

Radiolabeled Iron-Based Nanomaterials for Cancer Diagnosis and Therapy

Yan-Xi Ma*, Kun-Long Dai*, Na Sun, Song Zhang

Department of Nuclear Medicine, Xin Qiao Hospital, Army Medical University, Chong Qing, 400037, People's Republic of China

*These authors contributed equally to this work

Correspondence: Kun-Long Dai; Song Zhang, Email dai18393814467@163.com; cqsydzs@tmmu.edu.cn

Abstract: Cancer remains one of the leading causes of death worldwide, with diagnosis and treatment continuing to pose significant challenges. In recent years, iron-based nanomaterials (iron oxide-based nanomaterials, iron-based complex conjugates) have garnered unprecedented attention due to their excellent functionality, superior biocompatibility and potential for multifunctional integration. Due to the non-specific nature of radionuclides. Their integration with nanomaterials offers promising opportunities for precise cancer diagnosis and effective treatment by enabling targeted delivery, controlled release, and synergistic combination therapies. This review systematically elucidates the latest advancements in radiolabeled iron-based nanomaterials for cancer diagnosis and therapy, with a focus on radiolabeling methods, multimodal imaging, and the combination of radiotherapy with various treatment modalities, including photothermal therapy (PTT), magnetic hyperthermia therapy (MHT), photodynamic therapy (PDT), immunotherapy (IT), and chemodynamic therapy (CDT). Finally, the prospects for the development of radiolabeled iron-based nanomaterials are discussed, along with key research priorities for the future.

Keywords: radionuclides, iron-based nanomaterials, multimodal imaging, combination therapy

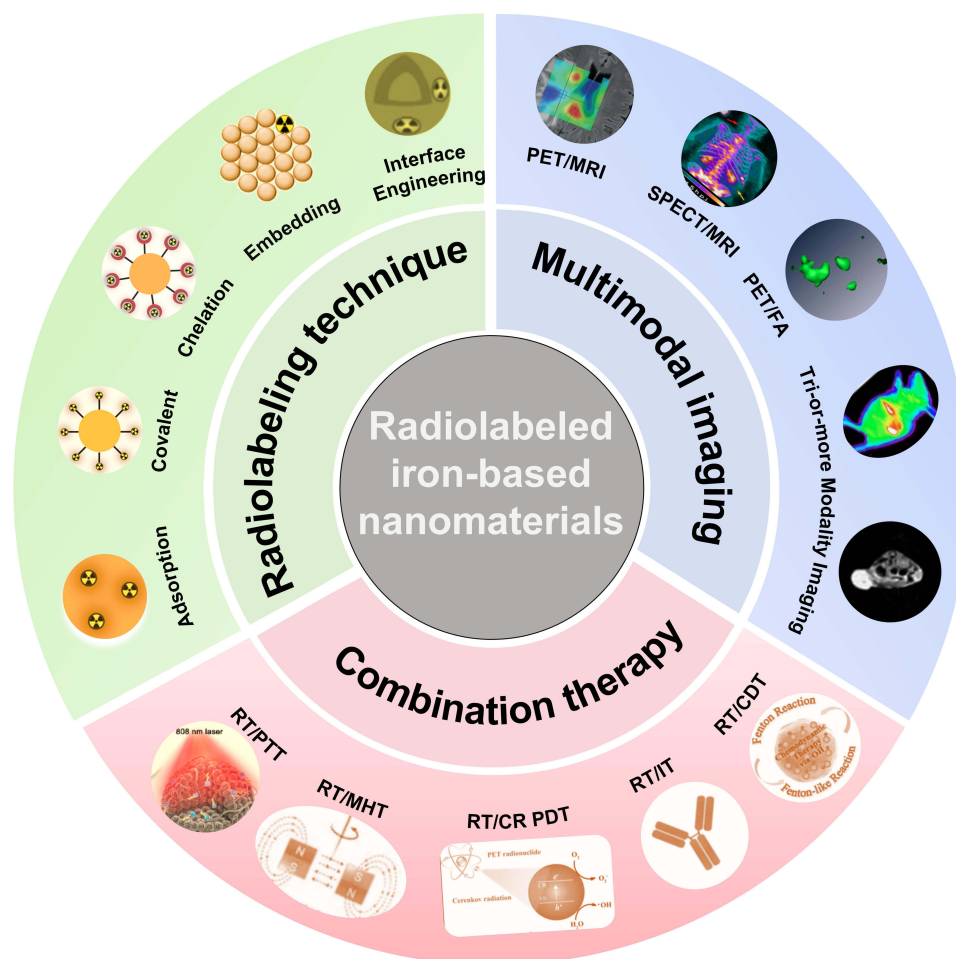
Introduction

Cancer ranks as the second most common cause of mortality globally. According to World Health Organization (WHO) projections, global cancer incidence may increase by 60% within the next 20 years.¹ The growing burden of cancer presents substantial challenges to both public health and economic systems, making early detection and effective treatment universally recognized priorities.² While modern oncology has made significant advances, conventional diagnostic and therapeutic approaches face limitations due to tumor heterogeneity, drug resistance, and adverse effects. Current screening methods primarily rely on biomarkers and imaging techniques (eg, X-ray, ultrasound, MRI); however, definitive diagnosis often requires invasive biopsy or surgical sampling.

The current options for cancer therapy modalities include surgery, chemotherapy, radiotherapy, immunotherapy, monoclonal antibodies, targeted therapy, photodynamic therapy, and laser ablation. However, each approach has inherent drawbacks.³ Conventional cancer treatment often entails surgical intervention, which serves as the first-line approach for most malignancies by enabling direct removal of the tumor. Despite its efficacy, surgery is associated with significant risks and considerable physical trauma. Chemotherapy induces severe systemic toxicity. External beam radiotherapy, though widely used, delivers suboptimal radiation doses to tumors due to energy absorption by surrounding healthy tissues, resulting in collateral damage.^{4,5} In contrast, internal radiotherapy (radionuclide therapy) offers a targeted approach by delivering cytotoxic radiation directly to tumors or their microenvironment. Unlike biological therapies that modulate signaling pathways, radionuclides induce tumor cell death via localized ionizing radiation, which induces DNA strand breaks.^{6,7} This method improves therapeutic precision while minimizing off-target effects.

Radionuclides are categorized into diagnostic and therapeutic nuclides. Diagnostic radionuclides are essential for patient stratification planning, leading to enhanced outcomes in targeted radionuclide therapy. Additionally, radionuclides

Graphical Abstract



can be utilized in conjunction with positron emission tomography (PET) and single photon emission computed tomography (SPECT) techniques to precisely monitor systemic disease lesions and patient stratification (Table 1).^{8–10}

Molecular delivery systems play a crucial role in enhancing the tumor-targeting capabilities of various radionuclide constructs, encompassing small molecules, polypeptides, antibodies, nanomaterials, and microspheres.^{11,16–20} Despite advancements, radionuclide-based therapies encounter significant challenges in both diagnosis and treatment. Some cancers exhibit resistance to radionuclide therapy, while issues such as non-specific distribution, limited bioavailability, and ionization-induced damage to non-target organs further complicate their efficacy.^{12,13,21} To address these challenges, the integration of nanomedicine offers a promising avenue to broaden the diagnostic and therapeutic landscape. Radionuclide nano systems are emerging as powerful tools for tumor diagnosis and treatment. Specifically, leveraging nanomaterials for targeted delivery of radionuclides to tumor tissues holds potential to enhance bioavailability and reduce toxicity to normal tissues.^{7,14}

Recent advancements in radiopharmaceuticals have demonstrated the utilization of nanomaterials in diagnosing and treating various cancers, leveraging their distinctive physical and chemical properties.^{22–24} Nanomaterials have emerged as pivotal players in diverse nuclear medicine domains, notably in the creation of radionuclide nanoparticle carriers for deployment as contrast agents in computed tomography (CT) imaging.²⁵ These carriers enable the loading, transport, and delivery of a multitude of radionuclides within a single nanomaterial. In contrast to numerous small molecule

Table I Radionuclide properties^{11–15}

Type	Radionuclide	Mode of Decay	Half-Life	Max Energy (Mev)	Particle Range in Tissue (mm)	Production	Application
Positron emitter	¹¹ C	β+	20.36min	0.961	3.8	Accelerator	PET Imaging
	¹³ N	β+	9.97min	1.199	5.0	Accelerator	PET Imaging
	¹⁵ O	β+	2.13min	1.732	8.0	Accelerator	PET Imaging
	¹⁸ F	β+	109.77min	0.634	2.4	Accelerator	PET Imaging
	⁶¹ Cu	β+	3.34h	1.216	4.5	Accelerator	PET Imaging
	⁶⁴ Cu	β+	12.7h	0.656	2.2	Accelerator	PET Imaging
	⁶⁶ Ga	β+	9.49h	4.153	16	Accelerator	PET Imaging
	⁶⁸ Ga	β+	67.71min	1.899	9.0	Generator	PET Imaging
	⁸² Rb	β+	1.26min	3.378	15.5	Generator	PET Imaging
	⁸⁹ Zr	β+	78.41h	0.900	3.5	Accelerator	PET Imaging
α-emitters	¹²⁴ I	β+	4.17d	2.100	10.5	Accelerator	PET Imaging
	²¹¹ At	α,γ	7.2h	5.9	0.05	Accelerator	α-Therapy
	²¹³ Bi	α	46min	5.87 (α); 5.55 (β ⁻)	0.05–0.08	Generator	α-Therapy
	²²⁵ Ac	α	9.92d	5.8	0.05–0.08	Reactor	α-Therapy
	²²³ Ra	α	11.4d	5.9	0.05–0.08	Generator	α-Therapy
	²²⁷ Th	α	18.7d	5.9	0.05–0.08	Generator	α-Therapy
	²¹² Bi	α, β ⁻ ,γ	1.0h	6.09 (α);6.05 (β ⁻)	<0.1/0.05	Generator	α-Therapy
	¹⁴⁹ Tb	α	4.2h	0.4	<0.1	Generator	α-Therapy
	³² P	β ⁻	14.27h	1.710	8	Reactor	β-Therapy
	⁴⁷ Sc	β ⁻	3.35d	0.440	1.5	Accelerator	β-Therapy, SPECT Imaging
β-emitters	⁶⁷ Cu	β ⁻	61.83h	0.577	1.8	Accelerator	β-Therapy, SPECT Imaging
	⁸⁹ Sr	β ⁻	50.56d	1.5	2.4	Reactor	β-Therapy
	⁹⁰ Y	β ⁻	64.05h	2.282	12	Reactor	β-Therapy
	¹³¹ I	β ⁻	8.03d	0.606	2	Reactor	β-Therapy, SPECT Imaging
	¹⁶⁶ Ho	β ⁻	26.82h	1.773	8.5	Reactor	β-Therapy, SPECT Imaging
	¹⁷⁷ Lu	β ⁻ ,γ	6.65d	0.498	1.5	Reactor	β-Therapy
	¹⁸⁶ Re	β ⁻	3.72d	1.08	5	Reactor	β-Therapy
	¹⁸⁸ Re	β ⁻	17.00h	2.12	10	Reactor	β-Therapy, SPECT Imaging
	²¹² Pb	β ⁻	10.62h	0.57	0.05–0.08	Reactor	α/β-Therapy
	¹⁵³ Sm	β ⁻ ,γ	1.90d	0.81003	0.4	Reactor	β-Therapy
γ-emitters	¹⁹⁸ Au	β,γ	2.70d	0.96	4	Reactor	β-Therapy
	⁶⁷ Ga	γ	78.3h	0.3	10nm	Accelerator	SPECT Imaging, Auger therapy
	^{99m} Tc	γ	6.00h	0.14	1μm	Generator	SPECT Imaging
	¹¹¹ In	γ	2.80d	0.0074	500nm	Accelerator	SPECT Imaging, Auger therapy
Auger electron emitters	¹²³ I	γ	13.22h	0.159	10nm	Accelerator	SPECT Imaging
	⁷⁷ Br	Auger e-	57.04h	2.96	11	Accelerator	Auger therapy
	¹²⁵ I	Auger e-	59.41d	0.159	10nm	Reactor	Auger therapy
	¹⁹¹ Pt	Auger e-	2.83d	0.03	<0.01	Reactor	Auger therapy

radiopharmaceuticals, nanomaterials possess a superior specific surface area-to-volume ratio, rendering them optimal candidates for targeted radionuclide delivery. Furthermore, many nanoparticles offer supplementary optical, magnetic, and other imaging and therapeutic functionalities.^{26,27}

Transition metal nanomaterials are one of the most representative nanomaterials in the field of nanomedicine. Iron-based nanomaterials have been widely used in tumor diagnosis and treatment due to their unique magnetism, good biocompatibility, chemical stability, and various morphologies.^{28–30} Among various candidates, iron-based nanomaterials present distinct advantages over other materials like gold, which is also notable for imaging and radiosensitization. (1) Biocompatibility and Clinical Translation: Iron oxide-based nanomaterials (eg, Ferumoxytol) have received approval from the U.S. Food and Drug Administration (FDA) as MRI contrast agents and drug carriers, providing a clear regulatory pathway and established safety profile.³¹ (2) Multifunctionality: They possess unique magnetism enabling MRI contrast, magnetic targeting, and magnetic hyperthermia (MHT).^{32,33} (3) Fenton Activity: Iron ions can catalyze the production of reactive oxygen species (ROS) via Fenton reactions, facilitating chemodynamic therapy (CDT). (4) Cost-Effectiveness and Abundance: Iron is more abundant and less expensive than gold, facilitating scalable production. While gold nanoparticles exhibit excellent surface plasmon resonance for photothermal therapy, iron-based materials offer a broader spectrum of inherent therapeutic mechanisms and easier clinical integration, making them a compelling platform for radiolabeled theranostics.³⁴

This review aims to provide a comprehensive and critical update specifically on radiolabeled iron-based platforms. It also serves as a valuable supplement to existing earlier reviews. An area that has evolved rapidly but lacks a recent dedicated synthesis comparing labeling strategies, multimodal applications, and translational challenges. It summarizes the latest research progress and key radiolabeling technologies of radioisotope iron-based nanomaterials, focusing on their breakthrough applications and innovative strategies in multimodal imaging-guided precision diagnosis and targeted radiotherapy. It also discusses the key challenges and future plans for clinical translation.

Loading Radionuclides in Nanomaterials

A key factor in designing radio nanomedicines is radio stability the firm attachment of radionuclides to the material during storage, administration, and delivery to the target site. Otherwise, free radionuclides may cause systemic toxicity to normal tissues through undesired radiation exposure. To date, various strategies have been developed for labeling iron-based nanomaterials. Based on the location of radionuclides within the material, these methods can be categorized as surface conjugation, internal incorporation and interface engineering.^{28,35,36} Specific techniques include adsorption (physical binding), chelation (for metallic radionuclides, eg, ^{64}Cu , ^{68}Ga , ^{89}Zr), covalent conjugation (for non-metallic radionuclides, eg, ^{124}I , ^{131}I) and encapsulation (core-shell entrapment).

Surface Conjugation

Surface conjugation is a method for immobilizing radionuclides onto material surfaces, comprising two categories: direct surface labeling and indirect surface labeling. In the direct method, radionuclides form chemical bonds directly with the material surface. Most examples rely on coordination bonds between chemical groups on the nanomaterial surface—such as Fe_2O_3 , $-\text{PO}_3\text{H}$, $-\text{SH}$, or $-\text{OH}$ —and the radionuclides. The indirect method involves introducing chelating agents or prosthetic groups onto the material surface to enable binding with both metallic and non-metallic radionuclides.

The direct surface labeling of radionuclides, sometimes referred to as chemisorption, is a highly efficient and straightforward technique that relies on the unique chemical properties of nanomaterial surfaces to achieve robust attachment of radionuclides.³⁷ This method has been employed in catalysis and analytical chemistry to elucidate interaction mechanisms between metals and materials.³⁸ In 2013, Cai et al reported the first application of this technique to label iron-based nanomaterials, attributing the radiolabeling mechanism to the formation of stable $\text{As-Fe}_3\text{O}_4$ complexes, where $\text{As}^{\text{III}}\text{O}_3$ trigonal pyramids or $\text{As}^{\text{V}}\text{O}_4$ tetrahedra can occupy vacant tetrahedral sites on the octahedrally terminated (111) surface of Fe_3O_4 .³⁹ For non-metallic radionuclides, their strong affinity for iron-based materials is often exploited for labeling. For example, Zhu et al used ^{125}I to label $\text{Fe}_3\text{O}_4\text{-Ag}$ heterodimers, achieving MRI/SPECT dual-modality imaging probes through rapid binding of ^{125}I with Ag in the nanoparticles.⁴⁰

In addition, radiolabeling methods based on surface adsorption have been developed for clinically approved iron oxide drugs (eg, Feraheme, Ferumoxytol, and Ferucarbotran).^{41–43} By heating the reaction mixture at 120°C for 1 hour, ⁶⁴Cu tightly binds to the iron oxide core, achieving a radiochemical yield of $66 \pm 6\%$. The same reaction conditions are applicable to other metallic radionuclides in different oxidation states, such as ⁸⁹Zr and ¹¹¹In, with labeling yields of $93 \pm 3\%$ and $91 \pm 2\%$, respectively.⁴⁴ The variation in yields can be attributed to differences in the coordination chemistry, ionic radius, and optimal oxidation state for surface binding for each metal ion (Cu^{2+} , Zr^{4+} , In^{3+}). Both in vitro stability assays and in vivo biodistribution studies demonstrated that the resulting ⁸⁹Zr radiolabeled nanoparticles exhibit favorable pharmacokinetic profiles, with negligible impact on their physical and biological properties.

Recently, Patrick et al introduced the concept of surface radio-mineralization (SRM) to describe the heat-induced radiolabeling (HIR) method for iron oxide and ferrite nanoparticles. By applying HIR to label bare polymer-coated multinuclear and surface-functionalized iron oxide nanoparticles with ¹¹¹In and ⁸⁹Zr, they found that the radio-mineralized metal oxides on the nanoparticle surface did not alter the nanoparticles' original physical properties.⁴⁵

Compared to indirect labeling methods requiring chelators or prosthetic groups, direct surface radiolabeling offers distinct advantages: 1) Operational Simplicity: Most protocols can be completed via a straightforward one-step procedure. This approach also enables labeling of radionuclides difficult to chelate conventionally (eg, ⁷²As, ⁶⁹Ge). 2) Reduced Interference: Avoids potential side effects associated with chelators/prosthetic groups. Enhanced Functionalization Capacity: Without surface-bound chelators/prosthetic groups, more space remains for multifunctional engineering (eg, conjugation of fluorophores, targeting ligands, or therapeutic agents to create versatile nanoplatforms). 3) Improved Distribution Accuracy: Prevents inconsistencies in biodistribution caused by ligand dissociation, enabling more precise tracking of nanomaterial metabolism in vivo. However, the primary technical challenge lies in the high-temperature requirements (typically 100–120°C), which may compromise the integrity of thermolabile nanoparticle formulations, thereby limiting applicability.

Indirect Surface Labeling Using Chelating Agents

Radionuclides with metallic characteristics typically require chelating agents to connect them to nanomaterials through coordination chemistry methods. The choice of chelating agent is crucial for achieving stable radiolabeling. Factors such as the coordination number, coordination geometry, ionic radius, and charge of the radionuclide must generally be considered to ensure proper matching with the radionuclide. Additionally, according to the hard/soft acid-base theory, the hardness of different metallic radionuclides determines whether they coordinate more readily with hard or soft donor ligands.⁴⁶ Therefore, the “hardness” of the metal ion must be evaluated, and the selected ligand should have appropriate hard/soft donor atoms and correct electronic properties to improve the kinetic inertness of the complex.⁴⁷

Chelating agents are mainly divided into two categories: acyclic/linear chelators and macrocyclic chelators (Figure 1). Acyclic or linear chelators can rapidly form complexes with metal ions, making them suitable for applications requiring fast reactions. Due to their structural flexibility, complexes formed by linear chelators may be less stable than those formed by macrocyclic chelators.⁴⁸ In contrast, macrocyclic chelators have rigid and predetermined structures, providing a more stable coordination environment.⁴⁹ Although the complexation process is slower, the final products often exhibit improved stability, making them more suitable for long-term in vivo applications. The ideal chelating agent should be capable of functioning under mild conditions (eg, neutral pH and room temperature) while demonstrating sufficient kinetic inertness and thermodynamic stability in biological systems to ensure the stability and efficacy of radiolabeled compounds during imaging and therapy.⁴⁸

A critical consideration for chelator design is functionality within the tumor microenvironment (TME), which is often slightly acidic (pH ~6.5–6.8). Some chelators may exhibit reduced binding affinity or kinetic stability at lower pH, potentially leading to premature release of the radionuclide. Therefore, developing pH-resistant chelators or using macrocyclic chelators known for high kinetic inertness (eg, DOTA derivatives for trivalent metals) is crucial for applications in cancer theranostics.

Chelating agents can load metallic radionuclides through coordination. However, bifunctional chelators (BFCs) are typically required to successfully load metallic radionuclides onto nanoparticles.⁵⁰ BFCs can simultaneously bind to nanoparticles and chelate metallic radionuclides, improving labeling efficiency. During the conjugation process of

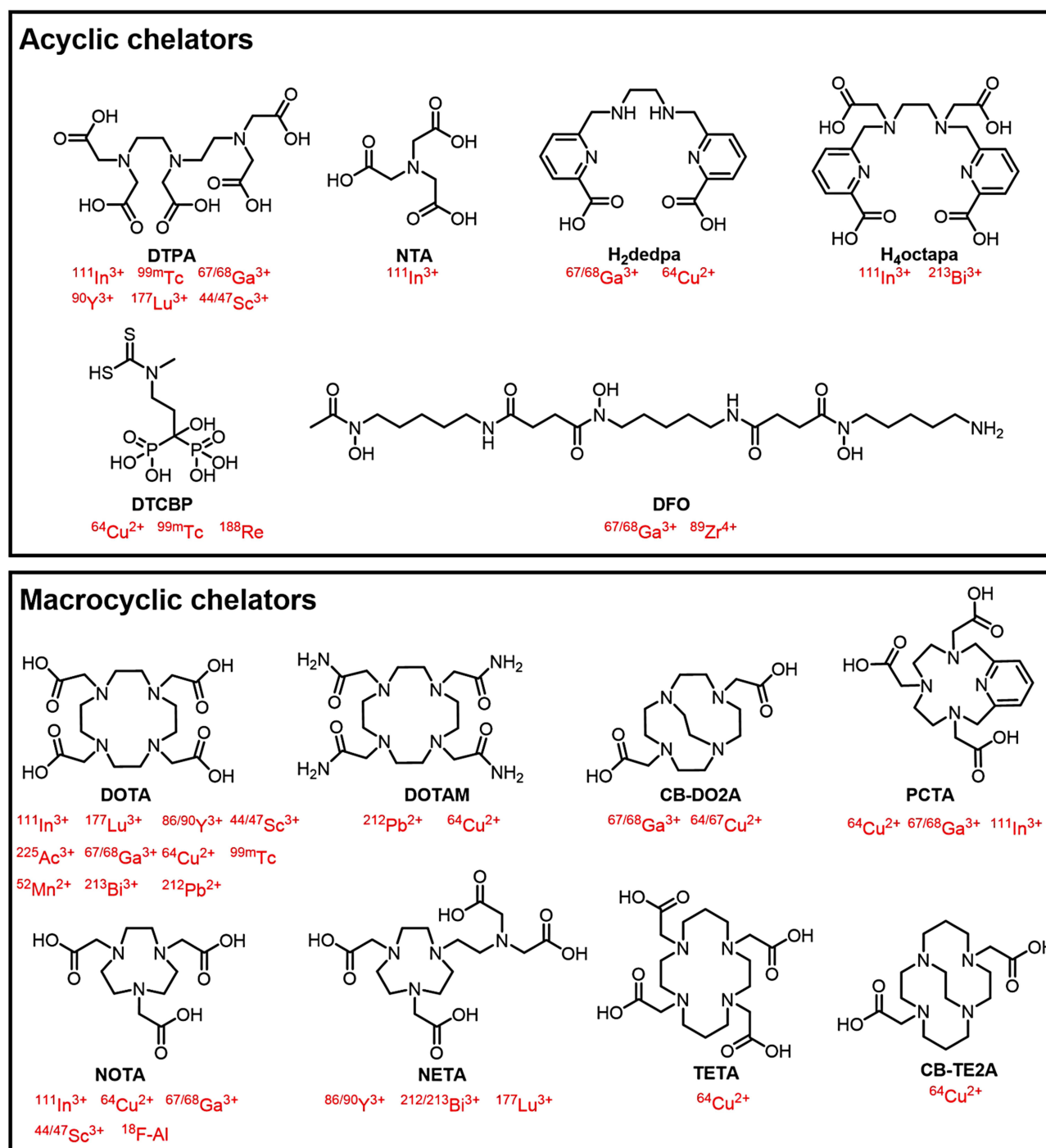


Figure 1 Common linear and macrocyclic chelators and matched radionuclides.

bifunctional chelators, the formation of chemical bonds between functional groups on the nanoparticle surface and the BFC is essential.⁵¹ These chemical bonds can be formed through various reactions, including amine coupling, carboxyl coupling, and thiol coupling. The choice of reaction depends on the functional groups present on the nanoparticle surface and the structure of the chelator. Click chemistry, noted for its rapid and efficient reaction characteristics, has been widely applied in radiolabeling of nanomaterials.⁵²

Gong et al successfully labeled cyclic arginine-glycine-aspartic acid (cRGD)-conjugated superparamagnetic iron oxide (SPIO) nanocarriers with ^{64}Cu using NOTA chelator for dual-modality PET/MRI imaging of tumors. The NOTA

chelator was conjugated to SPIO nanoparticles through a reaction between maleimide groups on the SPIO's polyethylene glycol (PEG) surface and thiol-functionalized NOTA, followed by efficient ^{64}Cu radiolabeling. This successful surface conjugation enabled quantitative comparison of tumor accumulation between targeted cRGD-SPIO and non-targeted SPIO formulations.⁵³ In another study, the Blower group reported a novel bifunctional chelator (dtcbp) featuring a dithiocarbamate group for binding ^{64}Cu and a bisphosphonate group with strong affinity for SPIO. The stability of $^{64}\text{Cu}(\text{dtcbp})_2$ -SPIO nanoparticles was tested in high concentrations of ethylenediaminetetraacetic acid (EDTA) and human serum, showing strong binding of ^{64}Cu to SPIO nanoparticles with minimal ligand dissociation.⁵⁴ Most recently, Grimm's research group achieved significant progress by constructing ^{89}Zr -labeled ferumoxytol (an FDA-approved iron oxide nanoparticle formulation) using desferrioxamine (DFO) chelator, significantly enhancing PET/MRI detection sensitivity for tumor-draining lymph nodes. This approach demonstrated remarkable radiolabeling efficiency exceeding 90% while maintaining the nanoparticles' critical physical properties including size distribution, surface charge, and magnetic relaxivity.⁵⁵

Indirect Surface Labeling Using Prosthetic Groups

Non-metallic radionuclides, such as $^{11}\text{C}/^{14}\text{C}$ and halogens (^{18}F , ^{76}Br , and iodine isotopes [^{123}I , ^{124}I , ^{125}I , ^{131}I]), are typically covalently conjugated to nanomaterials through reactive functional groups on surface ligands. The extremely short half-life of ^{11}C (20.4 minutes) necessitates rapid radiolabeling procedures. To label superparamagnetic iron oxide nanoparticles (SPIONs) with ^{11}C , [^{11}C]methyl iodide is used as a methylation agent, reacting with hydroxyl or amine groups on the nanoparticles via O-methylation or N-methylation. However, this approach suffers from low radiochemical yields (<3%), primarily due to particle agglomeration and low ligand surface density.⁵⁶ In contrast, ^{14}C has a much longer half-life (5.70×10^3 years) and relatively simpler labeling chemistry. Retterer et al successfully incorporated ^{14}C directly into the carbon backbone of organic molecules on Fe-Si-(COO^-)₃ nanoparticle surfaces, demonstrating that the ^{14}C -labeled nanoparticles exhibited identical chemical properties to their non-radioactive counterparts.⁵⁷ Furthermore, ^{18}F labeling of iron-based nanomaterials is commonly achieved using click chemistry approaches.⁵⁸

Halogen radiolabeling is a strategy that integrates radioactive halogens (primarily radioiodine) into nanomaterials through small-molecule radiochemical reactions. This method typically employs iodination reagents such as Iodogen,⁵⁹ Iodo-Beads,⁶⁰ Chloramine-T,⁶¹ and Bolton-Hunter reagents.⁶² These traditional iodination agents - Iodogen, Iodo-beads, and Chloramine-T - play a crucial role in radiolabeling biomolecules, particularly tyrosine residues and their derivatives. These reagents act as oxidants that rapidly react with iodide ions to generate highly reactive electrophilic species. The resulting electrophiles can efficiently substitute the ortho-position of phenolic hydroxyl groups on tyrosine residues, enabling effective radiolabeling of target molecules. This process is not only rapid (typically completed within seconds to minutes) but also achieves high radiolabeling efficiency, ensuring both the effectiveness and stability of the labeling. For instance, Gao et al developed a dual-modality molecular probe ($\text{Fe}_3\text{O}_4\text{-3H11-}^{125}\text{I}$) by using Iodogen method.⁶³

Internal Doping

Internal doping is commonly used to fabricate nanomaterials containing encapsulated radionuclides. This method effectively prevents radionuclide leaching, thereby avoiding *in vivo* labeling issues caused by ion migration, protein chelation, or ligand detachment. For iron-based nanomaterials, this approach includes techniques such as radiochemical doping and isotope exchange.

Radiochemical doping involves reacting a mixture of radioactive nuclide-containing precursors with non-radioactive ("cold") nanomaterial precursors in a one-step synthesis to produce radiolabeled nanomaterials. From a chemical perspective, trace amounts of radioactive nuclides ("hot" precursors) are introduced into the nanomaterial precursors, initiating co-precipitation and resulting in the incorporation of radionuclides into the nanomaterial's crystal lattice. As a widely used non-chelator-based radiolabeling techniques, this approach ensures high radiochemical stability while preserving the structural integrity of the material. The incorporation of radionuclides into the crystal lattice addresses the issue of signal loss associated with surface labels by physically shielding the radionuclide and integrating it into a stable matrix. These doped isotopes remain "inactive" in terms of unintended chemical interactions because they are substitutionally or interstitially placed within the lattice points, sharing the local chemical environment of the host atoms.

For instance, Moya et al employed a dual radiolabeling strategy: during nanoparticle synthesis, they doped Iron oxide nanoparticles (IONPs) with ^{111}In in the aqueous phase, encapsulated them in poly(lactide-co-glycolide) nanoparticles, and then attached ^{125}I to the surface-coating bovine serum albumin (BSA) via electrophilic substitution.⁶⁴ While aqueous-phase synthesis offers advantages such as high efficiency and easy post-processing, it often leads to undesirable nanomaterial morphology, low phase purity, and broad size distribution. These limitations can be mitigated by using organic solvents. For example, Gao et al synthesized ^{111}In -doped IONPs by thermally decomposing iron acetylacetonate in dibenzyl ether, yielding uniformly sized, highly crystalline nanoparticles.⁶⁵

Isotope exchange involves replacing (or exchanging) stable elements present on nanomaterials with radionuclides and can be categorized into heteroexchange and homoexchange. The distinction lies in whether the exchange occurs between different elements (heteroexchange) or between different isotopes of the same element (homoexchange). The advantage of this method is its operational simplicity. However, only a few examples in the literature have employed this technique for radiolabeling. For instance, Pospisilova et al reported the preparation of ^{59}Fe -IONP by incubating non-radioactive IONPs with $^{59}\text{FeCl}_3$ for 24 hours, achieving a radiolabeling yield of 83% and demonstrating high radiochemical stability (less than 2% of ^{59}Fe was released after 35 days of incubation in 0.1 M PBS at pH 7.4 and in rat serum).⁶⁶ However, the fate and long-term stability of such compounds within the complex tumor microenvironment (TME), characterized by hypoxia, acidity, and high protease activity, require further investigation. The safety of these radionuclides hinges on their retention within the nanocarrier. Potential release over very long periods (months to years) raises concerns about chronic radiation exposure. Therefore, comprehensive studies tracking isotope release kinetics, biodistribution over extended periods, and thorough toxicological evaluations are essential before clinical translation.

Interface Engineering

In addition to labeling radionuclides on the exterior or interior of nanomaterials, they can also be anchored at the interface between nanomaterials and ligands. Gao et al introduced an anchoring group-mediated radiolabeling strategy, in which bisphosphonate-functionalized PEG derivatives a dual function: acting as chelating groups for radionuclides and anchoring groups for surface PEGylation. This enables radionuclides to be immobilized between phosphate groups of adjacent PEG ligands. The SPECT tracer $^{99\text{m}}\text{Tc}$ was labeled onto Fe_3O_4 nanoparticles through the strong affinity of bisphosphonate-PEG toward both $^{99\text{m}}\text{Tc}$ and Fe_3O_4 nanoparticles. The $^{99\text{m}}\text{Tc}$ ions bridge phosphate groups on adjacent PEG ligands, further enhancing their binding stability to Fe_3O_4 particles. The reaction completes within 30 minutes at room temperature with a radiolabeling yield of approximately 50%.⁶⁷

Comparative Advantages and Challenges of Labeling Strategies

Direct surface labeling (eg, HIR) offers simplicity and avoids exogenous chelators but may require harsh conditions. Indirect labeling via chelators provides high stability for metallic radionuclides through well-optimized coordination chemistry but adds molecular complexity and potential immunogenicity. Internal doping boasts the highest stability by locking radionuclides within the lattice, making it ideal for long-term tracking or therapy, but synthesis is more complex and post-modification flexibility is reduced. Interface engineering cleverly integrates labeling with surface modification, offering stability and functionality at mild conditions, though radiolabeling yields can be variable. The optimal choice depends on the specific radionuclide, intended application (imaging or therapy), required stability, and the need for additional surface functionalization.

Nuclear Medicine Imaging-Related Multimodality Imaging

Accurate tumor imaging is of great significance for the early diagnosis of tumors and intraoperative imaging guidance. Currently, the mainstream imaging technologies used in hospitals include MRI, X-ray CT, PET, SPECT, and US imaging. However, each single imaging modality has its inherent limitations, resulting in poor detection sensitivity or low diagnostic accuracy.⁶⁸ Multimodal imaging combines the strengths of individual technologies, offering new opportunities for improved diagnostic strategies. For instance, SPECT/MRI or PET/MRI imaging technologies, which combine high-resolution MRI with SPECT or PET, not only provide high-resolution anatomical images but also offer physiological information, thereby enhancing the overall system's detection sensitivity and image resolution. Due to their excellent biocompatibility and

magnetic properties, numerous radiolabeled iron-based nanomaterials have been designed and developed as multimodal imaging probes to improve imaging performance, enabling more accurate and sensitive tumor diagnosis.

SPECT or PET/MRI Dual-Modality Imaging

MRI is a powerful non-invasive imaging technique that provides extensive information about the body, including anatomical, physiological, and molecular data. The principle of MRI technology is primarily based on the fact that different biological tissues produce distinct imaging signals due to variations in water content and hydrogen atom relaxation times under different external magnetic field conditions. When a tissue undergoes pathological changes, the relaxation time of hydrogen atoms in the diseased tissue differs from that in normal tissue. Therefore, this method can effectively detect pathological tissues. Owing to its excellent spatial resolution and deep tissue penetration, MRI is widely used in tumor diagnosis, treatment, and therapeutic monitoring.⁶⁹ However, overlapping relaxation times between healthy and lesioned tissues may compromise imaging sensitivity.⁷⁰ Integrating MRI with nuclear medicine imaging (SPECT or PET) overcomes the limitations of single-modal approaches, delivering synergistic information for accurate tumor diagnosis. By radiolabeling paramagnetic materials used as MRI contrast agents, a bimodal imaging platform combining high sensitivity and high spatial resolution can be established. Among these, iron oxide nanomaterials are extensively applied due to their high relaxivity (a measure of their efficiency in shortening the relaxation times of water protons, thus enhancing contrast), superior contrast enhancement, and low toxicity.⁷¹ Moreover, particles within specific size ranges exhibit paramagnetic properties at room temperature, preventing aggregation, significantly reducing the risk of capillary embolism and enhancing biosafety. (Table 2) summarizes representative examples of radiolabeled iron-based nanomaterials in nuclear medicine-related dual-modality imaging.

Table 2 Table Summarizes the Application of Iron-Based Nanomaterials in Dual-Modal Imaging

Nanomaterial Type	Radio Nuclide	Radiolabeling Strategy	Diagnosed Subject	Imaging	Refs.
SPION	^{99m} Tc	Surface radio-mineralization	Sentinel lymph node	SPECT/MRI	[72]
USPIO	^{99m} Tc	Chelation	Blood vessels and vascular organs	SPECT/MRI	[73]
USPIO	^{99m} Tc	Surface radio-mineralization	Hepatocellular carcinoma	SPECT/MRI	[74]
IONP	^{99m} Tc	Surface radio-mineralization	U87 MG glioblastoma	SPECT/MRI	[75]
USPIO	^{99m} Tc	Surface radio-mineralization	Breast cancer	SPECT/MRI	[76]
Fe ₃ O ₄ Nanoprobes	^{99m} Tc	Chelation	LS180 human colorectal cancer	SPECT/MRI	[67]
IONP	^{99m} Tc	Chelation	Breast cancer	SPECT/MRI	[77]
IONP	^{99m} Tc	Adsorption	M-165 tumor cells	SPECT/MRI	[78]
IONP	¹¹¹ In	Chelation	Mesothelin-expressing cancers	SPECT/MRI	[79]
IONP	¹¹¹ In	Chelation	Breast cancer	SPECT/MRI	[80]
Fe@Fe ₃ O ₄ Nanoparticles	¹²⁵ I	Indirect surface labeling using prosthetic group	U87 MG glioblastoma	SPECT/MRI	[81]
USPIO	¹²⁵ I	Indirect surface labeling using prosthetic group	Breast cancer	SPECT/MRI	[82]
Fe ₃ O ₄ nanocrystals	¹²⁵ I	Indirect surface labeling using prosthetic group	Gastric cancer cell line (BGC823).	SPECT/MRI	[63]
Iron-oxide nanorods	⁶⁸ Ga	Chelation	Liver malignancies	PET/MRI	[83]
IONP	⁶⁸ Ga	Chelation or adsorption	4T1 tumor	PET/MRI	[84]
MIONP (IO@G4PM)	⁶⁸ Ga	Chelation	Induction of fibrosarcoma tumors	PET/MRI	[85]
IONP	⁶⁸ Ga	Chelation	Prostate cancer	PET/MRI	[86]
IONP	⁶⁸ Ga	Chelation	Colon cancer	PET/MRI	[87]
IONP	⁶⁸ Ga	Chelation	4T1 breast cancer	PET/MRI	[88]
SPION	⁶⁸ Ga	Chelation	Breast cancer	PET/MRI	[89]
Fe ₃ O ₄ nanoparticles	⁶⁸ Ga	Chelation	CT-26 breast cancer	PET/MRI	[90]
Fe ₃ O ₄ nanoparticles	⁶⁴ Cu	Chelation	U87 MG glioblastoma	PET/MRI	[91]

(Continued)

Table 2 (Continued).

Nanomaterial Type	Radio Nuclide	Radiolabeling Strategy	Diagnosed Subject	Imaging	Refs.
SPION	^{64}Cu	Chelation	U87 MG glioblastoma	PET/MRI	[53]
MFNs	^{64}Cu	Chelation	U87 MG glioblastoma	PET/MRI	[92]
IONP	^{18}F	Chelation	/	PET/MRI	[93]
IONP	^{89}Zr	Chelation	Deep-tissue lymph nodes	PET/MRI	[55]
SPION	*As *=71, 72, 74, 76	Surface Conjugation	Lymph-node imaging	PET/MRI	[39]

Note: *Radioisotopes of As.

$^{99\text{m}}\text{Tc}$ ($t_{1/2} = 6$ h) is the most commonly used radionuclide in SPECT, accounting for over 80% of diagnostic radiopharmaceuticals in current nuclear imaging. $^{99\text{m}}\text{Tc}$ -based radioactive iron-based nanoparticles play a significant role in tumor diagnosis. For example, Rosales et al used radiolabeled bisphosphonate (BP) conjugated to the surface of ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles for T1-weighted MRI-SPECT multimodal imaging.⁷³ The resulting nanoparticles demonstrated good stability in water or saline, with a near-zero potential at neutral pH. Longitudinal (r_1) and transverse (r_2) relaxivity values measured at a clinically relevant magnetic field (3 T) showed an r_1 of $9.5 \text{ mM}^{-1}\text{s}^{-1}$ and an r_2/r_1 ratio of 2.97, making these USPIOs attractive as T1-weighted MRI contrast agents under high magnetic fields. Compared to non-functionalized USPIOs, these nanoparticles achieved comparable signal enhancement using only a quarter of the dose. Furthermore, the nanoparticles exhibited a long circulation time ($t_{1/2} = 2.97$ h), allowing high-spatial-resolution visualization of vasculature and vascular organs (Figure 2).

Gao et al developed a tumor-microenvironment-responsive SPECT/MRI dual-modal probe for enhanced tumor imaging⁶⁷ (Figure 3). In this work, a tumor-specific Arg-Gly-Asp (RGD) peptide for tumor targeting and a “self-marking” self-peptide were linked via a disulfide bond. The self-peptide helps the nanoprobe evade uptake by the reticuloendothelial system (RES) before reaching the tumor site via blood circulation. Upon reaching the tumor site, the disulfide bond is cleaved by the high concentration of glutathione (GSH) in the tumor microenvironment. Subsequently,

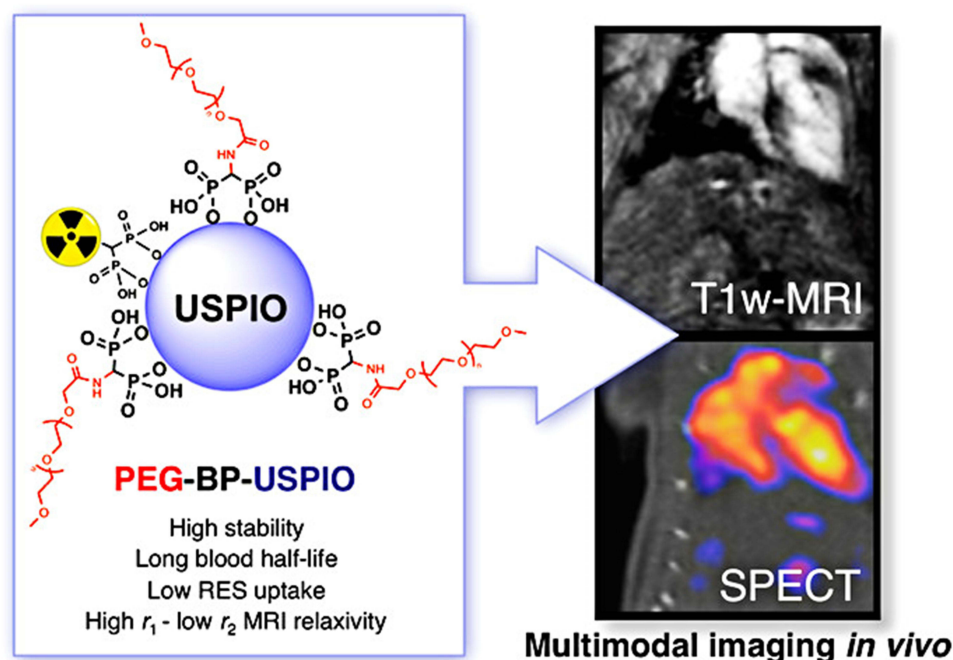


Figure 2 Showing a new stealth PEG polymer conjugate containing a terminal 1,1-bisphosphonate (BP) group for strong and stable binding to the surface of ultrasmall-superparamagnetic oxide nanomaterials (USPIOs). This polymer, PEG(5)-BP-USPIO Can be used for in vivo Multimodal (T1 MRI-SPECT) imaging through radioactive labeling technology. Reproduced with permission from Ref.⁷³ © 2012 American Chemical Society.

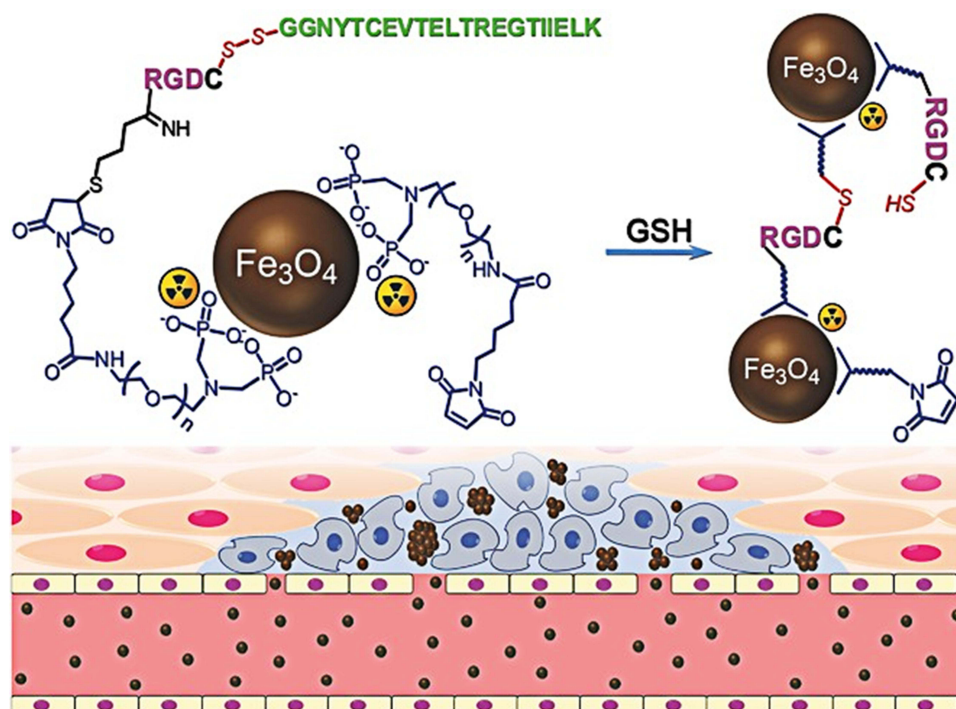


Figure 3 Schematic drawing of the antiphagocytosis ^{99m}Tc -labeled Fe_3O_4 nanoparticles and their responsiveness to GSH-triggering within tumor microenvironment for forming particle aggregates through interparticle crosslinking reaction. Reproduced with permission from Ref.⁶⁷ © 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

the RGD anchors the nanoprobes to the surface of cancer cells highly expressing the RGD receptor $\alpha\text{v}\beta 3$. The exposed thiol groups then react with maleimide residues on another adjacent particle to crosslink the particles, thereby significantly improving the contrast enhancement capability of the nanoprobes. Both in vitro and in vivo experiments demonstrated that the aggregates significantly improved the MRI contrast enhancement performance of the Fe_3O_4 particles. These results demonstrate the potential of radiolabeled iron-based nanoparticles as targeted multimodal imaging agents for molecular imaging.

In addition to ^{99m}Tc , other commonly used gamma-emitting radionuclides such as ^{111}In , ^{123}I , ^{125}I , ^{67}Ga and ^{177}Lu have been explored for SPECT imaging. Among these, radioiodine (^{123}I and ^{131}I) can be used for diagnosing thyroid cancer, ^{67}Ga for imaging lymphoma, and ^{111}In has been used for diagnosing neuroendocrine tumors. Furthermore, Lutetium-177 (^{177}Lu) is not only suitable as a radionuclide for SPECT imaging, but also applicable for therapeutic applications due to its low-energy (0.49 MeV) beta-minus (β^-) emission and gamma emissions (208 keV (11%), 113 keV (6.6%)).⁹⁴

Compared to SPECT, PET imaging offers higher accuracy, sensitivity, and resolution. Hybrid imaging combining high-resolution MRI and PET may provide a better solution for future early cancer diagnosis. Thanks to the multi-functional surface properties of the materials, iron-based nanomaterials can be used to prepare imaging probes by radiolabeling with PET imaging nuclides.

^{68}Ga ($t_{1/2} = 68$ min) is an ideal PET imaging radionuclide. Its short half-life ensures reduced radiation exposure for patients. Furthermore, due to its excellent chemical properties, it can form stable complexes with various nanoparticles.⁹⁵ For example, Jeong et al developed a prostate-specific membrane antigen (PSMA)-targeted iron-based nanoparticle. Iron oxide nanoparticles were encapsulated with three amphiphiles containing PEG, DOTA, and a PSMA-targeting ligand in an aqueous medium. PET and MRI imaging results showed that, in a dual-tumor xenograft mouse model study, the contrast agent was selectively taken up only by 22Rv1 (PSMA-positive) tumors, not by PC-3 (PSMA-negative) tumors. The dual-modal imaging not only exhibited high resolution but also provided quantitative information. Therefore, ^{68}Ga -DOTA-IO-GUL is a promising dual-mode agent for imaging prostate cancer (Figure 4).⁸⁶

^{64}Cu ($t_{1/2} = 12.7$ h) is a commonly used positron emitter that can be attached to nanoparticles via coordination with chelators. Shen et al developed a PET/MRI dual-modal imaging agent based on SPIONs.⁹¹ They prepared the PET/MRI

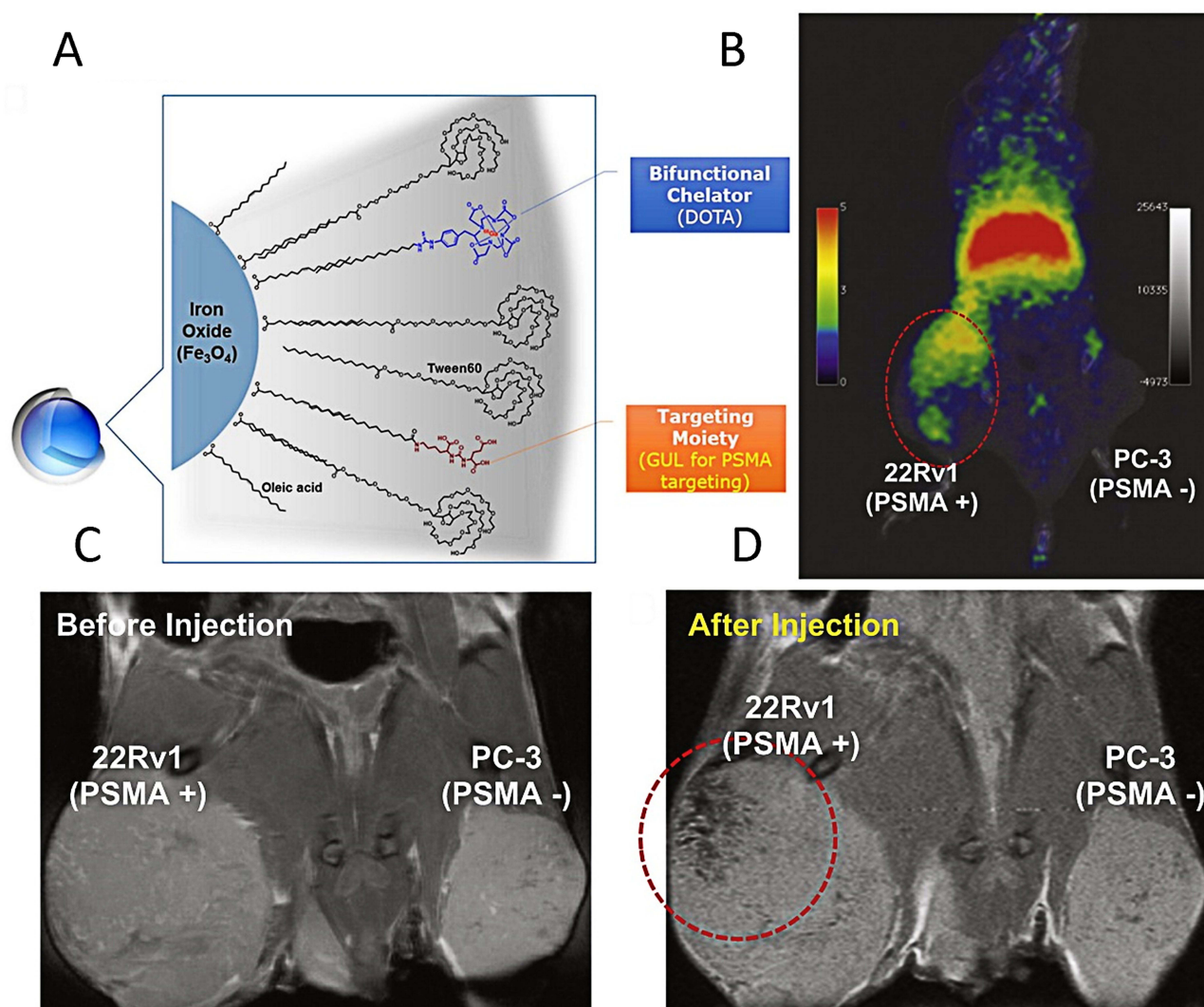


Figure 4 (A) showing the diagram of encapsulated DOTA-IO-GUL. (B) In vivo PET result. PSMA-selective uptake result in micro PET imaging. ($SUV_{mean} = 0.668$) ^{68}Ga -DOTA-IO-GUL (10.2 MBq, 0.1 mL) tail vein injection after 1 h imaging. Left tumor is PSMA-positive (22Rv1) and right tumor is PSMA-negative (PC-3). Red circle demonstrates the selective uptake of DOTA-IO-GUL to the left positive tumor. (C) In vivo micro MRI image results. Before injection, control image; (D) after injection of DOTA-IO-GUL (0.1 mL, 0.2 mM) through the tail vein (1 h). Left tumor is PSMA positive (22Rv1) and right tumor is PSMA-negative (PC-3). Red circle demonstrates the selective uptake of DOTA-IO-GUL to the positive tumor (49.1 Fe ng/g). Reproduced with permission from Ref.,⁸⁶ © 2015 The Authors Published by Elsevier Inc.

dual-modal imaging probe by attaching ^{64}Cu to the surface of DOTA-modified SPIONs. $\alpha(v)\beta(3)$ -targeting RGD (Arg-Gly-Asp) peptides were further conjugated to the SPIONs along with ^{64}Cu to achieve highly specific tumor targeting. Subsequently, using human glioblastoma tumor-bearing mice expressing $\alpha v \beta 3$ as the animal model, MRI and MicroPET were applied to observe the in vivo behavior of the probe. These results indicated that this probe possesses good tumor targeting capability and is a potential PET/MR imaging tool.

^{18}F ($t_{1/2} = 110$ min) is the most commonly used PET radionuclide in clinical practice, typically labeled onto organic molecules. Due to its strong affinity for Al^{3+} ions, it offers convenience for labeling nanomaterials. Cheng et al successfully prepared an ^{18}F -AIF-labeled dual-modal probe by reacting Al^{3+} ions and radioactive $^{18}\text{F}^-$ ions with NOTA-conjugated IONPs.⁹³ Thorek et al prepared ^{89}Zr -radiolabeled iron oxide nanoparticles, namely ^{89}Zr -ferumoxytol, for lymphatic system imaging.⁸⁵ Cai's group developed a chelator-free method for radiolabeling SPIONs with radioactive arsenic ($^{76}\text{As}^{\text{III}}$).³⁹ Owing to the strong affinity of arsenic for magnetic materials, $^{76}\text{As}^{\text{III}}$ is firmly adsorbed onto the SPION surface. Following intravenous injection of free ^{76}As and ^{76}As -IONP, PET imaging was performed to investigate the biodistribution of ^{76}As -IONP in Balb/C mice. The results revealed that free ^{76}As exhibited high bladder uptake at

0.5 h and 3 h post-injection. *As-IONP underwent hepatic and splenic clearance, with the significant bladder signal likely corresponding to *As desorption from nanoparticles in vivo.

PET/Fluorescence Dual-Modality Imaging

Fluorescence imaging is clinically used to differentiate pathological tissues from normal tissues and to guide surgical resection, and it has been widely applied in tumor diagnosis and treatment.⁹⁶ It is categorized into visible light imaging and near-infrared (NIR) imaging, with NIR imaging being more commonly used due to its deeper tissue penetration. Based on wavelength, NIR imaging can be further divided into NIR-I (650–950 nm) and NIR-II (1000–1700 nm) fluorescence imaging.⁹⁷ Compared to visible light and NIR-I fluorescence imaging, NIR-II fluorescence imaging utilizes longer excitation and emission wavelengths. This reduces scattering of both incident and emitted light by biological tissues, resulting in higher spatial resolution and greater penetration depth.^{98,99} Furthermore, significantly lower autofluorescence occurs in NIR-II imaging due to reduced tissue absorption of NIR-II photons.¹⁰⁰ Consequently, NIR fluorescence imaging has become a prominent research focus in in vivo fluorescence imaging in recent years.

Radiolabeled iron-based nanomaterials conjugated with fluorescent dyes can be engineered into PET/fluorescence dual-modality imaging probes.¹⁰¹ For instance, Weissleder et al functionalized aminated dextran-coated iron oxide nanoparticles by “clicking” fluorescent dyes, the PET radionuclide ¹⁸F, and targeting ligands onto the material. This probe was used for PET/FMT dual-modality imaging of macrophages in BALB/c mice bearing CT26 colon carcinoma tumors on their flanks. In vitro and in vivo results demonstrated excellent correlation between FMT and PET in terms of probe concentration ($r^2 > 0.99$) and spatial signal distribution ($r^2 > 0.85$), indicating strong quantitative capabilities. These findings suggest that FMT can serve as a valuable imaging modality complementary to radionuclide-based techniques.⁵⁸

Tri-Modality or Multimodality Imaging

Building on the successful application of dual-modality imaging probes in tumor diagnosis, researchers have developed tri-modality or multimodality imaging probes to integrate their respective advantages and obtain complementary diagnostic information. For instance, tri-modality imaging materials have been reported, such as PET/NIRF/MRI,¹⁰² PET/PAI/MRI,^{103,104} SPECT/PAI/MRI,¹⁰⁵ Optical/PET/MRI,⁶⁰ and SPECT/OFI/MRI.¹⁰⁶ Quad-modality imaging materials, such as PET/NIRF/PAI/CT,¹⁰⁷ have also been documented.

Chen et al modified the surface of IONPs with dopamine to generate nanoconjugates that can be readily encapsulated within a human serum albumin (HSA) matrix—a clinically utilized drug carrier.¹⁰² The HSA-coated IONPs (HSA-IONPs), dual-labeled with ⁶⁴Cu-DOTA and Cy5.5, were tested in a subcutaneous U87 MG xenograft mouse model. In vivo PET/NIRF/MRI tri-modality imaging demonstrated that HSA-IONPs exhibited high retention, favorable extravasation efficiency, and low macrophage uptake in tumor regions.

Liu et al functionalized IONPs and self-assembled them onto the surface of two-dimensional molybdenum disulfide (MoS₂) nanosheets via thiol chemistry, followed by ⁶⁴Cu adsorption onto the nanoparticles.¹⁰³ PET/PAI/MRI imaging in 4T1 tumor-bearing mice revealed that the hybrid nanoparticles possessed excellent serum stability and effective tumor retention. This combined imaging approach not only provided physiological information about the tumor but also enabled the non-invasive acquisition of molecular and anatomical data at varying depths.

Yoo et al developed an Optical/PET/MRI tri-modality imaging probe leveraging the Cherenkov radiation (CR) phenomenon.⁶⁰ Cherenkov radiation is light emitted when charged particles traverse a dielectric medium at a speed greater than that of light in the same medium. While Cherenkov luminescence (CL) imaging is limited by low penetration depth due to its short wavelength, its integration with nuclear imaging effectively overcomes this limitation. The study combined a PET radionuclide (¹²⁴I) with an MRI probe to fabricate a tri-modality nanoprobe. This probe enabled accurate imaging of sentinel lymph nodes (SLNs), and by eliminating the need for an external light source, it effectively avoided background interference from external fluorescence.

A representative example of quad-modality imaging probes was reported by Liu et al, who modified Bi₂Se₃ nanosheets with FeSe₂ nanoparticles (FeSe₂/Bi₂Se₃) and radiolabeled them with ⁶⁴Cu for PET/MRI/CT/PAI multimodal imaging in tumor-bearing mice.¹⁰⁷ The probe exhibited a high r^2 relaxivity, strong X-ray attenuation capability, and intense NIR absorption. At 24 h post-injection, the tumor site showed: darkening effects on MRI, significantly increased

CT Hounsfield unit values, enhanced photoacoustic signals, and pronounced tumor contrast in PET. These concordant imaging results demonstrated pronounced tumor accumulation of $\text{FeSe}_2/\text{Bi}_2\text{Se}_3$ -PEG via the EPR effect.

Applications of Nanomaterials for Cancer Treatment

In recent years, iron-based nanomaterials have played a pivotal role in cancer therapy owing to their exceptional functional versatility and biosafety.¹⁶ Their magnetic properties, biocompatibility, and ease of functionalization enable diverse therapeutic applications—from targeted drug delivery to hyperthermia- and immunotherapy-based strategies. Inherent magnetism ensures precise tumor-site localization, conferring superior targeting capabilities. Furthermore, their catalytic activity (eg, in Fenton reactions) allows efficient generation of reactive oxygen species (ROS) for oxidative stress-induced tumor cell death.¹⁰⁸ Radiolabeled iron-based nanomaterials can also incorporate organic molecules or other ions to create multifunctional nanoplateforms for multimodal theranostics, enhancing radiotherapeutic efficacy while reducing radiation dosage. This section highlights recent advances in radiolabeled iron-based nanoplateforms for cancer treatment, focusing on TRT and its synergistic applications in MHT, PDT, CDT, and immunotherapy, with emphasis on underlying mechanistic principles.

Targeted Radionuclide Therapy (TRT)

TRT is an emerging therapeutic approach that delivers radionuclides specifically to tumor-associated targets. Due to its efficacy and safety, TRT has evolved into a promising cancer treatment.¹⁰⁹ The demand for TRT in oncology is growing rapidly, and the FDA has approved more than 50 radiopharmaceuticals.¹¹⁰ MRI, a widely used clinical tool, offers excellent tissue penetration, high sensitivity, and precise imaging capabilities. It plays a crucial role not only in tumor diagnosis but also in monitoring the accumulation of therapeutic agents within tumors, thereby guiding radionuclide therapy in real time.¹¹¹

In 2024, Gao et al reported a multifunctional iron oxide nanomedicine-based TRT system. Beyond enhancing MRI contrast for imaging, this nanodrug also exhibits mucoadhesive properties and bioorthogonal functionality. Specifically, magnetic iron oxide nanoparticles were coated with hyaluronic acid co-labeled with Dibenzocyclooctyne (DBCO) and ^{177}Lu . Upon intravesical instillation, DBCO groups on the nanoparticle surface underwent click reactions with azide groups on engineered cancer cells, enabling bioorthogonal targeting and efficient internalization into tumor cells. MRI visualized bladder cancer lesions, and significant tumor growth inhibition was observed. The results demonstrated the nanoprobe's exceptional ability to reduce tumor size and downstage bladder tumors. This study provides a valuable strategy for integrating MRI with therapeutic radionuclides to achieve theranostics—a unified diagnostic and therapeutic approach¹¹² (Figure 5).

Combination of RT and PTT

PTT is an effective non-invasive cancer treatment¹¹³ that utilizes heat generated from photothermal agents (PTAs) irradiated by specific wavelengths of light to eliminate tumor cells while sparing healthy tissues. Traditional radiotherapy relies on oxygen within the tumor microenvironment; however, hypoxia and insufficient blood supply in solid tumors limit RT efficacy. Combining PTT with RT substantially enhances therapeutic outcomes. A novel cancer treatment technology has emerged that leverages metallic nanostructures to absorb NIR light through surface plasmon resonance (SPR) and convert it into heat via PTT. An intriguing example of this strategy was reported by Liu et al in 2016¹⁰⁷ (Figure 6). The study developed a unique and simple method to construct novel two-dimensional FeSe_2 -decorated Bi_2Se_3 nanosheets. These nanomaterials were then labeled with the radioisotope ^{64}Cu using a chelator-free approach, demonstrating excellent biocompatibility and efficient tumor accumulation. The further combination of near-infrared laser and X-ray irradiation enabled a synergistic effect between photothermal therapy and radiotherapy in vivo. The combined treatment group demonstrated significant cooperative tumor destruction and highly effective inhibition of tumor growth, fully highlighting the substantial application value of the composite material. After systemic administration, the material was rapidly excreted with minimal retention within 30 days, and no obvious toxic or side effects were observed. These results indicate promising clinical translation potential for this material.

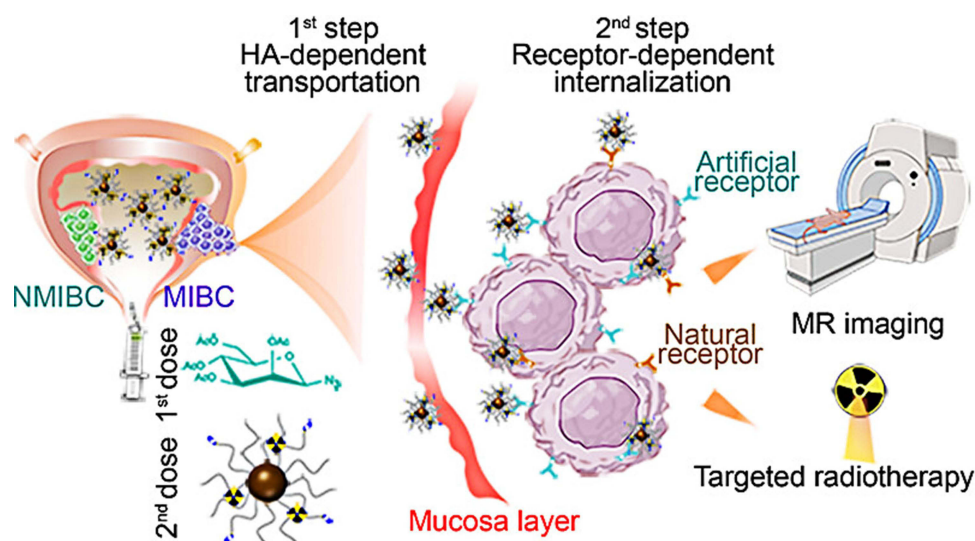


Figure 5 A scheme showing the iron oxide nanoparticle was used as a carrier that was coated with hyaluronic acid (HA) for facilitating mucosa penetration. Dibenzocyclooctyne (DBCO) was introduced into the HA coating layer to react through bioorthogonal reaction with azide as an artificial receptor of bladder cancer cells, to improve the cellular internalization of the nanoprobe labeled with ^{177}Lu . Through magnetic resonance imaging, the targeted imaging of both nonmuscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) was realized after intravesical instillation of the multifunctional probe. Reproduced with permission from Ref.,¹¹² © 2024 American Chemical Society.

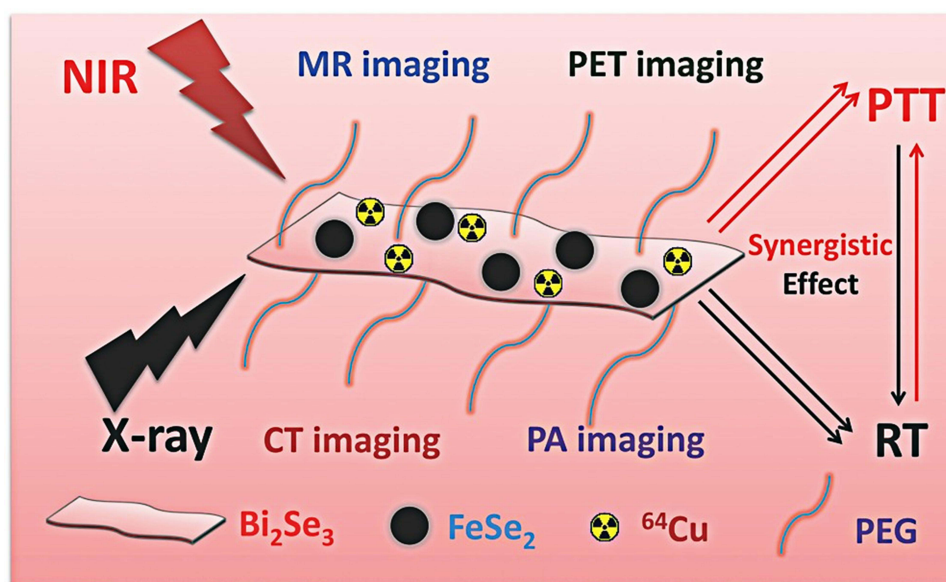


Figure 6 A scheme showing the structure of $\text{FeSe}_2/\text{Bi}_2\text{Se}_3$ composite-nanostructure for multimodal imaging and photothermal-radiation combined tumor therapy. Reproduced with permission from Ref.,¹⁰⁷ © 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Combination of RT and MHT

Magnetic hyperthermia therapy involves exposing magnetic nanomaterials (such as iron oxide) to an appropriate alternating magnetic field, utilizing the generated heat to kill tumor cells. When the materials are concentrated in the tumor region, the thermal effect is localized to that area without harming normal tissues. Thus, this method offers advantages such as excellent selectivity, biocompatibility, and deep tissue penetration. In 2010, it was officially approved for clinical use.¹¹⁴ When combined with radiotherapy, the two modalities integrate their strengths and overcome the limitations of individual therapies, opening new avenues for cancer treatment.

Zhang et al constructed a novel combined therapeutic system for liver cancer using PEI-Mn_{0.5}Zn_{0.5}Fe₂O₄ nanoparticles (PEI-MZF-NPs) as both a magnetic medium and gene delivery vector.¹¹⁵ They evaluated the therapeutic efficacy and safety of the pHRE-Egr1-HSV-TK/¹³¹I-antiAFP McAb-GCV/MFH system against liver cancer in vitro and in vivo. Due to the excellent magnetic properties of the nanoparticles, they generate heat under an alternating magnetic field, enabling hyperthermia therapy. Meanwhile, ¹³¹I not only kills liver cancer cells but also activates the Egr1 promoter, initiating gene therapy. The anti-AFP monoclonal antibody ensures targeted treatment, thereby achieving multi-modal targeted killing of liver cancer through gene therapy, radionuclides, and hyperthermia.

Stanković et al conjugated ¹³¹I-radiolabeled CC49 antibodies to SPIONs via the reactive groups of 3-aminopropyltriethoxysilane (APTES).¹¹⁶ After intratumoral administration in NOD-SCID mice bearing LS174T human colon adenocarcinoma xenografts, the nanoparticles exhibited specific and prolonged local retention. Compared to the untreated group, the combined therapy induced significant tumor growth inhibition. Histological analysis confirmed necrosis and apoptosis in tumor cells without systemic toxicity.

In a recent study, Bilewicz et al synthesized SPIONs coated with a radioactive gold (¹⁹⁸Au) layer, designed for multimodal hepatocellular carcinoma (HCC) treatment combining radionuclide therapy and magnetic hyperthermia.¹¹⁷ The synthesized nanoparticles exhibited superparamagnetic properties with a saturation magnetization of 50 emu/g, reaching a temperature of 43°C under a magnetic field frequency of 386 kHz. In vitro results demonstrated significant cytotoxicity, with cell viability dropping below 8% after 72 h at a radioactive concentration of 2.5 MBq/mL.

Radionuclide Therapy-Enhanced Cherenkov Photodynamic Therapy

PDT is a minimally invasive medical technology with broad application prospects, already utilized in both fundamental research and clinical settings for treating various diseases, including fungal infections, skin conditions, and multiple cancers.^{118,119} However, conventional external light irradiation in PDT often suffers from rapid tissue attenuation, limiting its clinical use primarily to superficial lesions. To overcome this limitation, various nano-photosensitizers have been engineered to enable PDT activation using different excitation sources, including NIR light,^{120,121} X-ray radiation,¹²² and self-illumination.¹²³ Among these, Cherenkov radiation -induced PDT-where Cherenkov luminescence (CL) generated by radionuclides activates the photosensitizer to produce ROS-represents a novel PDT approach that eliminates the need for external light excitation.¹²⁴ Combining CR with nanoparticles, particularly metal-based nanomaterials, enhances both cancer diagnosis and therapy.

Cai et al designed a magnetically targeted nanostructure based on high-performance magnetic (Zn_{0.4}Mn_{0.6})Fe₂O₄ nanoparticles (MNPs), surface-conjugated with meso-tetra(4-carboxyphenyl)porphyrin (TCPP) and chelator-free-labeled ⁸⁹Zr (⁸⁹Zr-MNP/TCPP), for magnetically enhanced CR-induced PDT.¹²⁵ The ⁸⁹Zr-labeled MNP surface enables PET imaging to track in vivo distribution, while the excited TCPP generates singlet oxygen to destroy tumor cells. Results demonstrate that ⁸⁹Zr-MNP/TCPP nanostructures serve as an efficient magnetic carrier, achieving high tumor accumulation under an external magnetic field, thereby significantly enhancing the therapeutic efficacy of CR-induced PDT by overcoming the depth and external light dependency of conventional PDT. This magnetically targeted CR-induced PDT achieves rapid and substantial suppression of tumor growth in vivo. Moreover, this strategy integrates multiple imaging modalities, providing a highly precise tool for evaluating tumor treatment progression.

Combination of RT and Immunotherapy

The combination of PD-1/PD-L1 inhibitors with radiolabeled nanomaterials not only enables tumor radiotherapy but also enhances positive immunomodulation while suppressing negative immune resistance, achieving dual anti-tumor effects and improving survival outcomes.

For example, Tian et al synthesized FeTA nanoparticles via coordination between ferric iron (Fe³⁺) and tannic acid (TA), followed by chelation-free loading of radionuclides (¹³¹I, ⁹⁰Y, ¹⁷⁷Lu, and ²²⁵Ac) onto the nanomaterial.¹²⁶ These nanoparticles were further functionalized with tetra-arm PEG-SH via a Michael addition reaction, yielding a biocompatible brachytherapy hydrogel. Finally, imiquimod (a TLR7 agonist) was loaded to synergize with anti-PD-L1 antibody therapy, triggering a potent anti-tumor immune response and inhibiting metastatic tumor growth. This combined radionuclide-immunotherapy was tested in a CT26 colon cancer metastasis model. Results demonstrated that the combination therapy effectively inhibited the growth of metastatic tumors by activating CD8⁺ T cell-mediated anti-

tumor immune responses. In addition, the treatment had no significant adverse effects on healthy tissues (including the heart, liver, spleen, lungs, and kidneys). In conclusion, this imageable brachytherapy hydrogel provides a novel strategy for developing clinically translatable radiopharmaceuticals (Figure 7).

Ferroptosis, a non-apoptotic form of regulated cell death (RCD) discovered by Stockwell in 2012, is characterized by the accumulation of labile iron in the cytoplasm and excessive lipid peroxidation.¹²⁷ The regulation of ferroptosis offers a novel approach for cancer treatment, with advantages including the ability to combat therapy-resistant tumor cells, effectively inhibit tumor growth, and generate mild immunogenicity.¹²⁸ Several small-molecule drugs have been developed as ferroptosis-inducing compounds (FINs) to trigger tumor ferroptosis. However, organic molecules face limitations such as poor solubility, nonspecific distribution, systemic toxicity, and low bioavailability.¹²⁹ Consequently, researchers have designed various ferroptosis inducers based on metal complexes and nanomaterials. Among these, iron-based nanomaterials have recently shown promise for efficient ferroptosis therapy and immunotherapy.¹³⁰

Recently, Sun et al developed ¹³¹I-labeled single-crystal ultrasmall iron nanoparticles (USINPs) to explore the relationship among radiotherapy, ferroptosis, and immunotherapy¹³¹ (Figure 8). The study involved the preparation of renal-clearable USINPs and ¹³¹I-aPD-L1 nanoassemblies through the affinity between fluorophenylboronic acid-modified USINPs and ¹³¹I-aPD-L1. This assembly demonstrated stable circulation in the bloodstream and excellent tumor-targeting capability. Both in vitro and in vivo experiments revealed that USINPs exhibit excellent tumor-targeting capability and effectively inhibit tumor growth. USINPs-induced ferroptosis enhanced tumor radiosensitization to ¹³¹I, while ¹³¹I-mediated RT further potentiated ferroptosis. Simultaneously, immunogenic cell death (ICD) triggered by radiotherapy and ferroptosis, when combined with PD-L1 immune checkpoint blockade therapy, exhibited robust antitumor immunity. This study provides a novel strategy to improve the accumulation of ferroptosis inducers and radiopharmaceuticals in tumors.

Radionuclide Therapy-Enhanced CDT

CDT is an emerging cancer treatment strategy based on the Fenton or Fenton-like reactions of transition metals.¹³² It converts the abundant H₂O₂ in the tumor microenvironment (TME) into highly oxidizing hydroxyl radicals ($\cdot$ OH), which cause irreversible damage to cellular components such as lipids, proteins, and nucleic acids, ultimately leading to tumor

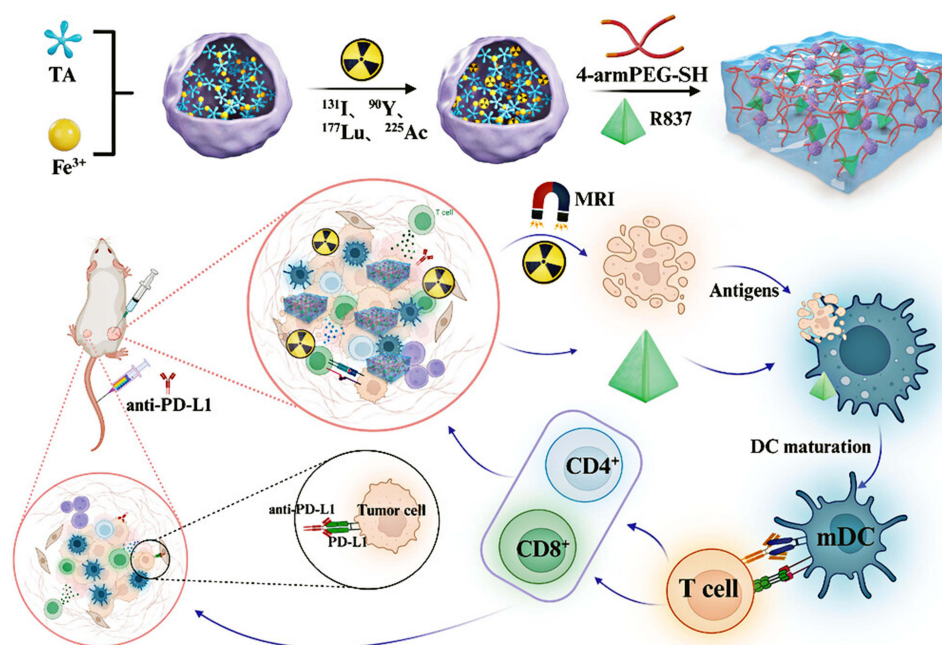


Figure 7 The schematic illustration of imageable brachytherapy with chelator-free radiolabeled FeTA-PEG hydrogel combining immune checkpoint-blockade therapy to activate antitumor immune responses for inhibiting cancer metastases. Reproduced with permission from Ref.,¹²⁶ © 2024 Wiley-VCH GmbH.

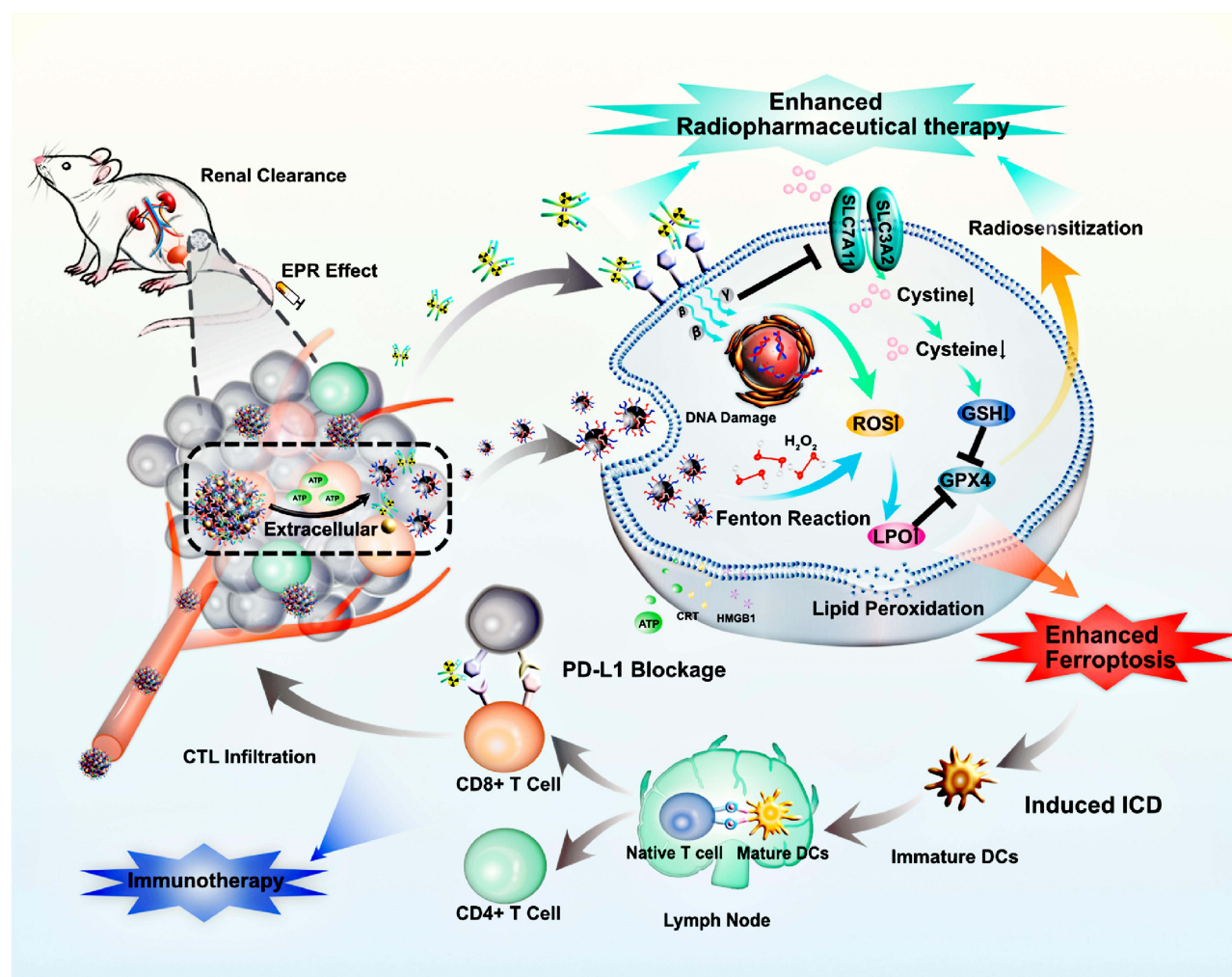


Figure 8 USINAs (^{131}I -aPD-LI) accumulate in the tumor sites due to the EPR effect and PD-L1 targeting and disassemble into USINPs and ^{131}I -aPD-LI upon extracellular ATP in the tumor microenvironment. ^{131}I -aPD-LI bind to PD-L1 receptors on the surface of tumor cells for ^{131}I -mediated radiopharmaceutical therapy (RPT) as well as immune checkpoint blockade (ICB) therapy. On one hand, ^{131}I promote ferroptosis via ROS generation and SLC7A11 down-regulation; on the other hand, USINPs initiate ferroptosis with decreased GPX4 to sensitize cancer cells to ^{131}I with enhanced RPT efficacy. Combining ICB with ferroptosis and RPT further enhance antitumor immunotherapy. “↑” indicates a relative increase or accumulation of the indicator (eg, LPO, ROS), while “↓” denotes a relative decrease or reduction in the indicator (eg, GSH, cystine, cysteine). Reproduced with permission from Ref.,¹³¹ © 2024 Elsevier Ltd.

cell death.¹³³ Typically, the efficacy of CDT depends on the reaction rate of the introduced Fenton/Fenton-like reactions, which is influenced by factors such as the metal catalyst,¹³⁴ H_2O_2 concentration,¹³⁵ pH,¹³⁶ and external energy fields. Consequently, various strategies have been designed and reported to enhance intratumoral Fenton/Fenton-like reactions by manipulating these limiting factors to improve CDT outcomes.¹³⁷ However, these approaches face significant constraints due to the rate-limiting nature of the $\text{Fe}^{3+}/\text{Fe}^{2+}$ cycle, which severely restricts Fenton reaction efficiency.

Radionuclides emit various types of radiation (eg, α , β , γ rays) during decay, interacting with surrounding matter to generate low-energy electrons, such as hydrated electrons in aqueous solutions. Therefore, incorporating radionuclides into CDT nanomaterials can accelerate the reduction of transition metals from higher to lower oxidation states, thereby enhancing CDT efficacy.

In the study by Bu et al¹³⁸ iron-based metal-organic framework (MOF) nanoparticles were synthesized using FeCl_3 and 2-hydroxyterephthalic acid (2-HTP), followed by modification with PEG and radiolabeling with ^{125}I . The porous structure facilitated H_2O_2 enrichment, boosting the Fenton reaction. Simultaneously, the presence of ^{125}I induced continuous generation of hydrated electrons, promoting the conversion of Fe^{3+} to Fe^{2+} . This mechanism led to potent antitumor effects in both in vitro and in vivo pancreatic cancer models (Figure 9). Compared to the control group,

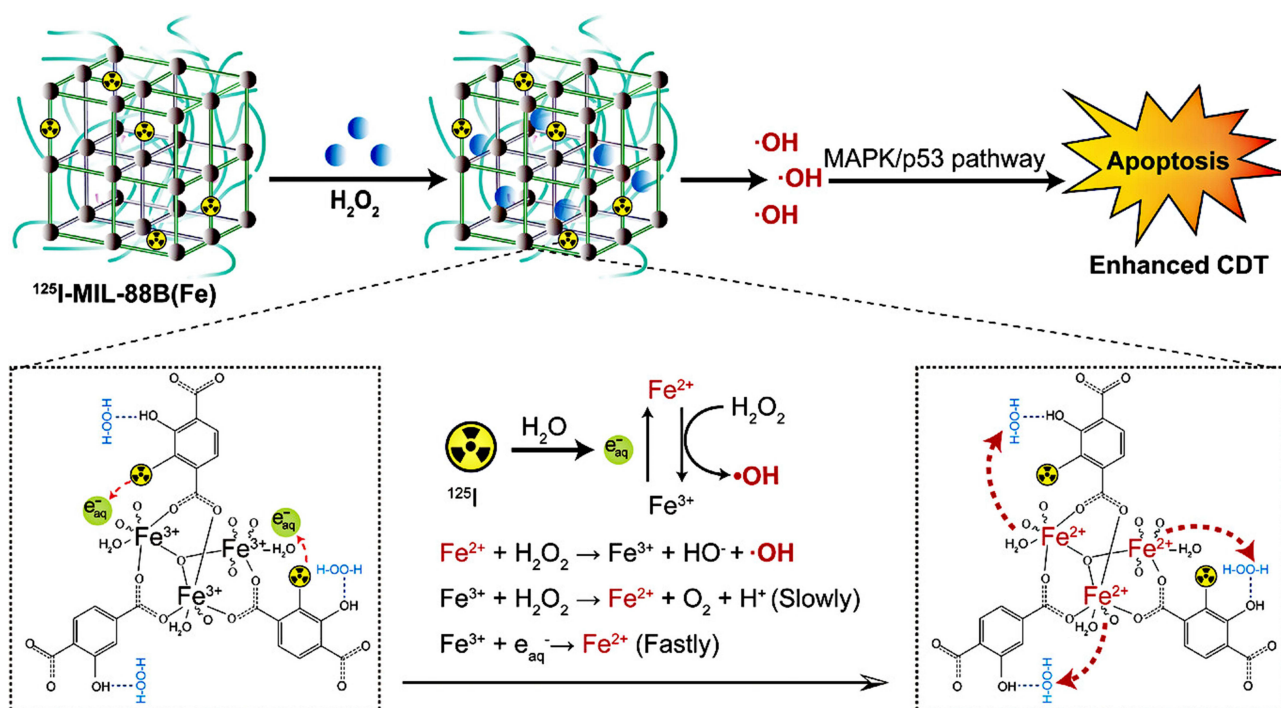


Figure 9 Radioiodine-induced e_{aq}^- generation promotes the conversion of $\text{Fe}^{3+}/\text{Fe}^{2+}$ in $^{125}\text{I-MIL-88B(Fe)}$ NPs-mediated Fenton reaction, resulting in accelerated OH production and enhanced CDT through the ROS/MAPK/p53 pathway-mediated cell apoptosis. Reproduced with permission from Ref.,¹³⁸ © 2024 Wiley-VCH GmbH.

$^{125}\text{I-MIL-88B(Fe)}$ NPs exhibited significant antitumor efficacy. Moreover, $^{125}\text{I-MIL-88B(Fe)}$ nanoparticles did not induce acute or chronic toxicity in mice and demonstrated satisfactory *in vivo* biocompatibility.

Summary and Outlook

Radiolabeled iron-based nanomaterials have shown great promise in tumor diagnosis and treatment. Their unique magnetism, excellent biocompatibility, and capability to integrate diagnostic and therapeutic modalities make them invaluable tools for overcoming the limitations of conventional cancer approaches. From enhancing imaging sensitivity and specificity in MRI applications to enabling precise and minimally invasive therapies—such as magnetic hyperthermia, photodynamic therapy, chemodynamic therapy, and immunotherapy—these materials contribute significantly to precision diagnosis and treatment of cancer. Moreover, the integration of nanomaterials with advanced technologies like radiomics offers direction for next-generation cancer treatment strategies. Despite these encouraging achievements, radiolabeled iron-based nanomaterials face challenges in transitioning from basic research to clinical trials.

Biosafety of Nanomaterials

The potential for large-scale clinical application of nanomaterials predominantly hinges on their biosafety,¹³⁹ as the sustainable advancement of nanomedicine relies on resolving nanotoxicological and biosecurity concerns. Iron-based nanomaterials, as inorganic metallic compounds, may induce chemical toxicity mediated by iron ions during practical use. These materials can accumulate in normal organs (eg, kidneys, liver, spleen), leading to prolonged *in vivo* retention in healthy tissues and consequent systemic side effects. Additionally, the retention of radioactive components may pose risks of radiation-induced damage. To address these challenges, we propose two strategic approaches: 1) Surface Engineering: Modifying material surfaces through techniques such as PEGylation to alter bio-interactions, thereby minimizing protein adsorption and extending circulation time to reduce *in vivo* toxicity. 2) Biodegradable Design: Developing intelligently engineered iron-based nanoproboscopes with controlled *in vivo* degradability. These materials should efficiently accumulate in target tissues while undergoing programmed degradation after completing imaging or therapeutic functions—requiring careful reconciliation of the trade-off between degradability and stability.

Scalable Production of Materials

Successful clinical integration of radiolabeled nanomaterials necessitates robust validation protocols to verify material stability, therapeutic efficacy, and safety profiles under clinically relevant conditions. Concurrently, synthesis and radiolabeling procedures must be simple, reproducible, and scalable with relatively low production costs. Pharmacological and toxicological parameters must demonstrate strict consistency across different batches of radiolabeled products. Therefore, the transition from preclinical studies to clinical application has been slow but this can be addressed by adopting standardized preclinical validation systems and Good Manufacturing Practice (GMP) to ensure safety and efficacy.^{140,141} A critical approach to addressing these challenges involves developing kit-based production systems, enabling repeatable, large-scale manufacturing to ensure safe clinical deployment.

Development of Novel Nanomaterials

As research advances, greater emphasis should be placed on constructing novel nanomaterials with innovative functionalities to meet personalized theranostic demands. For instance, integrating multifunctional modules into materials enables diagnostic-therapeutic integration.¹⁴² Furthermore, selecting endogenous components as surface modifiers presents a superior approach to reducing adverse reaction risks—such as utilizing biomimetic membrane camouflage to enhance nanomaterial targeting and biocompatibility.¹⁴³ Ultimately, integrating artificial intelligence (AI) and big data into cancer diagnosis and treatment processes offers compelling advantages.¹⁴⁴ These technologies will transform drug discovery, optimize personalized therapeutic strategies, and significantly enhance safety-efficacy profiles. By leveraging AI algorithms like Artificial Neural Networks (ANN), researchers can simulate critical parameters including particle size, zeta potential, and encapsulation efficiency to synthesize nanoparticles with optimized therapeutic performance.^{145–147}

Conclusions

This review has systematically explored the burgeoning field of radiolabeled iron-based nanomaterials for cancer theranostics. The most compelling benefits of these platforms include: (1) Multimodal Capabilities: The intrinsic properties of iron enable high-quality MRI, while radiolabeling provides sensitive PET/SPECT, allowing for anatomical, functional, and molecular imaging in a single agent. (2) Synergistic Therapeutics: Iron-based cores serve as hubs for combining radiotherapy with PTT, MHT, CDT, and immunotherapy, often leading to supra-additive antitumor effects. (3) Clinical Translation Potential: The established safety profile of iron oxide nanoparticles, coupled with FDA approval for some formulations, provides a significant head start for clinical adoption compared to many other nanoplatforms.

However, significant challenges remain to be addressed: (1) Long-Term Fate and Safety: The chronic biodistribution, degradation, and clearance pathways of these complex nanomaterials, especially when combined with radioactive components, require more comprehensive long-term studies. (2) Manufacturing and Quality Control: Reproducible, large-scale, and cost-effective synthesis of radiolabeled nanomaterials with stringent quality control for clinical use is non-trivial. (3) Targeting Efficiency: While passive targeting via the EPR effect is valuable, active and specific tumor targeting needs improvement to reduce off-target accumulation and enhance therapeutic indices. (4) Personalization: Developing strategies to select the right nanoplatform (material type, radionuclide, combination therapy) for the right patient based on tumor biology is a key future direction.

Future research should prioritize the development of “smart” nanomaterials with biodegradable backbones, stimuli-responsive activation, and enhanced tumor-specific targeting. Furthermore, the integration of artificial intelligence for nanomaterial design, treatment planning, and outcome prediction holds immense promise. With continued interdisciplinary efforts focusing on these challenges, radiolabeled iron-based nanomaterials are poised to make the critical leap from promising laboratory constructs to transformative clinical cancer therapies.

Abbreviations

SPECT, Single photon emission computed tomography; PET, Positron emission tomography; MRI, Magnetic resonance imaging; TRT, Targeted radiotherapy; RT, Radionuclide therapy; PTT, Photothermal therapy; MHT, Magnetic hyperthermia therapy; PDT, Photodynamic therapy; IT, Immunotherapy; CDT, Chemodynamic therapy; WHO, World Health

Organization; CT, Computed tomography; FDA, U.S. Food and Drug Administration; SRM, Surface radio-mineralization; HIR, Heat-induced radiolabeling; BFCs, Bifunctional chelators; Crgd, cyclic arginine-glycine-aspartic acid; SPIO, Superparamagnetic iron oxide; PEG, Polyethylene glycol; EDTA, Ethylenediaminetetraacetic acid; DFO, Desferrioxamine; SPIONs, Superparamagnetic iron oxide nanoparticles; IONPs Iron oxide nanoparticles; BSA, Bovine serum albumin; US, Ultrasound; BP, Bisphosphonate; USPIO, Ultrasmall-superparamagnetic oxide nanomaterials; MIONP, Multifunctional magnetic iron oxide nanoparticles; MFNs, Manganese ferrite nanoparticles; RES, Reticuloendothelial system; GSH, Glutathione; PSMA, Prostate-specific membrane antigen; NIR, Near-infrared; FMT, Fluorescence mediated tomography; NIFR, Near-infrared fluorescence; PAI, Photoacoustic Imaging; OFI, Optical fluorescence Imaging; HAS, Human serum albumin; CR, Cherenkov radiation; CL, Cherenkov luminescence; SLNs, Sentinel lymph nodes; ROS, Reactive oxygen species; DBCO, Dibenzocyclooctyne; NMIBC, Nonmuscle-invasive bladder cancer; MIBC, Muscle-invasive bladder cancer; PTAs, Photothermal agents; SPR, Surface plasmon resonance; APTES, 3-aminopropyltriethoxysilane; HCC, Hepatocellular carcinoma; TCPP, Meso-tetra(4-carboxyphenyl)porphyrin; TA, Tannic acid; RCD, Regulated cell death; FINs, Ferroptosis-inducing compounds; USINPs, Ultrasmall iron nanoparticles; ICD, Immunogenic cell death; RPT, Radiopharmaceutical therapy; ICB, Immune checkpoint blockade; TME, Tumor microenvironment; MOF, Metal-organic framework; 2-HTP, 2-hydroxyterephthalic acid; AI, Artificial intelligence; ANN, Artificial Neural Networks.

Data Sharing Statement

No data were used for the research described in the article.

Consent for Publication

We confirm that the details of any images can be published. Copyright permission is granted.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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