Recent Advances of Manganese-Based Hybrid Nanomaterials for Cancer Precision Medicine

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Cancer precision medicine (CPM) could tailor the best treatment for individual cancer patients, while imaging techniques play important roles in its application. With the characteristics of noninvasion, nonionized, radiation-free, multidimensional imaging function, and real-time monitoring, magnetic resonance imaging (MRI) is an effective way for early tumor detection, and it has become a tower of strength in CPM imaging techniques. Due to linkage with nephrogenic systemic fibrosis (NSF), gadolinium (Gd)-based contrast agent (CA), which was long used in MRI, has been restricted by the Food and Drug Administration (FDA). In this review, we would like to introduce the manganese (Mn)-based CAs that could significantly increase the safety of MRI CAs by realizing more superior performance and functions simultaneously in the diagnosis and treatment of tumors. Also, recent advances in Mn-based hybrid nanomaterials for CPM are summarized and discussed.

Keywords: cancer precision medicine, magnetic resonance imaging, manganese, nanotheranostic, nanomaterials

INTRODUCTION

Cancer precision medicine (CPM), evolved with the development of novel nanoparticles (NPs) for cancer diagnosis and treatment, could tailor the best treatment for individual cancer patients. Nowadays, CPM has become popular in clinical and bioscience worldwide, with the conventionally used cancer therapies (e.g., chemotherapy, radiotherapy, and surgery) suffering from lower therapeutic efficiency and ineluctable side effects (1–4).

With a large number of nanomaterial-based new cancer therapies being emerged [e.g., photothermal therapy (PTT)/photodynamic therapy (PDT), sonodynamic therapy (SDT), magnetic hyperthermia therapy, etc.], CPM includes an extensive range of cancer management, such as cancer screening and monitoring, drug selection/prediction, and personalized immunotherapy (2, 5–8). CPM relies heavily on imaging methods, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and optical imaging (OI), to provide distinct and precise pathological features for patients.

Owing to superb soft tissue imaging contrast, high spatial resolution, multidimensional imaging, and absence of ionizing radiation, MRI becomes increasingly available for early detection of tumors with gadolinium (Gd)-based contrast agents (CAs) most frequently used (9, 10). Unfortunately, Gd-based CA is in restricted use by the Food and Drug Administration (FDA) due to possibly Gd-based CA-linked medical conditions known as nephrogenic systemic fibrosis (NSF), chronic kidney...
disease (CKD), and severe complexities, which led to new concerns on the safety of Gd as MRI CAs clinically (11–14).

To increase the safety of MRI CAs, manganese (Mn) ion (Mn^{2+}), a non-lanthanide metal, a necessary element in cell biology, and the earliest reported CAs used for enhancing T1-weighted MRI, became an optimal choice due to its paramagnetic nature, low toxicity, and high biosafety (15).

Various Mn-based nanomaterials, such as MnCl₂, Mn chelates, and MnO nanoparticles, have been utilized for cancer diagnosis with great biocompatibility (15–18). Multiple Mn-based nanostructures, such as nanosheets, hollows, nanocages, and nanobubbles, could act as reservoirs for efficient drug delivery (19–22). Additionally, Mn-based hybrid nanomaterials could be adaptable and responsive to both endogenous compounds in the inner tumor microenvironment (TME) (23) and external environmental stimuli, such as acidity, glutathione, temperature, pH, enzyme, light, redox, and chemical signals. Due to those characteristics, Mn-based hybrid nanomaterials could realize demanded discharge of cargo molecular for imaging-guided cancer therapy, thus minimizing additional damage in normal tissues (24, 25).

To sum up, the paramagnetism and Fenton-like property of Mn^{2+} have made Mn-based hybrid nanoparticles with multiple effects, including great performance in MRI, drug delivery, and imaging-guided therapy theranostic systems to integrate diagnosis and treatment into a nanoplatform. Mn-based hybrid nanomaterials have brought a new dawn to the treatment of tumors (26).

In this review, we aimed to provide an overview of recent advances in a possible workflow of Mn-based hybrid nanomaterials used for CPM by reviewing recent emerging techniques and treatments that have been used or will be potentially used. The Mn-based hybrid nanomaterials as imaging agents, carriers for drug delivery, and theranostic agents are summarized in sections Manganese-Based Hybrid Nanomaterials as Imaging Agents, Manganese-Based Hybrid Nanomaterials as Carriers for Drug Delivery, and Manganese-Based Hybrid Nanomaterials as Theranostic Agents, respectively. We will discuss how Mn-based hybrid nanomaterials can be used as CAs for detecting and monitoring cancer progression; how they act as chemotherapeutic drug carriers to increase therapeutic index; and how they can function as theranostic agents in imaging-guided PTT, PDT, SDT, and radiation therapy, etc. Here, we highlight the Mn-based hybrid nanomaterials as theranostic agents, and such an imaging-guided nanotheranostic platform would help to develop optimized and individualized regimens in light of patient’s response and offer an opportunity to develop CPM. The progress and perspective are summarized in section Perspective.

### Manganese-Based Hybrid Nanomaterials as Imaging Agents

The noninvasive, nonionized, and radiation-free characteristics make MRI one of the most extensively utilized clinical imaging tools. However, conventional signal intensity-based MRI is still limited to its semiquantitative nature, which is susceptible to many factors. Recently, various Mn-based hybrid nanomaterials could increase T1-weighted MRI effect even in acid environment with good biocompatibility or multimodal imaging free from the effects of various conditions in the TME (14, 27, 28). The Mn-based hybrid nanomaterials as imaging agents are summarized in Table 1, with the schematic diagram and examples of imaging effect shown in Figure 1.

T1-T2 dual-modal CAs could enable both T1 bright and T2 dark contrasts. Zhao et al. (27) prepared the multifunctional DNA-Mn-based nanoflower (DMNF), showing enhanced T1-weighted MRI effect even in acid environment and high spatial resolution imaging of kidneys and liver. What is worth mentioning is that Zhou et al. (28) made a 1,4,7-triazacyclononane-N,N,N`-triacetic acid-conjugated truncated Evans blue (NEB), and after chelating with Mn (MnNEB) and bovine serum albumin (MnNEB+BSA), it could be used as novel T1-T2 dual-modal MRI CA. This study opens a new avenue for contrast-enhanced MRI diagnosis, and it also shows extraordinary promise for CPM (28).

### Manganese-Based Hybrid Nanomaterials as Carriers for Drug Delivery

Nanotechnology acts a great role in drug delivery to help revolutionize CPM. Mn-based hybrid nanomaterials, such as...

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**Table 1** Manganese-based hybrid nanomaterials as imaging agents.

| Agent name | Description | Tumor model | Research group and reference |
|------------|-------------|-------------|-----------------------------|
| Mn-NEB+BSA | As dual-modal MRI contrast agents, Mn-NEB+BSA could greatly eliminate suspicious artifacts and false-positive signals in mouse brain imaging. | U87MG tumor-bearing athymic nude mice | Jinhao Gao and Xiaoyuan Chen’s group (28) |
| DMNF      | DMNF showed high tumor-specific MRI with enhanced T1-weighted imaging effect, which was attributed to the synergistic effect of active targeting of AS1411 aptamer and acid-activated release of Mn²⁺ promoting the MRI signal enhancement. | MCF-7 tumor-bearing BALB/c nude mice | Dayong Yang’s group (27) |
| HMS       | Hollow manganese silicate (HMS) nanoparticles could release Mn²⁺ in physiological acidic condition as a liver-specific Mn contrast agent in hepatic tumor models. | HCC, NEC, and ADC tumor-bearing nude mice | Won Jae Lee and In Su Lee’s group (14) |

Mn, manganese; NEB, 1,4,7-triazacyclononane-N, N', N"-triacetic acid conjugated truncated Evans blue; BSA, bovine serum albumin; DMNF, DNA-Mn-based nanoflower; HMS, hollow manganese silicate.
nanosheets, hollow mesoporous nanoshells, and nanocubes, have a high surface-to-volume ratio fit for drug delivery and could produce Mn\(^{2+}\) for MRI (20). Currently fabricated composite nanoparticles used for drug delivery include the nanoparticle for the carrier and chemotherapeutic drug for cancer (e.g., doxorubicin [DOX], paclitaxel [PTX], methotrexate [MTX], arsenic trioxide [ATO], cisplatin [cis-diaminedichloroplatinum (CDDP)], etc.) or non-tumor-specific drugs (e.g., hydroxychloroquine, verteporfin, 5-fluorouracil, osteopontin siRNA, etc.) that is either adsorbed, dissolved, or dispersed throughout the nanoparticle complex or covalently attached to the surface of nanoparticles (5). Also, they hold great potential to simultaneously codeliver more drugs in combination therapy. The delivery of non-cytotoxic prodrugs to cancer cells is one of the newer applications (29).

Furthermore, drugs can be formulated at a nanoscale level to increase its therapeutic efficiency. Nanoscale drug delivery systems (nano-DDSs) have already been proposed as a promising way to realize tumor-specific treatment by being adaptable and responsive to many endogenous substances and external stimuli, such as acidity, overexpressed hydrogen peroxide (23), pH, enzyme, light, temperature, and magnetic field.

Hence, numerous smart hybrid nanomaterials with one or dual stimuli-responsive (e.g., lower pH, hypoxia, tumor-specific enzymes such as glutathione, etc.) drug-releasing and one or dual-mode diagnostic imaging functions (particularly MRI) have been developed to realize improved therapeutic specificity and efficacy (12, 13, 19, 21, 22, 24, 25, 30–48). The Mn-based hybrid nanomaterials as carriers for drug delivery are summarized in Table 2, with examples of the schematic diagram for drug delivery system, characterization analysis, and curative effect shown in Figure 2. It is worth noting that redox-sensitive Mn-SS (disulfide)/DOX@PDA (polydopamine)-PEG polymers (NCPs) designed by Zhao et al. (30) served as a T1 CA under MRI and showed a glutathione (GSH)-responsive release of DOX. Huang et al. (9) fabricated theranostic nanocomposites Mn-porphyrin&Fe\(_3\)O\(_4\)@SiO\(_2\)@PAA-cRGD and effectively used them in T1- and T2-weighted MRI and pH-responsive drug release. Wang et al. (49) reported the one-pot synthesis of biocompatible arginine-rich Mn silicate nanobubbles (AMSNs) with high tumor killing activity via the glutathione-dependent peroxidases 4 (GPX4)-mediated ferroptosis pathway. Such imaging-guided drug-carrying platforms would therefore tremendously promote the development of CPM.

**MANGANESE-BASED HYBRID NANOMATERIALS AS THERANOSTIC AGENTS**

Many efforts have been made for cancer therapy, and the idea of theranostics could help develop a smart nanoparticle to integrate cancer diagnosis, drug delivery, and therapy monitoring simultaneously in a system (50). The intelligent stimuli-responsive manner could offer an efficient strategy for CPM by employing the unique features of TME or clinical external irradiations. With the improvement of polymerization and emulsifying techniques, nanoparticles could be made with hydrophilic and hydrophobic facets to load with different

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**FIGURE 1** Manganese (Mn)-based hybrid nanomaterials as imaging agents and their application in tumor. (A) Diagram of the enhanced MRI of DNA-Mn-based nanoflower (DMNF)-treated tumor-bearing mice (27). (B) Preparation and characterization of DMNF imaging agents (27). (C) Representative T1- and T2-weighted images of mouse brain at pre- and post-contrast points. T1-T2 dual-modal MRI in brain tumor model through the synthesized MRI contrast agents, NOTA conjugated NEB chelating with Mn\(^{2+}\) (Mn-NEB) and BSA (Mn-NEB+BSA) (28). DMNF, DNA-Mn-based nanoflower; NOTA, N, N', N'''-triacetic acid.
active materials for theranostics. The Mn-based hybrid nanomaterials as imaging agents and carriers for drug delivery have been summarized and discussed in this section, and the Mn-based hybrid nanomaterials as theranostic agents are summarized in Table 3, with the schematic diagram and examples shown in Figure 3.

**Imaging-Guided Photothermal Therapy**

PTT, a combination of photothermal nanomaterials and light irradiation, becomes a clinically promising modality for cancers. It could controllably and selectively heat the target area to minimize thermal damage.

Many Mn-based hybrid nanomaterials used for imaging-guided PTT have been developed (11, 48, 71, 73–77), such as nanopetals of MnO4 hybrid nanomaterials for multifunctional imaging-guided PTT (51), a 2-D nanoplatform based on Cu2MnS2 nanolates for MRI/multiplespectral optoacoustic tomography (MSOT) dual-modal imaging-guided PTT (52, 78), a plasmonic modulation strategy of Gold Nanorods (GNRs) through MnO2 core–shell nanostructure as a GSH-triggered smart theranostic agent for PA and MR dual imaging-guided PTT (53, 68).

**Imaging-Guided Photodynamic Therapy**

PDT has emerged as a promising therapeutic option for cancers, and it could generate cytotoxic oxygen-based

| Delivered molecules | Agent name | Description | Tumor model | Research group and reference |
|---------------------|------------|-------------|-------------|-----------------------------|
| DOX                 | HMnO2       | Hollow mesoporous MnO2 (HMnO2) nanoshells with DOX loaded could be used for tumor-specific therapy in pH-responsive MRI. | 4T1 tumor-bearing Balb/c mice | Zhuang Liu’s group (24) |
| DOX                 | MnSS       | Redox-sensitive MnSS (disulfide)/DOX@PDA (polydopamine)-PEG polymers (NCPs) for T1-contrast MRI and glutathione (GSH)-responsive release of DOX | 4T1 tumor-bearing Balb/c mice | Zil Ge and Zhuang Liu’s group (30) |
| DOX                 | MnO2-PEG-FA/DOX nanoshells | A redox/pH dual responsive nanotheranostic platform, MnO2-PEG-FA/DOX nanoshells through MnO2 nanoshells combined with FA and DOX for MRI and chemotherapy | S180 tumor-nearing nude mice | Zhenzhong Zhang and Yun Zhang’s group (35) |
| DOX                 | BMDN MnO2-PEG-NCPs | A pH-responsive DOX-loaded glucose oxidase (Gox) with MnCaP spherical nanomaterials for MRI and cascade reaction-enhanced cooperative cancer treatment | 4T1 tumor-bearing Balb/c mice | Peng Huang’s group (39) |
| DOX                 | USMO@MSNs  | USMO@MSNs loading DOX for pH-switching MRI and chemotherapy | MCF-7/ADR tumor-bearing mice | Huabing Chen and Hu-Lin Zhang’s group (31) |
| DOX                 | Hollow MCO NPs | Hollow manganese/cobalt oxide nanoparticles (MCO-70 NPs) with a tunable size for GSH-responsive dual T1/T2-weighted MRI reporting drug release of DOX | H22 tumor-bearing Balb/c mice | Jinhao Gao’s group (38) |
| PTX                 | W-Ptx-PPR  | Three shaped Mn-Zn ferrite (MnO2-ZnO2-FeO2) MNPs for more efficient dual-mode MRI/fluorescence imaging-guided drug delivery | A549 tumor-bearing nude mice | Zhenzhong Zhang and Yun Zhang’s group (57) |
| MTX                 | MN(Cu)PEG NCPs | A chelating agent free, stoichiometry, and pH-responsive NCPs for MRI-guided MTX delivery | 4T1 tumor-bearing Balb/c nude mice | Youli Wang, Dawei Li and Xinyuan Zhu’s group (38) |
| ATO                 | Mn(IIIAsO3)@SiO2 | A pH-sensitive multifunctional trioxide (ATO) drug delivery system (MDDS) through hollow silica nanoparticles loading water-insoluble manganese-arsenite complexes (MnOsOx8SiO2) and ATO for real-time monitoring of ATO release by activatable MRI | H22 tumor-bearing Balb/c mice | Jinhao Gao’s group (36) |
| CDDP                | MnO2-HA/CDDP nanoshells | MnO2-HA/CDDP nanoshells (MnO2 nanoshells functionalized by HA, with CDDP absorbed) for pH-responsive MRI and delivering CDDP | A549 tumor-bearing nude mice | Zhenzhong Zhang and Yun Zhang’s group (57) |
| HCQ                 | HA-MnO2/HCQ | TME-responsive drug release and tumor targeting drug carriers-Hollow mesoporous MnO2 NPs conjugated with hyaluronic acid (HA) loading hydroxychloroquine (HCQ, traditional autophagy inhibitor) into the hollow core, for MRI-guided in situ autophagy inhibition | 4T1 tumor-bearing Balb/c mice | Lin Hou and Zhenzhen Zhang’s group (21) |
| BPD                 | MnO2/BPD NPs | MnO2/BPD nanocomposites for vessel embolization therapy with MRI, PA, and FL multimodal imaging as a predictor | Hep-G2 tumor-bearing Balb/c mice | Meng Niu, Ke Xu and Jie Tian’s group (19) |
| OPN                 | PEG-MnO2-siRNA | PEG-modified MnO2 nanoshells carrying osteopontin (OPN) siRNA for GSH-responsive MRI-guided gene delivery | 786-O tumor-bearing Balb/c mice | Kai Xua and Jingjing Li’s group (20) |

|MnO2, hollow mesoporous MnO2; DOX, doxorubicin; MRI, magnetic resonance imaging; PDA, polydopamine; SS, disulfide; GSH, glutathione; Gox, glucose oxidase; MnCaP, manganese-doped calcium phosphate; BMDN, BSA-MnO2-DOX nanoparticles; USMO@MSNs, Ultrasmall manganese oxide-capped mesoporous silica nanoparticles; MCO-70 NPs, Hollow manganese/cobalt oxide nanoparticles with an average size of 70 nm; MTX, methotrexate; MDDS, multifunctional drug delivery system; MnAsOx8SiO2, hollow silica nanoparticles loading water-insoluble manganese-arsenite complexes; HA, hyaluronic acid; CDDP, cis-diaminedichloroplatinum; TME, tumor microenvironment; HA, hyaluronic acid; HCQ, hydroxychloroquine; BPD, benzoporphyrin derivative; MnO2, manganese trioxide; OPN, osteopontin; ZIF, zeolitic imidazolate framework.
molecular species via photosensitizer to ablate tumor growth by inducing cell apoptosis, necrosis, or autophagy. As a new noninvasive modality, PDT could enhance the conventional cancer treatment by overcoming drug resistance or escape pathways.

A lot of Mn-based hybrid nanoparticles were synthesized for imaging-guided PDT diagnosis and treatment (10, 54, 55, 79, 80). For example, Zhang et al. (10) have proven that Mn-doped iron oxide nanoparticles modified with denatured BSA (MnIO-dBSA) and Fmoc-L-L/Mn2+/Ce6 nanoparticles (FMCNPs) could improve antitumor PDT efficacy. Also, oxygen-generating theranostic nanoparticles (CDM NPs) with MnO2 could be applied for trimodal imaging-guided combined PDT in breast cancer (69). A multifunctional DNA-templated silver nanoclusters/porphyrin/MnO2 nanoplatform could be used for non-labeled fluorescence images of Zn2+ and 635-nm red light-triggered PDT (56). The MnO2 NP-based PDT nanocomplex could generate oxygen to overcome the limitation of insufficient oxygen level in tumors (55).

**Imaging-Guided Sonodynamic Therapy**

SDT is an alternative promising method for cancers by generating reactive oxygen species (ROS), ROS to induce cell death with low-intensity ultrasound irradiation combined with nontoxic sonosensitizers (81, 82). It is characterized by high therapeutic efficiency with the advantages of noninvasiveness and mitigated side effects.

Mn-based theranostic agents could integrate imaging and therapy into a single nano-platform for imaging-guided SDT. It has been reported that even in the presence of skull, sinoporphyrin sodium (DVDSM) chelating with Mn (DVDSM-Mn-LPs) could effectively inhibit the tumor growth (57). The efficacy of SDT could be severely inhibited by hypoxia and high glutathione in TME, while a Mn porphyrin-based metal-organic framework...
| Therapy | Agent name | Description | Tumor model | Research group and reference |
|---------|------------|-------------|-------------|-----------------------------|
| PPT     | Au@Mn$_2$O$_4$ magnetoplasmic nanoflowers | With great potential in T1-weighted MRI and photothermal therapy (PPT) in vitro and in vivo | 4T1 tumor-bearing mice | Aiguo Wu’s group (11) |
| PPT     | MONPs-BSA-EDTA | For multifunctional imaging-guided PPT | HCT116 tumor-bearing mice | Jing Zhou’s group (51) |
| PPT     | Cu$_2$Mn$_2$S$_4$ NPs | For MRI/MSOT dual-modal imaging-guided PTT of cancer in the NIR-II window | S180 tumor-bearing mice | Chunhua Lu and Huanghao Yang’s group (52) |
| PPT     | MNP-Mn | A multifunctional nanoplateform for MR/PA dual-modal imaging-guided PTT | Hep-2 tumor-bearing mice | Ruiping Zhang’s group (53) |
| PPT     | Mn$^{2+}$-doped PB nanocubes | Mn$^{2+}$-doped PB (PB : Mn) nanocubes for MRI-guided PTT with enhanced performance | 4T1 tumor-bearing Balb/c mice | Liang Cheng and Zhuang Liu’s group (49) |
| PDT     | FMCNPs | Amphiphilic amino acid-coordinated ionic manganese simultaneous encapsulation of chlorin e6 (FMCNPs) for MRI-guided PDT | MCF7 tumor-bearing mice | Xia Xin, Shiling Yuan, and Xuehai Yan’s group (54) |
| PDT     | MnO$_2$-dBSA | Manganese-doped iron oxide nanoparticles modified with denatured bovine serum albumin (MnO$_2$-dBSA) composites for efficient tumor MRI and PDT | 4T1 tumor-bearing mice | Zhiun Zhang’s group (10) |
| PDT     | ICM | By encapsulating a MnO$_2$ NP in an ICG-modified hyaluronic acid nanoparticle (HANP) for fluorescent and PA imaging-guided tumor PDT | SCC7 tumor-bearing mice | Guoping Zhao, Qingje Ma, and Lei Zhu’s group (55) |
| PDT     | P-AGNCs-MnO$_2$ | A novel multifunctional DNA-templated silver nanoclusters/porphyrin/MnO$_2$ theranostic nanoplatform for non-labeled fluorescence images of Zn$^{2+}$ and PDT | MCF-7 tumor-bearing mice | Daoud Yang and Fengjie Gao’s group (56) |
| SDT     | DVMS-Mn-LPs | Encapsulation of DVMS chelating with Mn into nanoliposomes for integrating imaging and therapy into a single nano-platform | U87 tumor-bearing mice | Fei Yan’s group (57) |
| SDT     | Mn-MOF | A nanosensitizer to self-supply O$_2$ and decrease GSH for enhanced SDT and ferroptosis | H22 and 4T1 tumor-bearing mice | Xiangliang Yang and Lu Gan’s group (58) |
| CDT     | MnS@BSA | Size-controllable, biodegradable, and metastable $\gamma$-phase manganese sulfide nanotheranostics using BSA as a biological template for tumor pH-responsiveness traceable gas therapy-primed CDT | 4T1 tumor-bearing mice | Peng Huang’s group (59) |
| CDT     | GSH-Gated MnO$_2$@PEI-IAA | For GSH-gated mRNA-21 signal amplification and GSH-activated MRI-guided CDT | MCF-7 tumor-bearing mice | Caiyu Xu and Huayu Tian’s group (60) |
| CDT     | MCDION-Se | Nanoselenium-coated MCDION-Se for MRI guided CDT | HeLa and HK-2 tumor-bearing mice | Duohong Zou and Zhengyan Wu’s group (61) |
| RIT     | $^{131}$I-HSA-MnO$_2$ NPs | Radionuclide $^{131}$I-labeled human serum albumin (HSA)-bound manganese dioxide nanoparticles ($^{131}$I-HSA-MnO$_2$ NPs) as a novel radioisotope therapy (RIT) nanomedicine platform for tumor microenvironment | 4T1 tumor-bearing mice | Kai Yang and Zhuang Liu’s group (62) |
| Gene therapy | f-L-SQDs | The (f-L-SQDs)-folic acid-conjugated liposome core–shell co-doped Mn : ZnSe/ZnS/ZnMSS sandwiched quantum dots (SQD) to deliver cancer cell-targeted siRNA for dual-mode imaging (MRI and fluorescence imaging) and gene therapy | Panc-1 (ATCC CRL-1469) tumor-bearing mice | Tze Chien Sum and Ken-Tye Yong’s group (63) |
| Photo- | DNA/Mn NPs | A multifunctional theranostic nanoplatform-DNA/Mn NPs by encapsulating indocyanine green (ICG)-labeled CHA-DNAzyme prodrugs and MnO$_2$ adjuvant into a biocompatible poly nanocarrier for photo-theranostics strategy | MCF-7 tumor-bearing mice | Fuan Wang’s group (64) |
| photothermal | | Novel room-temperature FIMO-NFs to harness the advantages and potential of T1-T2 dual-mode MRI and magnetic hyperthermia therapy for precision medicine | U87MG tumor-bearing mice | Jun Ding and Hai Ming Fan’s group (65) |
| hyperthermia therapy | | | | |
| | FIMO-NFs | Novel room-temperature FIMO-NFs to harness the advantages and potential of T1-T2 dual-mode MRI and magnetic hyperthermia therapy for precision medicine | U87MG tumor-bearing SCID mice | |
| PTT and CDT | PPN | A second near-infrared PFN for activatable MRI-guided synergetic PTT and CDT | Panc02 tumor-bearing mice | Ruizhi Wang, Yu Luo and Xiaolin Wang’s group (66) |
| photothermal-chemodynamic therapy | GNRs | A plasmonic modulation strategy of GNRs for imaging guided NIR-II photothermal-chemodynamic therapy | U87MG tumor-bearing mice | Peng Huang’s group (67) |
| photothermal-enhanced | GSH-triggered Au@MnO$_2$ | An Au@MnO$_2$ core–shell nanostucture as a GSH-triggered smart theranostic platform for PA and MRI-guided photothermal-enhanced chemodynamic therapy | 4T1 tumor-bearing mice | Qiwei Tian and Shiping Yang’s group (68) |

(Continued)
(Mn-MOF) could improve antitumor immunity and immunosuppressive microenvironment upon ultrasound irradiation to show great potential for hypoxic cancer therapy (58).

Other Imaging-Guided Therapies
Mn-based hybrid nanomaterials also hold great potential for many other traceable therapies for cancer, such as chemodynamic therapy (CDT) (60, 61), radiation therapy (83), magnetic hyperthermia therapy, and combination therapy (70, 84, 85).

For pH-responsive traceable gas therapy-primed CDT, a γ-phase Mn sulfide nanotheranostics using bovine serum albumin (MnS@BSA) could greatly suppress tumor growth (59). During radiation therapy, ionizing radiation will damage both normal
tissues and tumors, and hypoxia within TME would often lead to the resistance to radiotherapy. To improve the effect of radiation therapy, radionuclide $^{131}$I-labeled human serum albumin (HSA)-bound MnO$_2$ nanoparticles ($^{131}$I-HSA-MnO$_2$) could function as an effective agent to show great efficacy in tumor treatment. The novel room-temperature ferromagnetic wüstite iron-manganese oxide nanoflowers (FIMO-NFs) could harness the advantages and potential of dual-mode MRI and magnetic hyperthermia therapy to induce cancer cell apoptosis.

Mn$^{2+}$-doped bio-response theranostic NP could be designed for tumor-specific enhanced combination therapy under the guidance of multimodal imaging. Pd@Au bimetallic NP-decorated hollow mesoporous MnO$_2$ (H-MnO$_2$) NPs could achieve both nucleus-targeted PTT and TME hypoxia relief-enhanced PDT. An intelligent nanoflower composite with multistage H$_2$O$_2$/pH/GSH-responsive properties, FHPC@MnO$_2$ could realize the specific release of drugs in tumor and significantly increase the synergistic therapeutic effect.

**PERSPECTIVE**

Cancer still remains a significant challenge worldwide, and the new discovered theranostic nanomaterials, such as Mn-based hybrid nanomaterials, which make diagnosis and treatment together in a unified platform, provide a novel therapy specialized for tumors. Since nanomaterials for theranostics create great new opportunities in developing CPM, this review focused on Mn-based nanoparticles with various applications (used as imaging agents, drug delivery, and theranostic agents) in CPM. Although a multitude of Mn-based hybrid nanomaterials have not been successfully used in the clinic, several well-designed Mn-based hybrid nanoparticles provide a new promising treatment option in the near future. What is worth emphasizing is that the novel nanoparticles should be thoroughly characterized, whether used as imaging agents, carriers for drugs, or theranostic platforms, and the toxicity studies in both cell culture and animal models are needed before they can be applied clinically. A future perspective is proposed for further research and development of complex targeted, multistage responsive nanomedical drug delivery systems with high intelligence, precision, and minimum toxicity for personalized cancer diagnosis and effective therapy. A major obstacle in designing theranostic Mn-based hybrid nanomaterials might be that providing target specificity to biomaterials for enhancing therapeutic effect and visualization in CPM. With the aid of multimode imaging, theranostic nanoparticles can visualize and monitor drug delivery and therapeutic responses at tumor site.

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**AUTHOR CONTRIBUTIONS**

XL and PR contributed to the conception, design, writing, and final approval of the article. All authors contributed to the article and approved the submitted version.

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