⁺ T cells) are activated, and these cells can enter the bloodstream, migrate, and eliminate distant unirradiated tumor lesions. The abscopal effect and the bystander effect may share a common inflammatory basis. For example, the increase in systemic chemokine levels, especially the CCL3 signal that acts through the CCR1/5 axis, could serve as a bridge connecting local radiation exposure and distant biological responses (Figure 8B).²⁷⁴

Clinical evidence demonstrated that a combination of external beam radiotherapy and immunostimulant cytokine therapy induces repeatable abscopal effects in patients with metastatic solid tumors, and the survival period of responders is significantly prolonged.²⁷⁵ In the specific context of nuclear medicine treatment, recent studies have shown that some patients with mCRPC have experienced significant regression of non-target lesions after receiving PSMA-targeted therapy based on β emitters.²⁷⁶ A favorable baseline inflammatory spectrum characterized by a low neutrophil-lymphocyte ratio and evidence of systemic T-cell activation has become a consistent predictor of the *in vitro* response.²⁷⁷

Preclinical studies show α emitters induce DSBs and activate cGAS-STING,

driving type I interferon and dendritic cells,²⁷⁸ leading to CD8⁺ T cell expansion, distinct from β emitters but converging on common effectors.²⁷⁹ Significant progress has been made in the concurrent treatment engineering strategies through the co-delivery system based on nanocarriers, enabling the simultaneous administration of radionuclide-labeled ICIs and immunomodulators. This comprehensive approach has been proven to induce complete remission in a considerable proportion of experimental animals, accompanied by synchronous regression of the unirradiated contralateral tumors.²⁸⁰ Comprehensive spatial transcriptomics analysis has revealed a profound remodeling of the tumor microenvironment, characterized by M1 macrophage polarization, regulatory T cell depletion, and the expansion of effector memory T cell populations, features consistent with the immune hot tumor phenotype.^{281–282}

Combination therapies

The research on the combination strategies of RPT has currently formed two major cutting-edge directions: one is radioimmunotherapy, which utilizes the immunomodulatory properties of ionizing radiation to make tumors sensitive to ICIs. The second is the synthetic lethal strategy, which rationally pairs with DNA damage response inhibitors based on the radionuclide-specific DNA damage spectrum. These two paths jointly mark the transformation of RPT from a single treatment model to a combined treatment platform that integrates multiple tumor vulnerabilities.²⁸³

Radio-immunotherapy. Radiation-induced immunogenic cell death (ICD) is a complex mechanism centered on cytoplasmic DNA sensing, among which the cGAS-STING pathway plays a key role. Meanwhile, radiation can also upregulate the expression of major histocompatibility complex class I (MHC-I) molecules on the surface of tumor cells, enhance the antigen presentation ability, and promote the release of pro-inflammatory cytokines.²⁷⁹ However, this radiation-induced immune activation can also trigger a compensatory negative feedback mechanism, mainly manifested as the adaptive upregulation of PD-L1 in tumor cells and the increased expression of PD-1 in activated T cells. This inherent drug resistance mechanism provides a solid theoretical basis for the combination of RPT and PD-1/PD-L1 inhibitors.²⁸⁴ Recent studies have shown that poly ADP-ribose polymerase (PARP) inhibitors can also activate the cGAS-STING pathway by accumulating cytoplasmic chromatin fragments produced by stress. This discovery offers a theoretical possibility of a triple combination approach: RPT induces DNA damage, PARP inhibitors impede repair and enhance STING signaling, while ICI releases the anti-tumor immune response, thus triggered (Figure

8C).^{285–286}

Realizing the above potential still faces several key challenges: it is necessary to discover predictive biomarkers that can be used for patient screening; The pairing algorithm for radionuclide characteristics and tumor types needs to be optimized. It is necessary to explore dose and timing schemes that can maximize the synergy effect while maintaining safety. It is even more necessary to obtain strict validation in prospective randomized trials. The precise matching of the physical properties of radionuclides with systemic treatment regimens will become the core proposition in clinical practice.²⁸⁷

Synthetic lethality. In addition to radioimmunotherapy, synthetic lethality provides an alternative theoretical basis for enhancing RPT efficacy. Synthetic lethality refers to a genetic interaction where the concurrent loss of two distinct but compensatory pathways, individually tolerable but together lethal, leads to selective cell death.²⁸⁸ The synthetic lethal strategy provides a theoretical basis for the combined application of RPT and DNA damage repair (DDR) inhibitors. The key to achieving this strategy lies in the precise selection of DDR targets, which must match the physical properties of the radionuclides used and the types of DNA damage they induce, such as complex double-strand breaks (DSBs) induced by α emitters corresponding to DNA-dependent protein kinase inhibition, and single-strand breaks (SSBs) induced by β emitters corresponding to PARP inhibition, to achieve precise synergies. This complements the immunotherapy strategy of RPT combined with ICIs.^{289–290}

This principle has been validated in clinical trials. The low LET radiation produced by β nuclides mainly induces single-strand breaks, which can be effectively repaired through base excision repair mediated by PARP1. PARP inhibitors not only block SSB repair but also exert cytotoxic effects by capturing PARP-DNA complexes and through synthetic lethal mechanisms. This makes the combined strategy of β RPT and PARP inhibitors highly attractive, especially for tumors with inherent or radiotherapy-induced replication stress.^{291–292} In contrast, α nuclides produce high LET radiation that induces high-density complex DSBs, which are significantly resistant to non-homologous end joining (NHEJ) and homologous recombination (HR). The repair of this damage mainly relies on the collaborative action of NHEJ mediated by DNA-dependent protein kinase catalytic subunit (DNA-PKcs) and HR regulated by ataxia telangiectasia mutated (ATM), but the repair efficiency is significantly reduced. Therefore, inhibition of DNA-PKcs or ATM becomes a reasonable choice for the α -RPT combined strategy.^{293–294} The COMRADE trial (NCT03317392) provides key clinical validation for this strategy. This study demonstrated that the combination of ^{223}Ra and olaparib significantly improved the radiological progression-free survival, although there was no significant difference in overall survival. It is noteworthy that the benefit of radiological progression-free survival (rPFS) was independent of the HR repair mutation status, which challenges the traditional view that the synergy of PARP inhibitors must be based on HRR defects and indicates that α emitter induced high LET DNA damage may enhance the sensitivity to PARP inhibitors through non-classical mechanisms.²⁹⁵

Based on these strategies for DDR, the development of the next-generation inhibitors has further expanded the range of options for combined therapy. For instance, the first-of-its-kind dual-target ATM/DNA-PKcs inhibitor demonstrates a potent radio-sensitizing effect in preclinical models by simultaneously inactivating the two core kinases responsible for DSB signal transduction and NHEJ execution.²⁹³ This dual-target approach is particularly attractive for the α -RPT combination, as it can overcome the compensatory pathway activation observed with single-agent DDR inhibitors. Additionally, ATR inhibitors targeting the replication stress response are being evaluated in combination with RPT to take advantage of radiation-induced replication fork collapse. However, the rational development of these strategies requires careful attention to normal tissue toxicity, especially myelosuppression, which may need to be optimized through fractionated RPT administration or time adjustment (Figure 8D).^{296–297}

Radiomics and AI

AI is now enabling next-generation innovative radiopharmaceuticals through intelligent molecular design, predictive modeling, and image-based patient stratification.

AI-empowered molecular design of radiopharmaceuticals. Therapeutic

efficacy and safety depend on the carrier's ability to bind targets with high affinity and optimal PK. AI is now breaking these bottlenecks: deep learning and generative models enable navigation of chemical space with unprecedented precision, streamlining the pipeline from target identification to clinical-grade radioligand optimization.¹⁴

The first critical step in this pipeline is to identify appropriate molecular targets. Ideal targets show high overexpression in diseased cells, stable high-affinity binding, and minimal healthy tissue expression for a favorable therapeutic index. AI integrates multi-omics data, with network analysis to screen for targets meeting these criteria.²⁹⁸ The next challenge is to predict and optimize the interaction between ligands and proteins to assess the affinity of drug targets. Traditional methods like molecular docking are useful, but they can be computationally expensive. AI offers sequence-based, image-based, and graph-based models. However, for radiopharmaceuticals that typically involve complex molecular structures and chelating sites, graph-based models are particularly promising.²⁹⁹

Based on affinity predictions, generative AI designs novel radioligands, creating new molecular entities with optimized attributes.³⁰⁰ For radiopharmaceuticals, the design challenges are more complex because they require an integrated design approach. Radioactive decay processes, such as the recoil effect of α emitters like ^{225}Ac , can lead to bond breaks and molecular instability, resulting in the release of free radionuclides and subsequent off-target toxicity. Future AI models need to learn from experimental data to predict which chelating structures and ligand configurations are most resistant to the stress caused by this decay, ensuring that the designed molecules can maintain their integrity and functionality even under the continuous bombardment of their own radiation.³⁰¹

Clinical translation of this combined strategy has progressed most rapidly in mCRPC. A Phase I trial using a single dose [^{177}Lu]Lu-PSMA-617 followed by maintenance treatment with pembrolizumab showed encouraging anti-tumor activity, with an objective response rate of approximately 50%, and the biochemical response persisted. Meanwhile, α -nuclides, due to their unique physical properties, are becoming highly promising partners in immune combination strategies. Taking the Phase I trial of [^{225}Ac]Ac-J591 as an example, this regimen has established safety and preliminary efficacy in mCRPC patients who have received multiple lines of treatment. At the mechanism level, the dense ionization trajectory of α particles can generate many cytoplasmic DNA fragments, efficiently activate the cGAS-STING axis, and induce a stronger type I interferon response compared with β nuclides.³⁰² This makes α -RPT not only a cytotoxic approach but also an in-situ immunostimulatory strategy capable of reshaping the tumor immune microenvironment (Figure 8E).³⁰³

Synthesizing these advances, AI is transforming the paradigm from an accidental, trial-and-error process to a rational, data-driven science. This molecular-level precision is a necessary foundation for the subsequent success of molecular imaging and personalized treatment.³⁰⁴

From fixed-dosing limitations to AI-driven image analysis

The limitations of the fixed-dosing paradigm. While radioimmunotherapy and synthetic lethality strategies have demonstrated preclinical and early clinical efficacy, their optimal application requires a shift from empirical treatment selection to precision-based patient stratification. Unfortunately, current clinical practice is still confined to a one-size-fits-all model, characterized by a fixed active dose and a primary visual image interpretation. This traditional approach neglects the vast amount of quantitative information contained in conventional PET/CT scan data, which may be the key to initiating truly personalized treatment. The integration of radiomics and AI is now preparing to address this limitation and promote a paradigm shift towards precision therapeutics.³⁰⁵ Traditional PET/CT evaluations have long relied on semi-quantitative indicators, such as SUVs. SUVs can only capture a small portion of the complex phenotypic information contained in tumors. Radiomics addresses this gap by extracting hundreds of quantitative features, which collectively reflect potential tumor biology, intratumoral heterogeneity, and microenvironmental characteristics. For instance, intratumoral heterogeneity is closely related to genomic instability and treatment resistance. Pre-treatment ^{68}Ga Radiological features of [^{68}Ga]Ga-PSMA-11 PET/CT are associated

with tumor grade and treatment response of prostate cancer, and ^{68}Ga PET radiomics can identify phenotypic heterogeneity associated with differential outcomes after ^{177}Lu treatment.^{306–307}

AI solutions: Pre-therapeutic PET/CT modeling for patient stratification. The combination of radiomics and machine learning enhances predictive capabilities. Recent studies have demonstrated the clinical application of this synergy. Seifert et al. developed a prognostic risk score for mCRPC using PSMA PET-derived tumor volume, which demonstrated superior performance compared with traditional PET parameters.³⁰⁸ Similarly, a study strictly validated the AI-based model on five external PET/CT datasets, confirming the accuracy of predicting the progression-free survival of lymphoma patients (Figure 8E).³⁰⁹

In RPT, a key unmet need is the ability to prospectively distinguish patients who benefit from those at increased risk of toxicity. Radiomics-based stratification can address this need by capturing tumor heterogeneity—a key determinant of treatment resistance.³¹⁰ However, the clinical implementation of radiomics analysis mainly depends on powerful automated segmentation tools. Manually describing the volume of interest remains time-consuming, operator-dependent, and impractical for high-throughput analysis. Recent developments in AI are beginning to overcome this bottleneck. A deep learning architecture has been developed, enabling fully automated tumor volume segmentation in lymphoma PET/CT with strong multi-center generalizability.³¹¹ Additionally, automated lesion segmentation tools for ^{68}Ga -PSMA and ^{18}F -FDG PET images have been introduced, thereby facilitating large-scale radiomic analyses essential for clinical translation and prospective validation.³⁰⁹

Predictive dosimetry: From population averages to individualized dosing. Among the promising applications of AI in RPT, predictive dosimetry stands out as particularly impactful—enabling estimation of post-treatment absorbed dose distributions from pre-treatment imaging alone. Conventional dosimetry methods, which require multiple post-treatment imaging sessions and labor-intensive manual segmentation, remain impractical for routine clinical use. Deep learning addresses this limitation by enabling voxel-level dose prediction from diagnostic PET/CT scans alone, thereby streamlining the dosimetry workflow and supporting personalized treatment planning.^{312–313}

Recent studies have demonstrated that 3D U-Net architectures can specifically predict post-treatment dosimetry for ^{177}Lu -PSMA using solely pre-treatment PET/CT scans, achieving accuracy comparable to Monte Carlo simulations. Extending beyond mere dose prediction, the clinical objective has evolved from simple absorbed dose calculations to biologically effective dose estimation for tumors and organs at risk, which incorporates dose-rate effects and cell repair kinetics to provide more biologically meaningful metrics for predicting treatment response and normal tissue toxicity.³¹⁴ By integrating biodistribution simulation with dose-volume histogram generation, AI models can now prospectively identify patients whose prescribed activities may exceed organ tolerance thresholds, bridging the gap between predictive dosimetry and clinical decision-making.³¹⁵

In short, radiomics and AI constitute a powerful driving force for precision therapeutics. These techniques directly address the heterogeneity that limits the current fixed-dose paradigm by transforming conventional PET/CT images into stratified quantitative biomarkers and individualized dosimetry prediction tools. The ability to identify exceptional responders, non-responders who need combination therapy, and patients at increased risk of toxicity works together to achieve truly personalized RPT.³¹⁵ When combined with complementary strategies such as radioimmunotherapy and synthetic lethality, AI-driven RPT is expected to provide the right dose to the right patients at the right time, maximize therapeutic efficacy, and minimize toxicity.³¹⁶

TRANSLATION, REGULATORY & GLOBAL SUPPLY CHAIN

Toxicity

RPT toxicity management must address both clinical dose-limiting toxicities (DLTs) and public exposure risks, as patients become temporary radiation sources.³¹⁷ Risks include external exposure, environmental contamination via excreta, and the entry of radioactive materials into waste management systems.^{35,318} Thus, toxicity management should address not only clinical DLTs and organ dosimetry assessment but also broader considerations, including patient release criteria, discharge approvals, and radioactive waste

regulations.⁸⁸

International standards: Risk control principles for post-therapeutic excreta. The international radiation protection framework focuses on management principles grounded in risk stratification and dosimetric data.³¹⁹ The ICRP guidelines for the release of patients treated with unsealed radionuclides specify that decisions regarding hospitalization, isolation, or special excreta management should be based on the estimated effective doses to others, not solely the administered activity.³²⁰ Public dose limits and the ALARA (As Low As Reasonably Achievable) principle are core components of decision-making.¹²⁰

For short-lived β or α emitting radionuclides, discharging patient excreta into municipal sewage systems typically does not exceed public dose limits, provided the sewage system can adequately dilute and manage radioactive waste.^{321–322} As a result, international standards generally do not mandate urine collection or decay systems.⁴¹ The focus is on personalized dose assessments and behavioral strategies to manage risk.^{323–325}

International regulatory and procedural frameworks. The regulatory framework for managing excretion and release in RPT typically requires coordination between medical regulatory bodies and nuclear safety agencies.³²⁶

The regulatory frameworks vary: the United States (NRC Guide 8.39) focuses on dose calculations for patient release.³²⁷ The International Atomic Energy Agency (IAEA) documents stress that national policies should consider local infrastructure and societal factors, with stricter restrictions in areas with limited sewage treatment or high population density.³²⁸ The EU (Directive 2013/59/Euratom) requires discharge authorization and annual reporting.³²⁹ In China, the system integrates health oversight with environmental discharge regulations.³³⁰ Decisions about patient discharge are based on dose assessments, ensuring public exposure stays within national limits.³²⁶ Japan (Radionuclide Act) emphasizes precise dosimetric modeling and delay-and-decay systems for liquid waste.³³¹

Overall, international practices have developed a comprehensive management framework based on dosimetric evidence, behavioral controls, licensing systems, and interagency coordination. This approach avoids overly simplistic universal containment strategies while minimizing public exposure risks and ensuring a sustainable safety foundation for the clinical use of RPT.³²⁶

Global distribution of radionuclides

^{18}F is the most commonly used medical radionuclide globally, supported by an extensive regional production network based on cyclotron systems.³³² Its global distribution is concentrated in developed countries, with gradual expansion in developing regions.^{14,333} And ^{68}Ga , derived from the $^{68}\text{Ge}/^{68}\text{Ga}$ generator system, allows on-site preparation without the need for large accelerators, offering a critical pathway for PET development in resource-limited areas.³³⁴ However, the supply of high-purity ^{68}Ge raw materials and generator production remains concentrated in a few countries, raising concerns about supply chain security.³³⁵ For β emitting radionuclides, global production relies mainly on research reactors or accelerator-based methods, with Europe and Canada serving as key supply hubs.³³⁶ As indications expand and patient populations grow, demand for β emitting radionuclides has increased, making production capacity and high-specific-activity preparation technologies crucial.³³⁷ β -radionuclide therapy is evolving from late-stage salvage treatment to frontline combination therapy.^{318,338} Meanwhile, global production of ^{225}Ac is limited, mainly sourced from ^{229}Th stockpiles with rapidly growing accelerator routes, leading to significant supply shortages.³³⁹ High production costs, complex radiochemistry, and stringent radiation-protection requirements hinder large-scale use.³⁴⁰ The U.S. and Europe are actively developing a radionuclide production systems, while Asia is still catching up (Figure 9).³⁴¹

Global challenges

The supply chains for key radionuclides are concentrated in a few developed countries. The production of medical nuclides relies heavily on a limited number of research reactors and accelerators. This concentration, combined with reliance on aging reactor infrastructure, poses risks to the reliable supply of critical radionuclides.^{14,342} In developing countries, nuclear medicine infrastructure is often inadequate, with shortages in equipment and personnel.³⁴³ Additionally, there is heavy dependence on imported radionuclides, and price

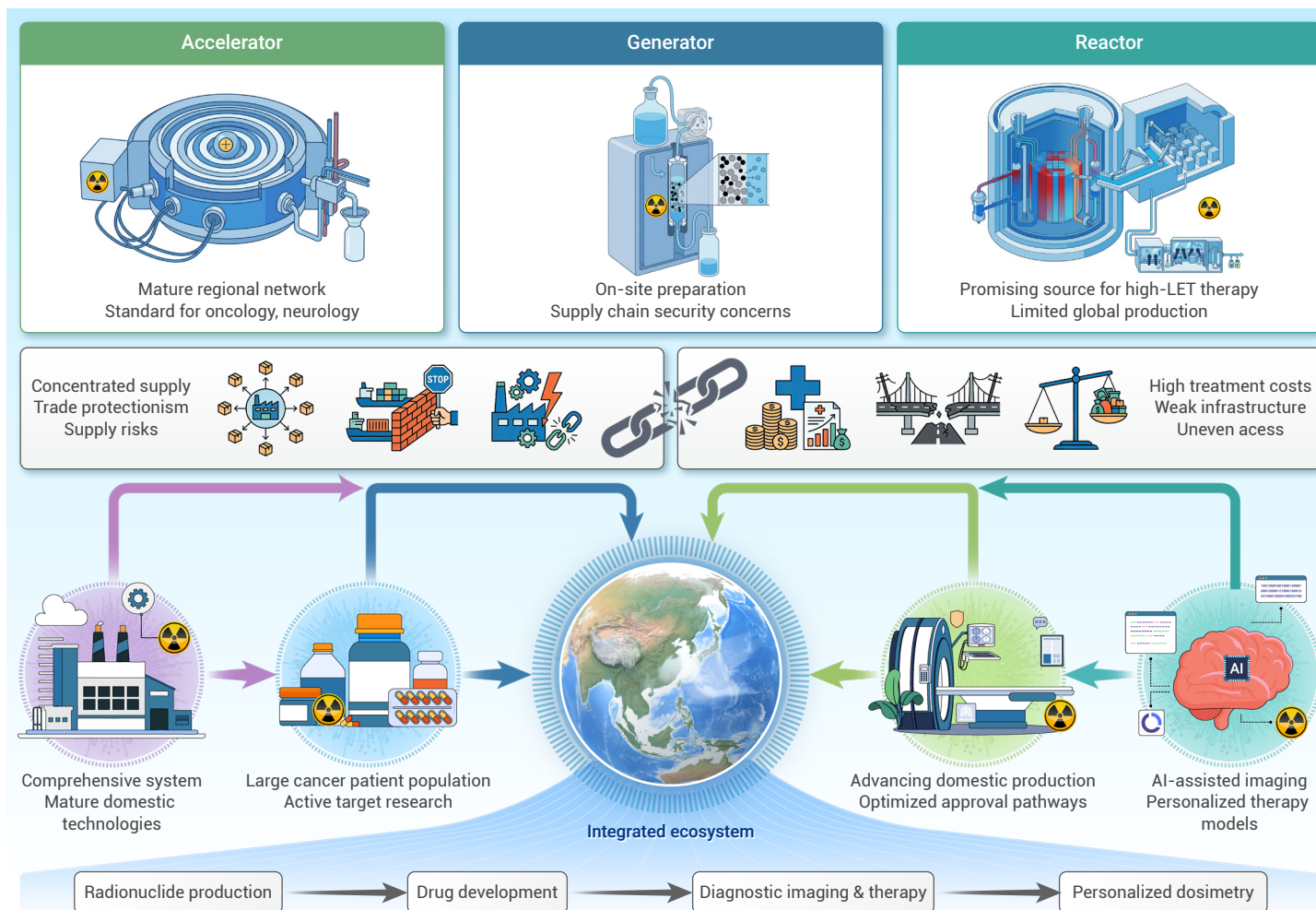


Figure 9. The production, distribution, and challenges faced in the radiopharmaceutical industry

fluctuations directly impact patient access.³⁴⁴ Regulatory systems and GMP standards are also not fully developed, hindering the progress and industrialization of domestic radiopharmaceuticals. The IAEA has highlighted the uneven distribution of nuclear medicine resources, with low-income countries having far fewer PET scanners than high-income countries.³⁴⁵

Global production bottlenecks, especially for α emitting radionuclides, restrict clinical expansion. Geopolitical tensions or trade barriers could disrupt global supply chains, impacting the progress of precision nuclear medicine. Establishing diversified, regionalized supply systems for medical nuclides has become a key global strategic challenge.

Regional ecosystems

Rather than a single dominant supplier, the contemporary radiopharmaceutical landscape is best understood as a set of interdependent regional ecosystems, each with distinctive strengths and structural vulnerabilities across the value chain including reactor and accelerator isotope production, precursor and chelator supply, clinical translation, regulatory approval, and commercialization. No region is presently self-sufficient across all of these layers, and this interdependence is itself a defining feature of the field.

The United States hosts arguably the most mature clinical-translational and commercial ecosystem. The FDA has approved most of the field's flagship theranostics, from $[^{223}\text{Ra}]\text{RaCl}_2$ ⁷⁶ and $[^{177}\text{Lu}]\text{Lu-DOTATATE}$ ⁸⁸ to the PSMA-directed diagnostics^{190–191} and $[^{177}\text{Lu}]\text{Lu-PSMA-617}$.³⁵ Its national laboratories, together with the Department of Energy Isotope Program, underpin much of the global research supply of ^{225}Ac and other emerging α emitters, including the ^{229}Th -generator source that has anchored actinium availability for two decades.^{42–43,340} The consolidation of the ^{177}Lu therapeutic franchise within a single multinational, alongside a broader wave of acquisitions of radioligand

therapy developers, has concentrated substantial capital and manufacturing investment in the region.³¹⁷ Yet the US ecosystem has historically depended entirely on imported $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$, with domestic ^{99}Mo capacity established only recently.^{346–347} Reimbursement pathways for radiopharmaceuticals remain administratively complex and as professional bodies have repeatedly noted, the specialized radiochemistry and nuclear medicine workforce is a growing constraint on scale-up.

Europe combines a deep tradition of foundational radiochemistry and clinical innovation. Much of the pioneering work on peptide receptor radionuclide therapy, PSMA- and FAP-directed agents originated in European academic centers with a central role in global isotope supply.^{5,348} A network of research reactors across several member states, historically together with Canada, has supplied the majority of the world's ^{99}Mo ,^{346–347} while JRC-Karlsruhe remains a key source of ^{225}Ac ,³⁴⁹ and regulatory and radiation-protection frameworks are harmonized supranationally through the European Medicines Agency and the Euratom Basic Safety Standards.^{328–329} The principal vulnerabilities are structural: much of the reactor fleet is aging and approaching end-of-life, creating recurrent risk of ^{99}Mo supply interruption; reimbursement and regulatory implementation remain fragmented across member states despite harmonization efforts; and a number of European-discovered agents have ultimately been commercialized through non-European companies.³¹⁷

China has moved rapidly to build an integrated domestic ecosystem. Expanding reactor and cyclotron infrastructure, maturing domestic radiochemistry and automated-synthesis platforms,^{14,350} and one of the world's largest cancer patient populations have together enabled unusually rapid, large-scale multicenter studies, particularly on PSMA- and FAP-directed agents, to which Chinese groups now contribute a substantial share of the global clinical literature.^{348,351} Sustained policy support was exemplified by the

Medium- and Long-Term Development Plan for Medical Isotopes (2021–2035), the country's first dedicated national isotope strategy, alongside the establishment of radiopharmaceutical industrial parks and streamlined approval pathways, has accelerated domestic translation, while a strong AI and imaging and manufacturing base offers further leverage in dosimetry and image-based patient selection.³⁵² Several gaps nonetheless temper this trajectory. Domestic supply security for key isotopes is still being established: China has historically relied on imported ⁹⁹Mo and precursor materials, and reactor-based isotope self-sufficiency has not yet been achieved. Capacity for α emitting radionuclide production (²²⁵Ac, ²¹¹At) and the associated handling and radiochemistry infrastructure remains nascent. And although the regulatory framework is maturing quickly, it is younger than its US and European counterparts, with much current output building on already-validated targets rather than first-in-class biology; originator target discovery, chelator and precursor intellectual property, GMP standardization, and international product registration remain areas of active development.^{312,353–355}

Viewed together, these ecosystems are complementary as much as competitive. The most consequential near-term risk is not the ascendancy of any single region but the fragility of a globally interdependent supply chain concentrated in a small number of aging facilities and exposed to geopolitical and trade disruption. Against this backdrop, the strategic priority for China as for the United States and Europe is the development of diversified, regionally resilient, and where feasible cooperative supply networks spanning reactor- and accelerator-produced isotopes, precursors, and chelators. China's combination of an emerging end-to-end industrial chain, exceptional clinical scale, coordinated policy, and digital-health capacity positions it to become one of the central nodes in this multipolar system; realizing that potential will depend on closing its remaining gaps in upstream isotope security, α emitter infrastructure, regulatory maturity, and originality of molecular design.

CONCLUSIONS & FUTURE PERSPECTIVES

Radiopharmaceuticals have firmly established themselves as a cornerstone of precision medicine, offering a combined diagnostic and therapeutic capability that traditional pharmacotherapy cannot match. In recent years, the clinical success of agents targeting prostate cancer and neuroendocrine tumors has validated the theranostic model, demonstrating that a companion diagnostic scan can identify the patients in whom a cytotoxic payload, delivered by the same targeting vector, will be retained by the tumor. Collateral damage is reduced but not eliminated, salivary gland uptake remains the dose-limiting toxicity of PSMA-directed α therapy, and renal and hematological exposure continue to constrain peptide receptor radionuclide therapy, which is precisely why patient-specific dosimetry has become a central rather than a peripheral concern of the field. The field is now expanding beyond its reliance on β^- emitters such as ¹⁷⁷Lu, which remain the clinical and commercial mainstay, toward targeted α therapy. This approach deposits high-energy radiation over a range of only a few cell diameters, producing clustered double-strand DNA breaks that are poorly repaired and that act largely independently of tumor oxygenation and cell-cycle phase, offering a route to cells refractory to conventional treatment.

Looking ahead, the future of radiopharmaceuticals lies in expanding beyond oncology into neurology, cardiology, and infectious diseases. In neurology, amyloid and tau PET tracers are already approved and now underpin patient selection and safety monitoring for anti-amyloid antibody therapy, with a synuclein, TDP-43, and neuroinflammation imaging representing the next frontier; in cardiology, FAPI tracers are being applied to image activated fibroblasts after myocardial infarction. Realizing this potential requires overcoming hurdles that are logistical as much as chemical. For short-lived diagnostic nuclides such as ⁶⁸Ga and ¹⁸F, decentralized production through medical cyclotrons and regional radiopharmacies is the answer. For therapeutic α emitters it is not: ²²⁵Ac ($t_{1/2} = 9.9$ d) is constrained not by decay but by supply, depending on a small number of ²²⁹Th generators, high-energy spallation, and emerging ²²⁶Ra-based accelerator routes, while ²¹²Pb is obtained from ²²⁸Th/²²⁴Ra generators. Scaling these routes, standardizing dosimetry, and training the radiochemists and medical physicists the field will require are the true rate-limiting steps. AI will contribute by accelerating dose calculation, automating organ segmentation, and supporting quality control, although the automation of GMP manufacturing itself will remain a matter of synthesis

modules, hot cells, and robotics. If these conditions are met and isotope supply, infrastructure, and reimbursement can be extended beyond the high-income centers in which the modality is currently concentrated, then nuclear medicine is positioned to move from a specialized field toward a genuine pillar of personalized healthcare.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.