

Advances in nanomaterial-enhanced ablation therapy for hepatocellular carcinoma

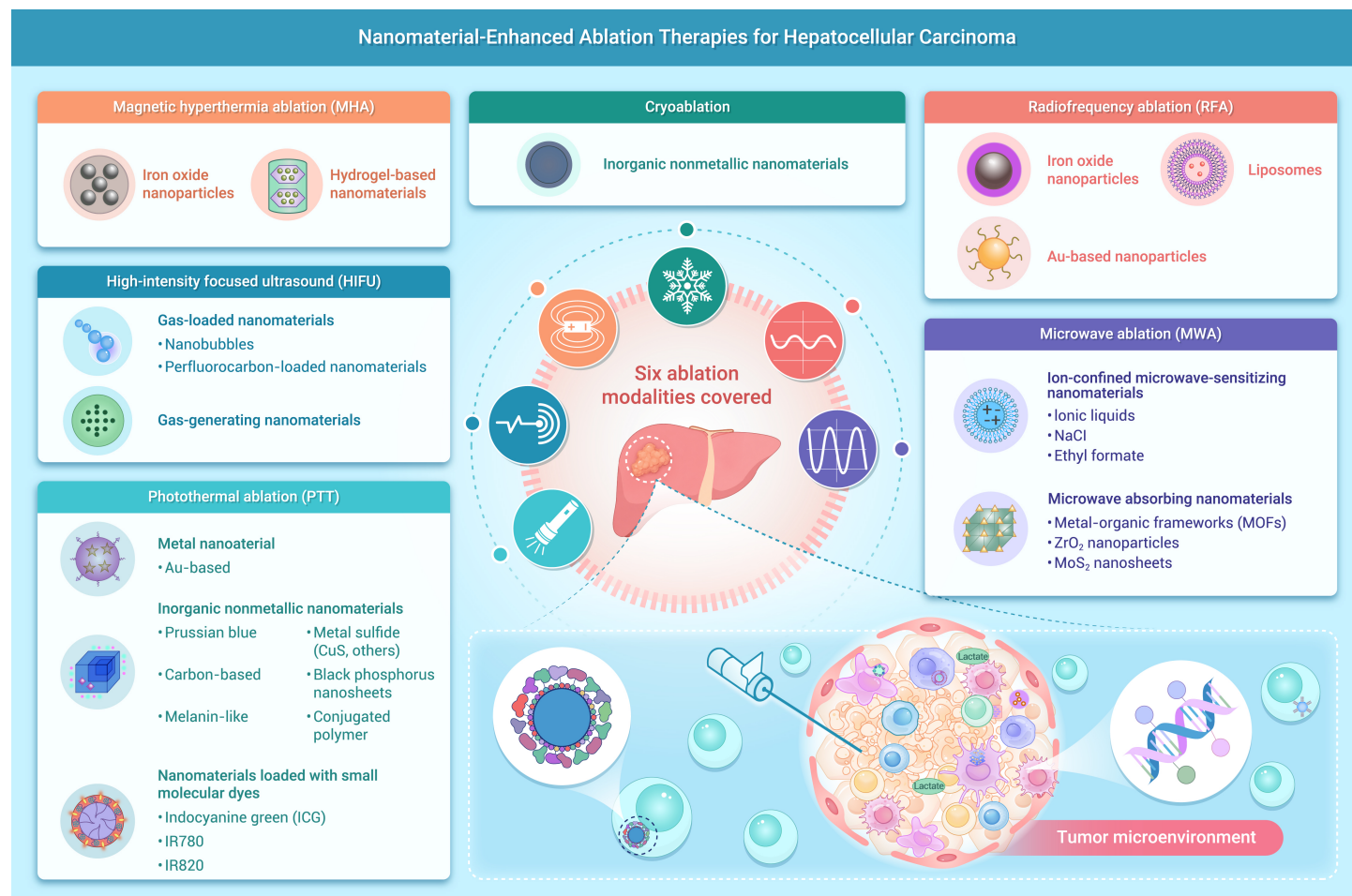
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Ablation therapy is important for HCC.
- Nanomaterials can be leveraged to potentiate ablation.
- Nanomaterial-enhanced HCC nerve ablation is a novel direction for future studies.
- We provide new insights and directions for improving anti-tumor therapy for HCC.

Advances in nanomaterial-enhanced ablation therapy for hepatocellular carcinoma

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Ablation therapy is a cornerstone locoregional treatment for hepatocellular carcinoma (HCC), particularly in patients with early-stage disease or those who are not surgical candidates. Despite its widespread use, ablation is limited by incomplete tumor destruction, heat-sink effects, and a high risk of local recurrence. Nanomaterials can enhance ablation efficiency, expand the effective treatment zone, and improve the tumor microenvironment. Therefore, effective HCC management strategies that leverage nanomaterials to potentiate ablation must be developed. Nanomaterials can augment imaging preoperatively, boost ablation efficacy intraoperatively, and modulate the tumor microenvironment postoperatively to prevent recurrence. In addition, nanomaterials can serve as carriers for chemotherapeutic, targeted, or immunomodulatory agents, enabling synergistic combinations of ablation with systemic or transarterial therapies. Building on the role of nanomaterials in potentiating ablation, this review systematically examines the mechanisms by which different classes of nanomaterials—including iron oxide nanoparticles, Au-based nanoparticles, liposomes, and hydrogels—enhance radiofrequency ablation, microwave ablation, high-intensity focused ultrasound, photothermal ablation, magnetic hyperthermia, and cryoablation for HCC. We also discuss the clinical translation potential of these nanomaterials, providing new perspectives and research directions to advance ablation therapy for HCC. Our findings provide novel insights on developing effective anti-tumor therapy strategies based on ablation treatment for patients with HCC.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed malignancy and the third leading cause of cancer-related mortality worldwide. Chronic liver diseases,¹ including hepatitis B virus infection, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis, are the principal drivers of cirrhosis and subsequent HCC development.¹ Owing to these varied etiological factors, HCC has diverse types of tumor microenvironments (TMEs). Currently, HCC is mainly classified into immune-activated, myeloid-enriched immune-suppressed, stroma-enriched immune-suppressed, immune-excluded, and immune-infiltrated types.² Therapeutic strategies for HCC are therefore diverse and stage-dependent. Systemic therapy mainly includes immunotherapy and targeted therapy.³ Among them, immunotherapies, such as anti-programmed cell death protein 1 (anti-PD-1) and anti-programmed death ligand 1 (anti-PD-L1) antibodies exert their effects by improving antigen presentation and blocking T-cell immunosuppression.⁴ Antiangiogenic agents, typified by tyrosine kinase inhibitors, act by inhibiting angiogenesis.⁵ Nevertheless, systemic therapy remains the mainstay of treatment for advanced HCC.⁶ Compared with systemic therapy, locoregional therapy plays an important role in the management of early-, intermediate-, and locally advanced-stage HCC.⁷ Among these, ablation for liver cancer has a long history and is widely used.⁸ This is partly because the liver, as a parenchymal organ with high water content, is conducive to heat conduction during abla-

tion.⁹ Moreover, ablation can be precisely guided by multiple imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US).¹⁰ In the locoregional treatment of early-stage HCC, ablation can serve as an alternative to surgical resection, offering advantages such as minimal invasiveness, fewer complications, and modulation of the TME.⁹ In the treatment of intermediate- and advanced-stage HCC, ablation combined with transarterial chemoembolization (TACE) has demonstrated favorable efficacy in intermediate-stage and selected advanced-stage disease.⁹ Therefore, ablation is one of the principal locoregional treatment options for HCC.

Compared with surgical resection, TACE, radiotherapy, and systemic therapy, ablation offers several clinically meaningful advantages: it is minimally invasive, percutaneously repeatable, preserves functional liver parenchyma, and carries low peri-procedural morbidity in appropriately selected patients — attributes that make it particularly valuable for early-stage HCC and for those who are poor surgical candidates owing to cirrhosis or portal hypertension.¹¹ These advantages are increasingly supported by high-level clinical evidence. The multicenter SURF trial demonstrated comparable five-year overall survival between surgery and radiofrequency ablation (RFA) for small HCC, establishing ablation as a viable curative-intent option in early-stage disease.¹² A randomized comparison of laparoscopic liver resection with percutaneous RFA reported equivalent long-term survival outcomes, suggesting that modality selection may reasonably be guided by patient preference and institutional expertise rather than oncologic hierarchy.¹³ In HBV-related HCC complicated by clinically significant portal hypertension — a population in which hepatectomy carries prohibitive risk under current guidelines — ablation-based interventional treatment achieved long-term survival comparable to partial hepatectomy with substantially fewer complications, directly demonstrating ablation's applicability in poor surgical candidates.¹⁴ In the recurrent setting, combined TACE-RFA achieved survival comparable to repeat resection while avoiding reoperation-associated morbidity, capitalizing on ablation's repeatability and parenchyma-sparing nature.¹⁵ For intermediate-stage disease, combination strategies extend ablation's reach further: TACE plus microwave ablation (MWA) improved outcomes over MWA monotherapy in HCC larger than 3 cm, and the ongoing CERFA trial is evaluating TACE-RFA in beyond-Milan disease.¹⁶ Beyond local tumor control, ablation has demonstrated immunological relevance: subtotal thermal ablation combined with the PD-1 inhibitor toripalimab improved progression-free survival over toripalimab monotherapy in previously treated unresectable HCC, illustrating how ablation-induced DAMP release may prime systemic anti-tumor immunity and enhance checkpoint blockade responses.¹⁷ Together, these data position ablation as a guideline-endorsed treatment option across early-stage disease, cirrhotic and portal-hypertensive patients, recurrent disease, and immunotherapy combination settings, providing the clinical rationale for nanomaterial-based enhancement strategies reviewed herein. However, ablation is limited by incomplete tumor eradication and post-treatment recurrence.¹⁰ Accordingly, enhancing ablation represents an effective antitumor strategy.

In light of these limitations of ablation therapy, leveraging nanomaterials to potentiate ablation has emerged as a promising antitumor strategy. Nanomaterials are a class of materials with nano-scale structures and diverse morphologies.¹⁸ They can be categorized into inorganic, organic, organic-inorganic hybrid, and bio-nanomaterials.¹⁹ Organic nanomaterials include metallic and non-metallic subtypes.²⁰ Nanomaterials possess several advantages, including good biocompatibility, high drug-loading capacity, and enhanced permeability and retention effect (EPR) in tumor tissues.²¹ The exceptionally high specific surface areas of nanomaterials stem from their enhanced surface-to-bulk atomic ratio.²² These distinctive structural properties lead to multiple effects, including increased defect densities, numerous unsaturated coordination sites, and observable lattice strain.²² These changes result in properties that are distinct from those of bulk materials, with significant alterations in thermal properties, spectral characteristics, mechanical behavior, and magnetic properties.²³ These modifications endow nanomaterials with the capacity to enhance tumor ablation.²⁴ However, these intrinsic physicochemical properties do not act in isolation; once administered, nanomaterials are continuously reshaped at the nano-bio interface through protein-corona formation, opsonization, endothelial transcytosis, stromal sieving, and microenvironment-triggered transformations, and HCC itself presents a spatially heterogeneous target composed of proliferative, hypoxic, fibrotic, infiltrative, vascularized, and variably immune-infiltrated compartments.^{25,26} A widely cited meta-analysis estimated that a median of only ~0.7% of an injected nanoparticle dose actually reaches solid tumors, underscoring that physicochemical design must be considered together with this dynamic biological interface to translate into therapeutic benefit.²⁷ Nanomaterials loaded with ablation enhancers, or engineered with ablation-potentiating architectures, can augment preoperative CT, MRI, or US imaging to facilitate ablation path planning and thereby improve procedural precision;²⁸ increase intraoperative ablation efficiency and patient tolerability;²⁹ and modulate the postoperative TME to activate antitumor immunity and prevent recurrence.³⁰ Furthermore, nanomaterials can be used to deliver clinically utilized antitumor agents—such as anti-PD-(L)1 antibodies, anti-Cytotoxic T-Lymphocyte-Associated protein 4 (anti-CTLA-4) antibodies, sorafenib (Sor), and lenvatinib—to enable combinations of ablation with immunotherapy or targeted therapy.³¹ Practically, nanomaterials loaded with doxorubicin (Dox) and endowed with embolic properties can realize the combination of ablation and TACE.³² Building on the advantages of nanomaterials in potentiating ablation and enabling combination regimens, this review summarizes the roles of metallic, nonmetallic, organic, and bio-derived nanomaterials in enhancing RFA, MWA, photothermal therapy (PTT), high-intensity focused ultrasound (HIFU), magnetic hyperthermia ablation (MHA), and cryoablation for HCC (Figures 1–10; Tables 1 & 2). Furthermore, we discuss the current challenges and future directions for clinical translation of these materials, providing new insights and avenues for strengthening ablation-based and combinatorial therapies for HCC.

NANOMATERIALS ENHANCE RFA FOR HCC

RFA is a minimally invasive technique in which high-frequency alternating current generates localized heat, inducing coagulative necrosis of tumor tissue.³³ Under imaging guidance, electrodes are inserted into the tumor, where resistive heating leads to cell death within the targeted region.³⁴ RFA is an effective treatment for HCC with a diameter of ≤ 3.0 cm.³⁵ There is no difference in overall survival (OS) and recurrence-free survival between patients treated with RFA and those undergoing surgical resection.³⁶ Additionally, compared to surgical resection, patients treated with RFA have a lower incidence of adverse events and shorter hospital stays.³⁷ Therefore, RFA is particularly important for patients with early-stage HCC who are unable to undergo surgical resection due to poor liver function or other comorbidities. However, RFA also faces many challenges. First, the efficacy of RFA depends on the tumor diameter and location.³⁸ When tumors are close to large vessels (hepatic or portal veins) or bile ducts, patients are likely to experience incomplete ablation due to rapid heat dissipation or proximity to the biliary tract.¹¹ Second, the heat generated by RFA can cause coagulative necrosis of liver tissue, which may subsequently block blood vessels and bile ducts.³⁹ Third, radiofrequency alternating current is affected by tissue conductivity, thermal conductivity, dielectric constant, and heat capacity.⁴⁰

Moreover, as ablation progresses, tissue dehydration and charring may occur, increasing tissue impedance.^{41,42} Finally, owing to technical and subjective limitations, the accuracy of determining the ablation margin around the lesion in RFA is relatively low.⁴³ However, nanomaterials can penetrate the perivascular or transitional areas of the tumor to release drugs,⁴⁴ enhance heat transfer between the RFA probe and target tissue,⁴⁵ improve imaging of the tumor margin,⁴⁶ and facilitate the combination of RFA with immunotherapy.⁴⁷ Therefore, the combination of nanomaterials and RFA may improve the therapeutic efficacy of HCC. Next, we will discuss the roles of metal nanomaterials and temperature-sensitive liposomes (TSLs) in RFA for HCC, as well as how nanomaterials can modulate immunotherapy to assist RFA in the treatment of HCC (Figures 1 & 2, Table 1). This section reviews recent advances in the application of nanomaterials to enhance RFA for HCC.

Iron oxide nanoparticles enhance RFA for HCC

Iron oxide nanoparticles (IONPs) are among the most extensively studied nanomaterials in oncology.⁴⁸ IONPs can induce significant static magnetic field inhomogeneity within the tissues where they are deposited, leading to increased transverse relaxation and a higher r_2/r_1 ratio, thus making them excellent T_2 relaxivity contrast agents.⁴⁹ Additionally, IONPs exhibit good biocompatibility and have been approved by the Food and Drug Administration (FDA) for clinical applications as inorganic nanomaterials.⁵⁰ Ferucarbotran is a type of IONP coated with carboxymethyl dextran and is a clinically approved superparamagnetic iron oxide NPs (SPIONs) for liver-enhanced MRI (Figure 1, Table 1).⁵¹ In an orthotopic rat hepatoma model, Nagai et al. provided quantitative evidence that systemic ferucarbotran administration before RFA markedly improves the accuracy of ablative-margin assessment and predicts curative outcome.⁵² The T_2 -weighted hypointense zone in ferucarbotran-pretreated livers closely matched the histologically confirmed coagulative necrosis (14.0 ± 0.6 mm² vs. 12.1 ± 2.4 mm²) and was far more reproducible than the corresponding measurement in saline-treated controls, where the MR-defined area (17.7 ± 7.4 mm²) substantially overestimated the true necrotic area (12.4 ± 1.2 mm²); the coefficient of variation of the MR-based area measurement decreased from approximately 42% without ferucarbotran to approximately 4% with ferucarbotran. This improvement was attributed to a 6-fold increase in iron deposition within the necrotic zone of ferucarbotran-treated animals relative to controls.⁵² Regarding curative efficacy, among six hepatic tumors followed after RFA, the four tumors exhibiting a complete ferucarbotran-induced low-signal rim on day 4 remained stable at day 7, whereas both tumors lacking a complete rim progressed markedly, growing to 235% and 268% of baseline size.⁵² This concordance between a complete ferucarbotran-defined margin and subsequent local tumor control suggests that ferucarbotran-enhanced MRI can accurately distinguish curative from incomplete ablation at an early post-treatment time point. To promote the clinical application of ferucarbotran, Fukuda et al. designed a clinical trial involving 76 patients with HCC who underwent RFA treatment within 8 h after taking ferucarbotran.⁴⁶ They found that ferucarbotran could accurately determine the ablation margins and recommended an ablation margin thickness of ≥ 2 mm for RFA to ensure therapeutic efficacy.⁴⁶ Notably, compared with enhanced CT, enhanced MRI using ferucarbotran as a contrast agent provides superior guidance for clinicians in planning the treatment area prior to RFA and assessing treatment efficacy.⁵³ Tokunaga et al. performed RFA on 42 patients with HCC and three patients with metastatic liver cancer, and conducted T_2 -weighted MRI one week later and enhanced CT one month later.⁵⁴ Their findings demonstrated that compared with enhanced CT, enhanced MRI using ferucarbotran as a contrast agent allowed for an earlier and more accurate assessment of the ablation margins.⁵⁴ Therefore, under MRI guidance, the combination of ferucarbotran and RFA has the advantages of preoperative guidance for ablation range, intraoperative enhancement of ablation efficacy, and postoperative monitoring of tumor recurrence.

To further enhance the MRI imaging capability of nanomaterials and the efficiency of RFA, Ashokan et al. combined single-phase calcium phosphate biomineral nanoparticles (nCP) with Fe^{3+} doping to form nCP:Fe.⁵⁵ nCP possesses dual-mode magnetic resonance contrast (T_1 - T_2) and radiofrequency thermal responsiveness.⁵⁵ Fe^{3+} can enhance MRI T_2 contrast and enhance RFA.⁵⁵ Under MRI guidance, the injection of nCP:Fe into orthotopic

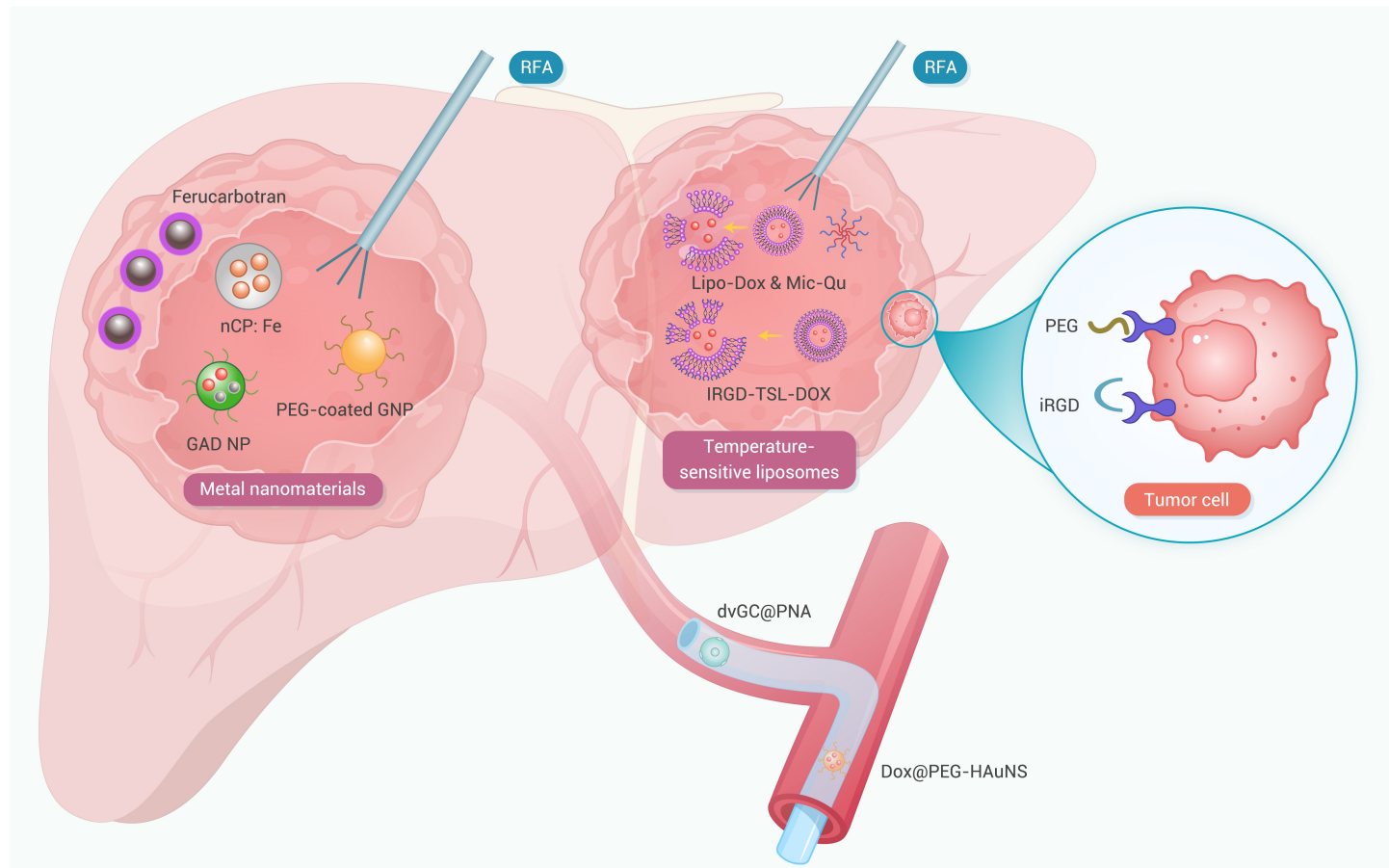


Figure 1. Enhancement of RFA in HCC using different types of nanomaterials Left panel: IONPs and GNPs enhance RFA for HCC. Right panel: TSLs enhance RFA for HCC. RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; TAE, transarterial embolization; TSLs, temperature-sensitive liposomes; PEG, polyethylene glycol; iRGD, internalizing sequence: CRGDRGPDC; Dox, Doxorubicin; HAuNS, hollow Au nanoshells; nCP: Fe, calcium phosphate biomineral nanoparticle: Fe; GNPs, Au nanoparticles; PEG-GNPs, GNPs coated with unmodified PEG molecules; dvGC@PNAs, dual-valent Au clusters coated with PNAs; Dox, Doxorubicin; HAuNS, hollow Au nanoshells; Dox@PEG-HAuNS, Doxorubicin-loaded PEG-coated hollow Au nanoshells; iRGD-TSL-DOX, Dox-loaded TSLs surface-modified with the iRGD.

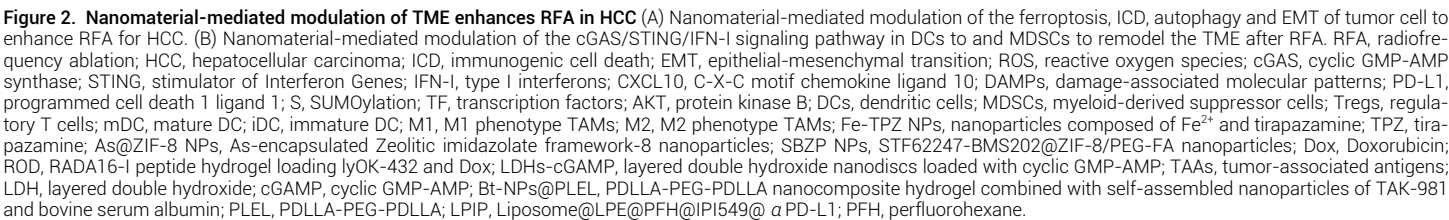
HCC in rats facilitates the quantification of its distribution within the tumor.⁵⁵ Using the clinically recommended RFA ablation standard (10 W, 13.3 GHz), the tumor region ΔT (final temperature: $81.3 \pm 1.5^\circ\text{C}$) of nCP:Fe was found to be elevated by $119 \pm 10\%$ compared to the untreated healthy liver region (final temperature: $51.3 \pm 2^\circ\text{C}$).⁵⁵ Preclinical studies have further demonstrated that iron-doped biomineral nanoparticles provide dual T_1/T_2 MRI contrast while amplifying radiofrequency-induced heating. These multifunctional properties highlight the potential of IONPs as integrated diagnostic and therapeutic enhancers in RFA for HCC.

Au-based nanoparticles enhance RFA for HCC

Alongside IONPs, Au-based nanoparticles (GNPs) rank among the most extensively studied metallic nanomaterials.⁵⁶ GNPs have been widely applied in cancer diagnosis and treatment owing to properties such as conductivity, high surface-to-volume ratio, low toxicity, surface plasmon resonance (SPR), and high permeability.⁵⁷ Notably, GNPs can be engineered into diverse shapes such as nanocages, nanoboxes, nanorods, nanowires, hollow nanospheres, and nanostars, each exhibiting distinct physicochemical properties and application potential.⁵⁸ Structurally, GNPs comprise pure Au and are frequently coated with polymers, including polyethylene glycol (PEG), or other organic compounds to form composite materials.⁵⁹ Furthermore, they can be 'doped' with metals like Ag, Se, Mo, Mn, Pt, and iron oxides, yielding hybrid materials with varied properties.⁵⁹ These coated, doped, or functionally modified GNP materials can be further conjugated with drugs or other specific molecules, significantly enhancing their cellular targeting ability and drug delivery efficiency. Critically, based on the principle of Joule heating, GNP-based materials and composites can effectively enhance the thermal effect during RFA therapy (Figure 1, Table 1).⁶⁰

Mocan et al. developed GNPs coated with unmodified PEG molecules (PEG-GNPs).⁶¹ Following direct intratumoral injection, PEG-GNPs significantly increased the ablation volume in porcine liver and sensitized RFA.⁶¹ Their application prevented tissue carbonization, indicating improved thermal conduction uniformity that may reduce heat-damage-related adverse effects.⁶¹ Further investigation revealed a non-dose-dependent relationship between ablation volume expansion and PEG-GNPs concentration, suggesting the existence of an optimal concentration threshold beyond which no additional therapeutic enhancement occurs.⁶¹ This effect originates from the high thermal conductivity of GNPs, as it enhances radiofrequency energy transmission through biological tissues, promoting more extensive coagulation necrosis and thereby reducing the risk of local recurrence. Collectively, this study provides proof-of-concept for nanotechnology-augmented conventional interventional therapies.

Building on the therapeutic potential of GNPs in HCC of RFA, a subsequent study developed dual-valent Au clusters (dvGC@PNAs).⁶² This nanostructure features an Au(0) core enveloped by an Au(I)-glutathione (GSH) complex shell, surface-functionalized with temperature-sensitive poly(N-isopropylacrylamide-co-acrylic acid) (PNA) polymer.⁶² Following transarterial administration, dvGC@PNAs exploit temperature-controlled sol-gel transition to occlude tumor vasculature, enabling efficient transarterial embolization (TAE) therapy.⁶² When combined with RFA (100 W, 5.0 min), tumor-accumulated dvGC@PNAs significantly enhanced RFA efficacy.⁶² Compared to conventional iodine-based contrast agents such as iohexol and Lipiodol, the superior X-ray attenuation of Au enables dvGC@PNAs to provide sustained CT imaging capability for up to 3 months.⁶² dvGC@PNAs enhance the therapeutic efficacy of combined TAE and RFA treatment, effectively suppressing HCC progression and metastasis while facilitating postoperative recurrence monitoring.



lating Dox.⁶³ Surface-functionalized methoxy PEG confers HCC-targeting capability, minimizing off-target tissue damage.⁶³ In comparative therapeutic assessments, the combination of TAE and RFA yielded the largest ablation volume under PET/CT guidance, showing significantly better outcomes than

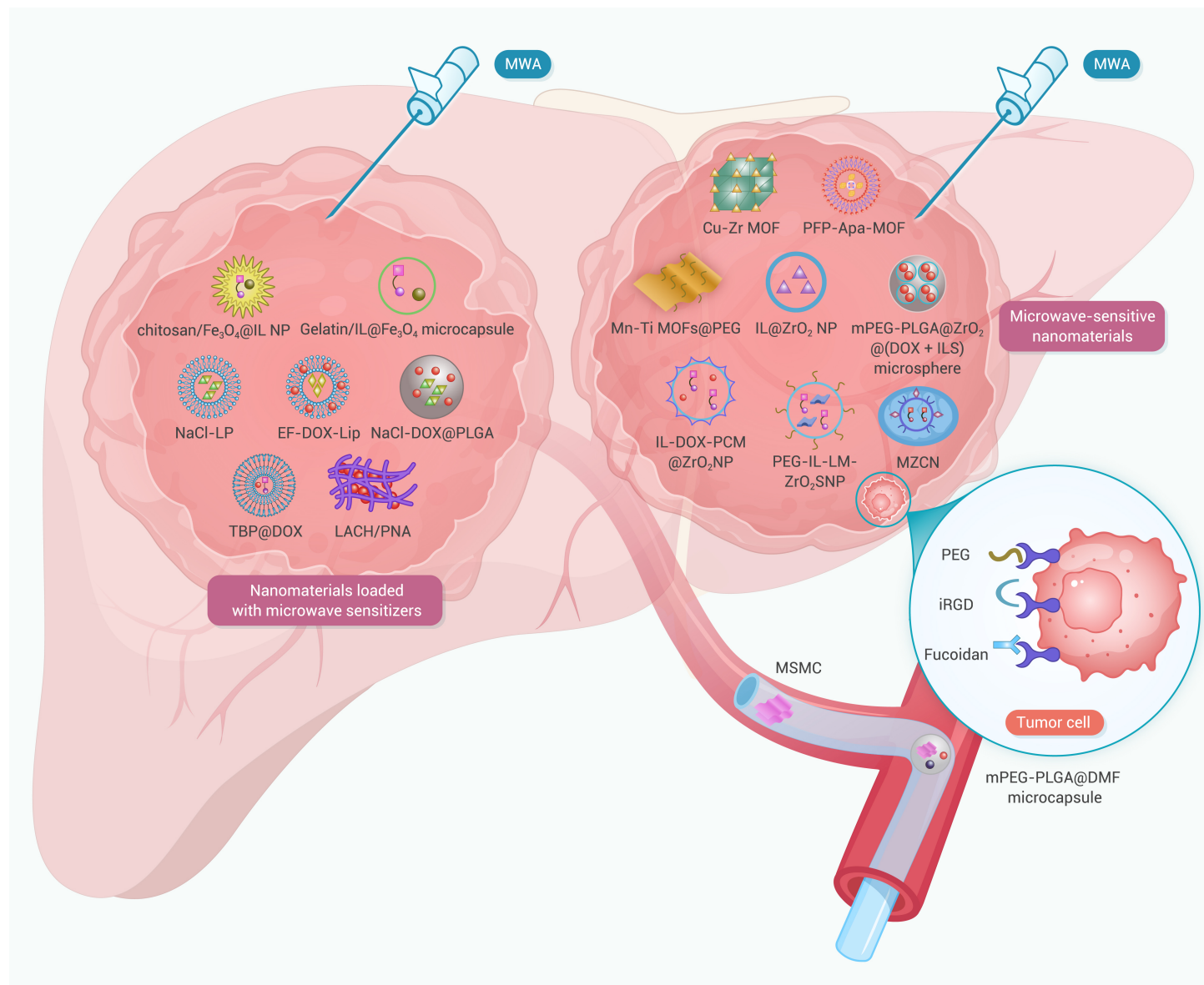


Figure 3. Enhancement of MWA in HCC using different types of nanomaterials Left panel: Nanomaterials loaded with microwave sensitizers, including IL, NaCl, and EF to enhance MWA in HCC. Right panel: Microwave-sensitive nanomaterials, including MOF, ZrO₂ NPs, and MoS₂ nanosheets, to enhance MWA in HCC. MWA, microwave ablation; HCC, hepatocellular carcinoma; IL, ionic liquid; EF, ethyl formate; MOF, metal-organic framework NPs, Nanoparticles; Chitosan/Fe₃O₄@IL NPs, co-encapsulating [Bmim][BF₄] and Fe₃O₄ NPs within a chitosan matrix; Gelatin/IL@Fe₃O₄ microcapsules, ionic liquid and Fe₃O₄ nanoparticles in gelatin microcapsules; TBP@DOX, DOX and 1-butyl-3-methylimidazolium-L-lactate into fucoidan conjugated liposomal nanoparticles; LACH/PNA, PNA, incorporating a multifunctional IL formed by α -lipoic acid and choline; NaCl-LPs, Liposomes packed with NaCl; NaCl-DOX@PLGA, NaCl and Dox loaded into hollow PLGA NPs; EF-DOX-Lips, EF and Dox encapsulated within liposomes; FCMs, Fe-doped Cu bimetallic MOFs; Cu-Zr MOF, microwave-activated Cu-doped zirconium MOF; PFP-Apa-MOF, MOF loading perfluoropentane and apatinib; Mn-Ti MOFs@PEG, Mn-doped Ti-based MOFs coated with PEG; MeOH, Methanol; IL@ZrO₂ NPs, Zirconia shells with hollow and mesoporous structures, encapsulating the [Bmim][PF₆]; mPEG-PLGA@ZrO₂@(DOX+ILS) microspheres, microspheres composed of mPEG-PLGA encapsulating hollow ZrO₂ nanoparticles co-loaded with Dox and IL; IL-DOX-PCM@ZrO₂ NPs, Ionic liquid, Dox, and phase change material-loaded ZrO₂ NPs; X@BB-ZrO₂ NPs, Ball-in-ball structured ZrO₂ nanoparticles loaded with ionic liquid, Dox, keratin, and tetradecanol; MZCNs, mitochondria-targeting ZrO₂ nanoparticles; PEG-IL-LM-ZrO₂ SNPs, PEG-modified supernanoparticles composed of ionic liquid and liquid metal loaded into mesoporous ZrO₂ nanoparticles; MSMC, MoS₂-loaded sodium alginate microcapsules; mPEG-PLGA@DMF microcapsules, mPEG-PLGA microcapsules to co-load Dox, MoS₂ nanosheets, and Fe₃O₄ nanoparticles; Mit, mitochondria; PEG, polyethylene glycol; iRGD, internalizing sequence: CRGDRGPDG.

TAE combined with either irreversible electroporation or PTT.⁶³ This suggests that combining TAE, RFA, and chemotherapy may enable a more complete tumor eradication. The synergistic mechanism involves transarterial nanomaterial delivery, reducing tumor perfusion via hepatic arteries, thereby diminishing heat-sink effects and enhancing subsequent RFA efficacy. This combinatorial approach warrants broader clinical translation. Notably, carbon nanotube (CNT) pretreatment prior to RFA achieves a more homogeneous temperature distribution by reducing central tissue hyperthermia, a distinct advantage over IONPs and GNPs.⁴⁵ Consequently, future development of CNT-integrated IONP or CNT-integrated GNPs hybrid materials may optimize precision control of ablation margins.

Temperature-sensitive liposomes enhance RFA for HCC

Liposomes are versatile nanocarriers capable of encapsulating both hydrophilic and hydrophobic drugs.⁶⁴ Dox-loaded liposomes have demonstrated promising anti-tumor efficacy in both preclinical and clinical studies.⁶⁵ The PEGylated liposomal Dox nanoparticle formulation, DOXIL[®], is FDA-approved for the treatment of Acquired Immunodeficiency Syndrome-related Kaposi's sarcoma, ovarian cancer, and multiple myeloma.⁶⁶ TSLs are designed to release the drugs when heated above 40 °C.⁶⁷ ThermoDox[®] is a lyso-TSL formulation encapsulating Dox.⁶⁸ When heated to temperatures ≥ 40 °C during RFA, ThermoDox[®] releases high concentrations of the drug at the periphery of the ablation zone.⁶⁸ ThermoDox[®] combined with RFA has progressed to Phase III clinical trials (NCT00617981, NCT02112656) for HCC

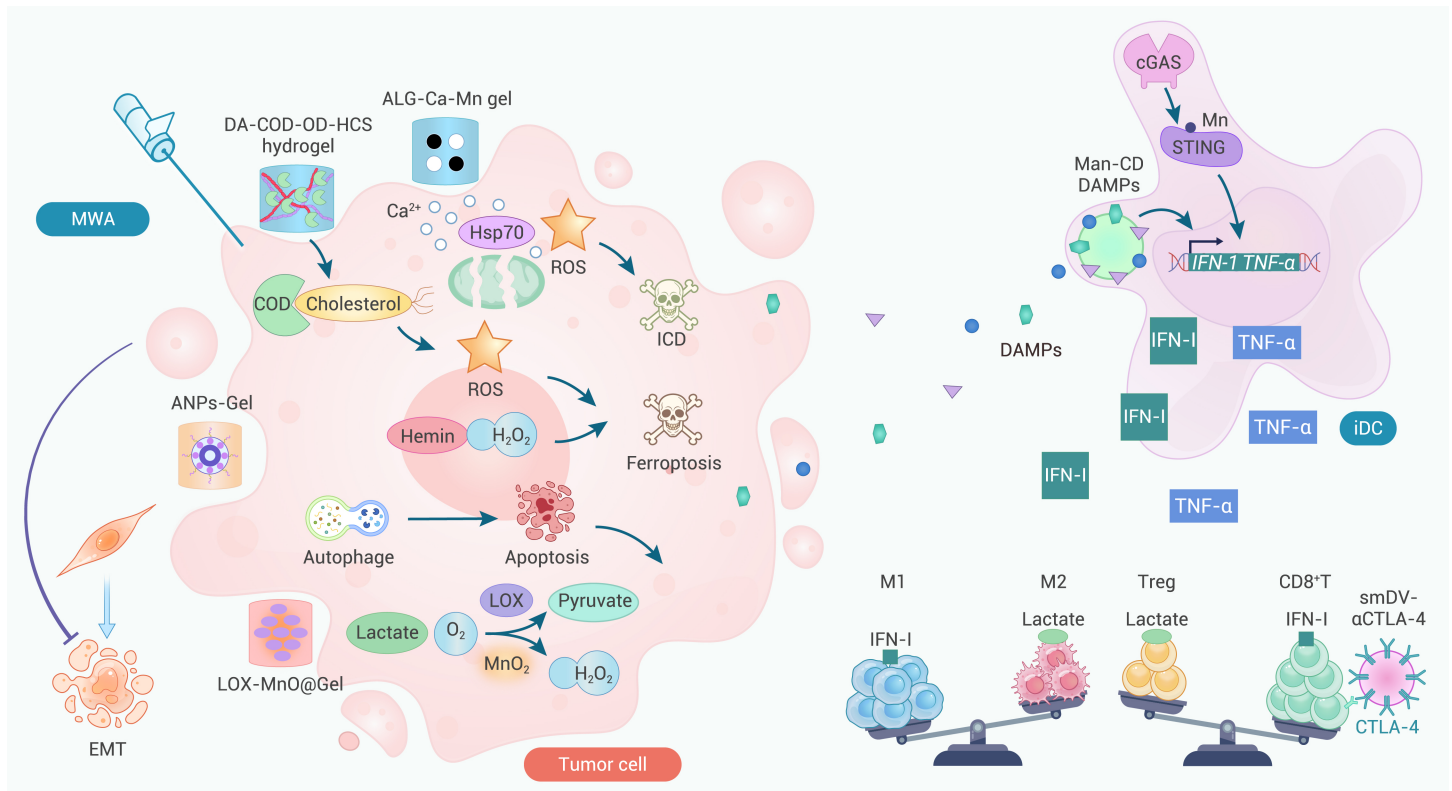


Figure 4. Nanomaterial-mediated modulation of TME enhances MWA for HCC Nanomaterial-mediated modulation of DCs, tumor cells, and lactate to remodel the TME and enhance MWA for HCC. MWA, microwave ablation; HCC, hepatocellular carcinoma; DCs, dendritic cells; TAMs, tumor associated macrophages; TME, tumor microenvironment; ICD, immunogenic cell death; EMT, epithelial-mesenchymal transition; ROS, reactive oxygen species; Hsp70, heat shock protein 70; cGAS, cyclic GMP-AMP synthase; STING, stimulator of Interferon Genes; IFN-I, type I interferons; TNF- α , tumor necrosis factor α ; DAMPs, damage-associated molecular patterns; Tregs, regulatory T cells; mDC, mature DC; iDC, immature DC; M1, M1 phenotype TAMs; M2, M2 phenotype TAMs; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; ALG-Ca-Mn gel, alginate hydrogel co-loaded with Ca^{2+} and Mn^{2+} ; Man-CDs, Mannose-derived carbon dots; DAMPs, damage-associated molecular patterns; sSiO₂NPs, solid silica nanoparticles embedded in a hydrogel composite system; ANPs-Gel, As₂O₃-NPs encapsulated within an injectable thermo-responsive hydrogel.

and demonstrating promising short-term results.^{33,68} However, long-term follow-up results were unsatisfactory, leading to study termination (OS: RFA vs. RFA and ThermoDox[®], 53.1 vs. 55.2 months).⁶⁹ Therefore, optimization of Dox-loaded TSLs is warranted to enhance the efficacy of RFA therapy for patients with HCC (Figure 1, Tables 1 & 2).

Yan et al. developed Dox-loaded TSLs surface-modified with the tumor-penetrating peptide iRGD (internalizing sequence: CRGDRGPDG), designated iRGD-TSL-DOX.⁴⁴ Upon intravenous administration into tumor-bearing mice, iRGD-TSL-DOX binds to $\alpha\text{v}\beta 3$ integrin and neuropilin-1 receptors on HCC cells.⁴⁴ The construct penetrates tumor tissue, particularly in perivascular regions and the transitional zone characterized by abundant tumor vasculature.⁴⁴ During RFA, iRGD-TSL-DOX undergoes phase transition at 42 °C, triggering rapid Dox release and consequent tumor cell death.⁴⁴ However, no significant difference in survival rate was observed between tumor-bearing mice treated with iRGD-TSL-DOX versus unmodified TSL-DOX.⁴⁴ These results indicate that the targeting advantage conferred by iRGD alone may be insufficient to significantly impact tumor growth in this specific animal model, with observed therapeutic outcomes likely driven primarily by the TSL-DOX platform.⁷⁰ Therefore, further studies are warranted to evaluate these therapeutic approaches in alternative animal models and tumor types, elucidating the relevance of targeting modifications in HCC and other malignancies.⁷⁰

Heat Shock Protein 70 (Hsp70), a molecular chaperone, facilitates the folding and remodeling of numerous cellular proteins.⁷¹ Hsp70 is overexpressed in cancers, promoting tumor progression through multifaceted mechanisms: inhibiting apoptosis and necrosis, bypassing selective cell advantage programs, interfering with senescence, promoting tumor angiogenesis, and supporting metastasis.⁷² Growing evidence indicates that RFA induces Hsp70 expression.⁷³ In HCC, upregulated Hsp70 post-RFA suppresses pyroptosis in tumor cells.⁷⁴ Moussa et al. demonstrated that the Hsp70 inhibitor micellar quercetin (Mic-Qu) combined with RFA suppresses peritumoral Hsp70 expression in rat breast cancer models.⁷⁵ To enhance RFA efficacy, they

employed Liposome Dox (Lipo-Dox[®]) co-administered with Mic-Qu, effectively inhibiting orthotopic HCC growth in animals.⁷⁶ This dual-drug regimen expanded RFA-induced coagulation zones and amplified tumor destruction through Hsp70 modulation.⁷⁶ While this combinatorial approach represents a promising multi-pathway strategy for HCC therapy, its long-term effects—including durable tumor control and OS—remain unassessed. Notably, the study utilized cumulative equivalent minutes at 43 °C as a thermal dose metric, which cannot predict hyperthermic responses in periablational normal or tumor tissues. Therefore, future research needs to further investigate the effects of different RFA parameters on tumors and normal tissues and consider developing multimodal drug regimens to target the diverse biological responses in the vicinity of RFA, thereby achieving more effective tumor treatment. In addition to enhancing the targeting of TSLs and augmenting drug adjuvants, Rossmann et al. designed a computational model to predict the drug delivery profile of TSLs.⁷⁷ This model takes into account factors such as tissue RFA, drug release from TSLs, drug transport between blood vessels and cells, and cellular uptake of the drug.⁷⁷ By simulating radiofrequency heating and ThermoDox[®] drug release, the model predicts the drug concentration distribution within tissues, which helps optimize drug delivery strategies in the treatment of HCC.⁷⁷ Future studies should focus on enhancing the efficacy of ThermoDox[®], combining adjuvant drugs, and refining drug prediction models to facilitate the clinical translation of TSL-RFA combination therapies.

Nanomaterial-mediated TME modulation to enhance RFA in HCC

TME is a complex milieu of tumor cells, stromal components, immune cells, extracellular matrix, metabolites, nutrients, and growth factors.⁷⁸ The stromal compartment primarily comprises endothelial cells and fibroblasts.⁷⁹ Immune cells mainly include T cells, natural killer (NK) cells, B cells, monocytes, macrophages, neutrophils, and dendritic cells (DCs).⁸⁰ RFA induces alterations in immune cells within the hepatic TME, thereby eliciting antitumor immune effects.⁸¹ During RFA, damaged HCC cells release TAAs and

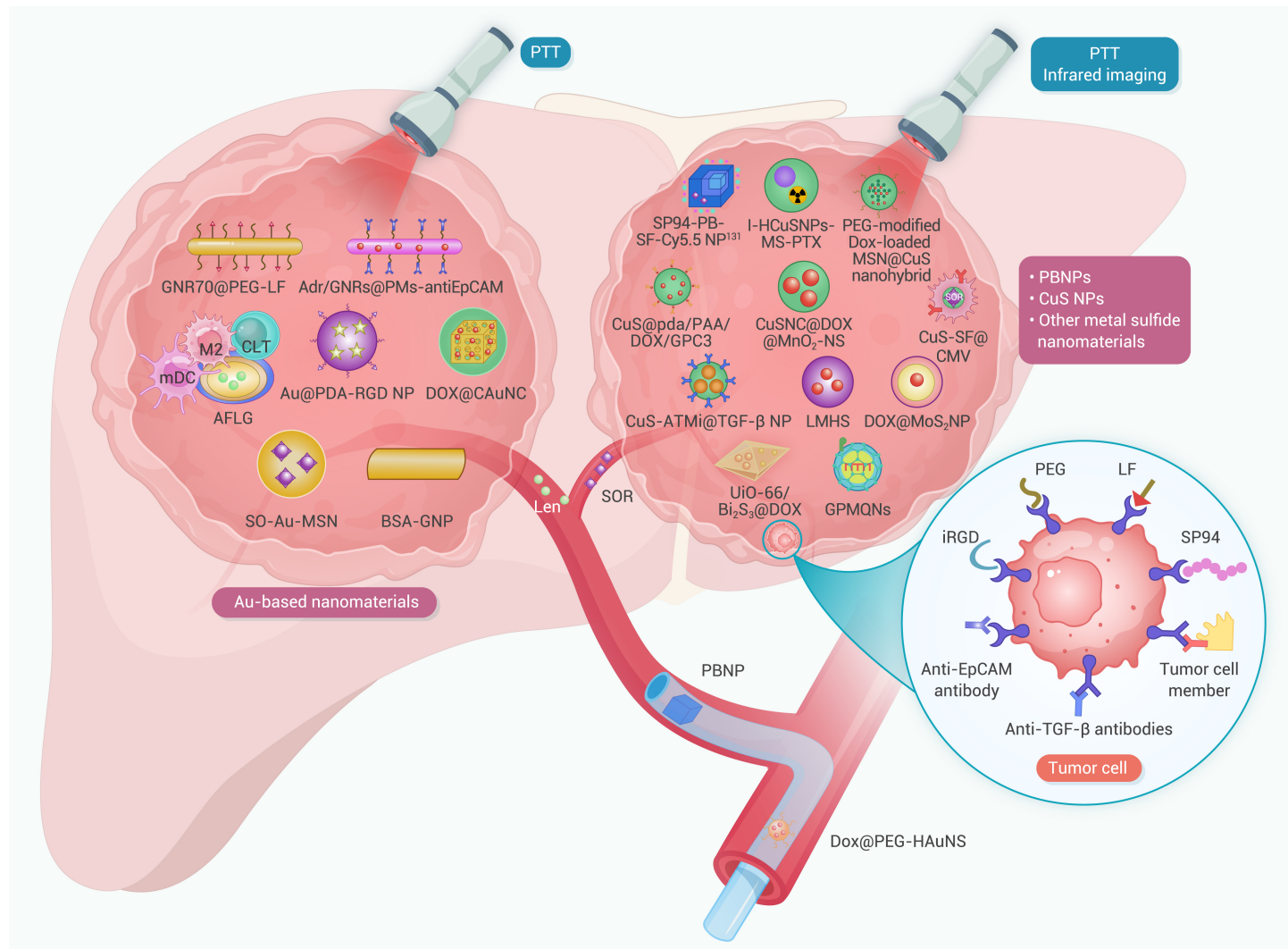


Figure 5. Metal-based nanomaterials and partial inorganic nonmetallic nanomaterials enhance PTT for HCC Left panel: Au-based nanomaterials, including Au nanorods, Au nanospheres, Au nanostars, Au nanocages, and other Au-based nanomaterials, enhance PTT in HCC. Right panel: PBNPs, CuS NPs, and other metal sulfide nanomaterials enhance PTT for HCC. HCC, hepatocellular carcinoma. PTT, photothermal ablation; GNR70@PEG-LF, GNRs surface-modified with PEG and LF; Adr/GNRs@PMS-antiEpCAM, polymeric micelles loaded with Dox and surface-modified with anti-epithelial cell adhesion molecule antibody and GNRs; AFLG, AuHNR@ γ -Fe₂O₃@Lenvatinib@ β -Glucan; Au@PDA-RGD NPs, polydopamine-coated GNSs conjugated with RGD peptides; DOX@CAuNCs, Au nanocages loaded with Dox and coated with HCC cell membranes; SO-Au-MSN, GNPs to coat mesoporous silica NPs loaded with sorafenib; BSA-GNPs, bovine serum albumin-conjugated GNPs; PBNPs, Prussian Blue NPs; SP94-PB-SF-Cy5.5 NPs, PBNPs were conjugated with Sor, SP94, and Cy5.5; 131I-HCuSNPs-MS-PTX, PLGA microspheres encapsulating hollow CuS nanoparticles and PTX, labeled with radioactive iodine-131; PEG-modified Dox-loaded MSN @CuS nanohybrids, PEG-modified Dox-loaded mesoporous silica nanoparticle@CuS nanohybrids; CuS@pda/PAA/DOX/GPC3, CuS@PDA nanocapsules loaded with Dox, PAA and anti-GPC3 antibodies; CuSNC@DOX@MnO₂-NS, hollow mesoporous CuS nanocages encapsulating Dox and further coated with MnO₂ nanoshells; CuSNC, hollow mesoporous CuS nanocages; CuS-SF@CMV, CuS nanoparticles encapsulating Sor and coated with a cancer cell-macrophage hybrid membrane, further modified with anti-VEGFR antibodies; CuS-ATMi@TGF- β NPs, ataxia telangiectasia mutated inhibitor-loaded hollow-structured CuS nanoparticles with surface modification with anti-TGF- β antibody; LMHSs, MoS₂ hollow spheres; DOX@ MoS₂ NPs, MoS₂ hollow spheres loaded with Dox; UiO-66/Bi₂S₃@DOX, compositing the MOF, UiO-66, with Bi₂S₃ and loading them with Dox; GPMQNs, graphene-P-gp loaded with miR-122-indium phosphide core and ZnS shell quantum dot nanocomposites.

damage-associated molecular patterns (DAMPs), which promote the infiltration of inflammatory cytokines and immune cells, including DCs.⁸² Subsequently, the antigenic material and DCs migrate to the draining lymph nodes (LNs), where tumor-specific CD4⁺ and CD8⁺ T cells are activated to mount an immune response and kill tumor cells.⁸³ However, there are also reports indicating that RFA may promote tumor growth. Plasma levels of interleukin (IL)-6 and IL-10 are elevated in patients after RFA.⁸⁴ IL-6 inhibits the activation of CD8⁺ T cells,⁸⁵ and suppresses mitochondrial oxidative phosphorylation, mitochondrial biogenesis, and the tricarboxylic acid cycle in tumor cells, thereby promoting the progression of HCC.⁸⁶ IL-10 primarily promotes the polarization of macrophages to the M2 phenotype, inducing an immunosuppressive microenvironment that facilitates the development of HCC.⁸⁷ Moreover, increased expression of Hsp70 and Hsp90 has been observed in patients after RFA, and these proteins also play a role in promoting the growth of HCC.⁸⁸

Incomplete radiofrequency ablation (iRFA) induces an immunosuppressive TME, suppresses antitumor immune responses, and promotes tumor recurrence and metastasis.⁸¹ iRFA promotes tumor progression, inhibits T-cell

maturation, increases the levels of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), and hinders the efficacy of anti-PD-1 therapy.^{47,89} Given the potential for RFA to induce an immunosuppressive microenvironment and promote tumor effects, combining RFA with immunotherapy has emerged as a strategy to activate the immune system, suppress recurrence caused by RFA, and improve the long-term prognosis of HCC. Against this backdrop, nanomaterials have demonstrated unique potential. Nanomaterials can induce the death of HCC cells, releasing immunogenic substances that activate immune cells and reverse the immunosuppressive TME.⁹⁰⁻⁹² Nanomaterials can also enhance the function of DCs directly to sensitize RFA and improve the immunosuppressive microenvironment. Additionally, nanomaterials can enhance RFA by inhibiting MDSCs.⁹³⁻⁹⁶ Next, we will provide a detailed introduction to these three key aspects: modulation of the tumor cells, enhancement of DCs function, and MDSCs inhibition (Figure 2, Tables 1 & S1).

Nanomaterial-mediated tumor cell modulation to enhance RFA in HCC.

Ferroptosis is an iron-dependent form of programmed cell death.⁹⁷ Iron

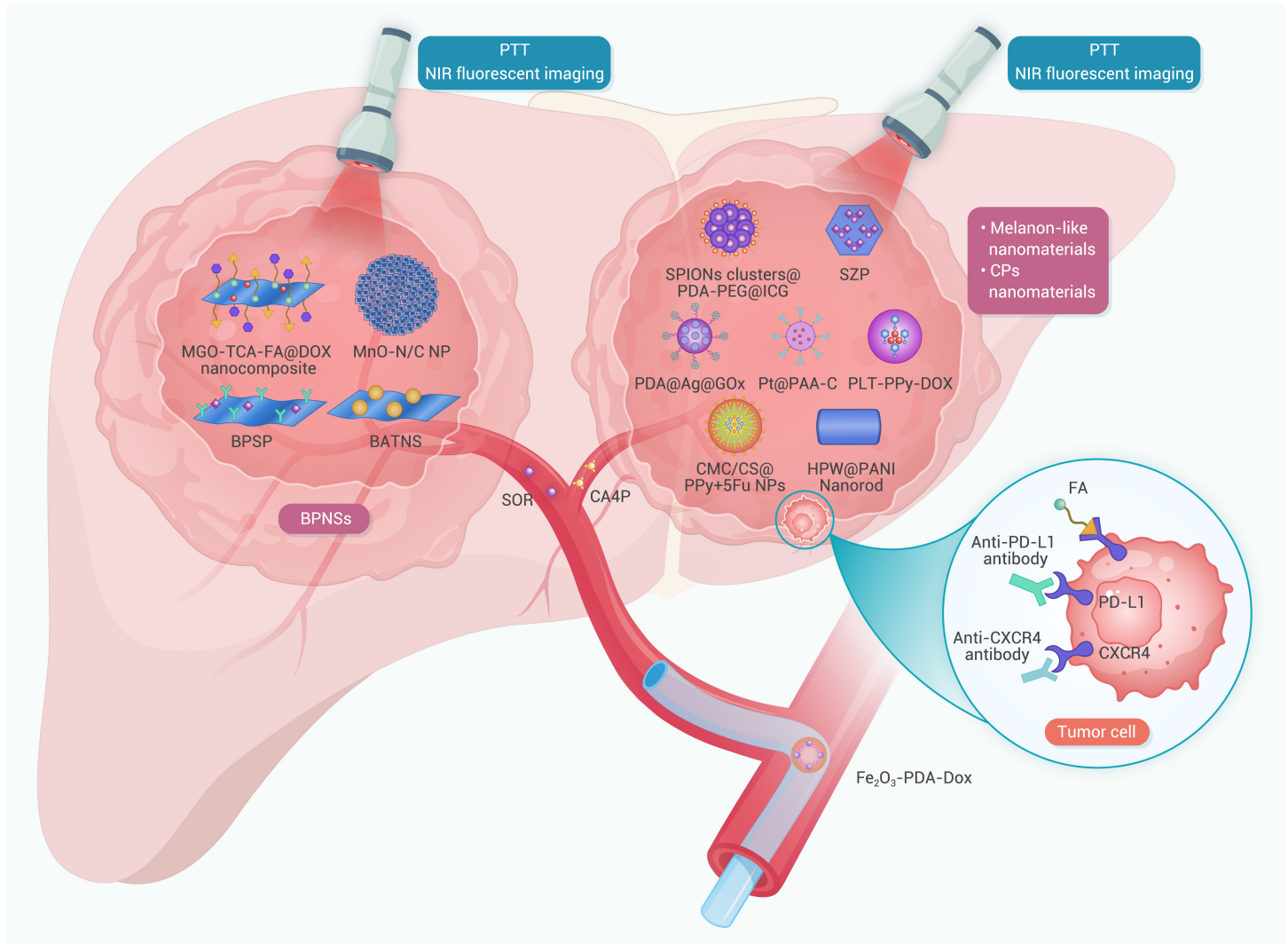


Figure 6. Other inorganic nonmetallic nanomaterials enhance PTT for HCC Left panel: BPNSs enhance PTT for HCC. Right panel: Melanin-like nanomaterials and CPs nanomaterials, including polypyrrole and polyaniline nanomaterials, enhance PTT for HCC. PTT, photothermal ablation; HCC, hepatocellular carcinoma; BPNSs, Black phosphorus nanosheets; CPs, conjugated polymers; MGO-TCA-FA@DOX nanocomposites, multifunctional hybrid material by modifying magnetic graphene oxide with trimethyl cholic acid and folic acid, and loading Dox; MnO-N/C NPs, MnO/nitrogen-doped carbon composite nanoparticles; BPSP, black phosphorus nanosheets loaded with Sor and anti-PD-L1 antibodies to form photothermal-boosted NanoBike; CA4P, combretastatin A-4 phosphate disodium; SZP, SOR@ZIF-8@PDA; PDA@Ag@GOx, PDA as the core for the in situ synthesis of AgNPs on its surface, followed by the loading of GOx; Pt@PDA-c, platinum-doped PDA nanomaterial; PLT-PPy-DOX, polypyrrole nanoparticles and Dox encapsulated within a platelet membrane; CMC/CS@PPy+5Fu NPs, carboxymethyl cellulose to encapsulate chitosan NPs loaded with PPy and 5-fluorouracil; HPW@PANI Nanorods, oxidatively polymerizing aniline with phosphotungstic acid as an acid catalyst and ammonium persulfate to synthesize PANI nanorods.

significantly accelerates lipid peroxidation of saturated fatty acids within the human body.⁹⁸ During mitochondrial oxidative phosphorylation, a process involving iron, cells generate reactive oxygen species (ROS) while simultaneously producing adenosine triphosphate (ATP).⁹⁹ ROS levels exceeding the cell's antioxidant capacity trigger an oxidative stress response, which directly or indirectly damages macromolecules such as proteins, nucleic acids, and lipids, leading to cellular injury or death.¹⁰⁰ Modulating ferroptosis in HCC cells is an emerging therapeutic strategy.¹⁰¹ The Fenton reaction refers to the reaction where iron or other metal ions decompose hydrogen peroxide to generate OH^- and other ROS.¹⁰² Excess iron induces ferroptosis in tumor cells by generating ROS via the Fenton reaction.¹⁰³

Zhu et al. engineered a composite NPs of Fe^{2+} and tirapazamine (TPZ), designated Fe-TPZ NPs.⁹⁰ TPZ is a hypoxia-activated prodrug whose cytotoxicity under hypoxic TME is 200-fold higher than that under normoxic conditions.¹⁰⁴ Leveraging the EPR, Fe-TPZ NPs rapidly accumulate within tumors.⁹⁰ Intracellular Fe^{2+} amplifies ROS via Fenton chemistry, disrupting cellular redox homeostasis and triggering ferroptosis (Figure 2, Table 1).⁹⁰ Moreover, residual tumors following iRFA exhibit intensified hypoxia, which potentiates TPZ activation, generating cytotoxic free radicals that induce DNA strand breaks and immunogenic cell death (ICD) in HCC cells.⁹⁰ This hypoxic transitional niche is also the site where sub-lethal thermal stress upregulates

the m6A methyltransferase METTL3 and stabilizes m6A-modified HIF-1 α and other survival-associated transcripts, producing a thermo-tolerant, anti-apoptotic phenotype that conventional RFA fails to eradicate.¹⁰⁵ Fe-TPZ NPs therefore target precisely the transcriptionally reprogrammed residual population that drives local recurrence.¹⁰⁵ DAMPs released during ICD repolarize tumor-associated macrophages (TAMs), activate cytotoxic T lymphocytes (CTLs), and suppress Tregs, thereby eliciting robust antitumor immunity.⁹⁰ Consequently, Fe-TPZ NPs function as potent adjuvants that enhance immune responses and oncotherapy, markedly reducing hepatic and pulmonary metastases.⁹⁰

In addition to inducing ferroptosis in hepatocellular carcinoma cells, enhancing tumor cell autophagy via nanomaterials is also a strategy for modulating the TME. Autophagy is an intracellular catabolic process that is up-regulated when cells are subjected to stress, enabling tumor cells to adapt to nutrient deprivation and hypoxia.¹⁰⁶ Under specific circumstances, however, autophagy can culminate in tumor cell death.¹⁰⁷ During autophagy-associated cell death, DAMPs—including ATP, Hsp90, and calreticulin (CRT)—are released.¹⁰⁸ Extracellular ATP plays a pivotal role in immune cell activation,¹⁰⁹ while Hsp90 and CRT bind to the CD91 receptor on DCs, initiating immune responses.¹⁰⁹ Thus, pharmacological induction of autophagy in HCC is an effective strategy that simultaneously triggers cancer cell death and

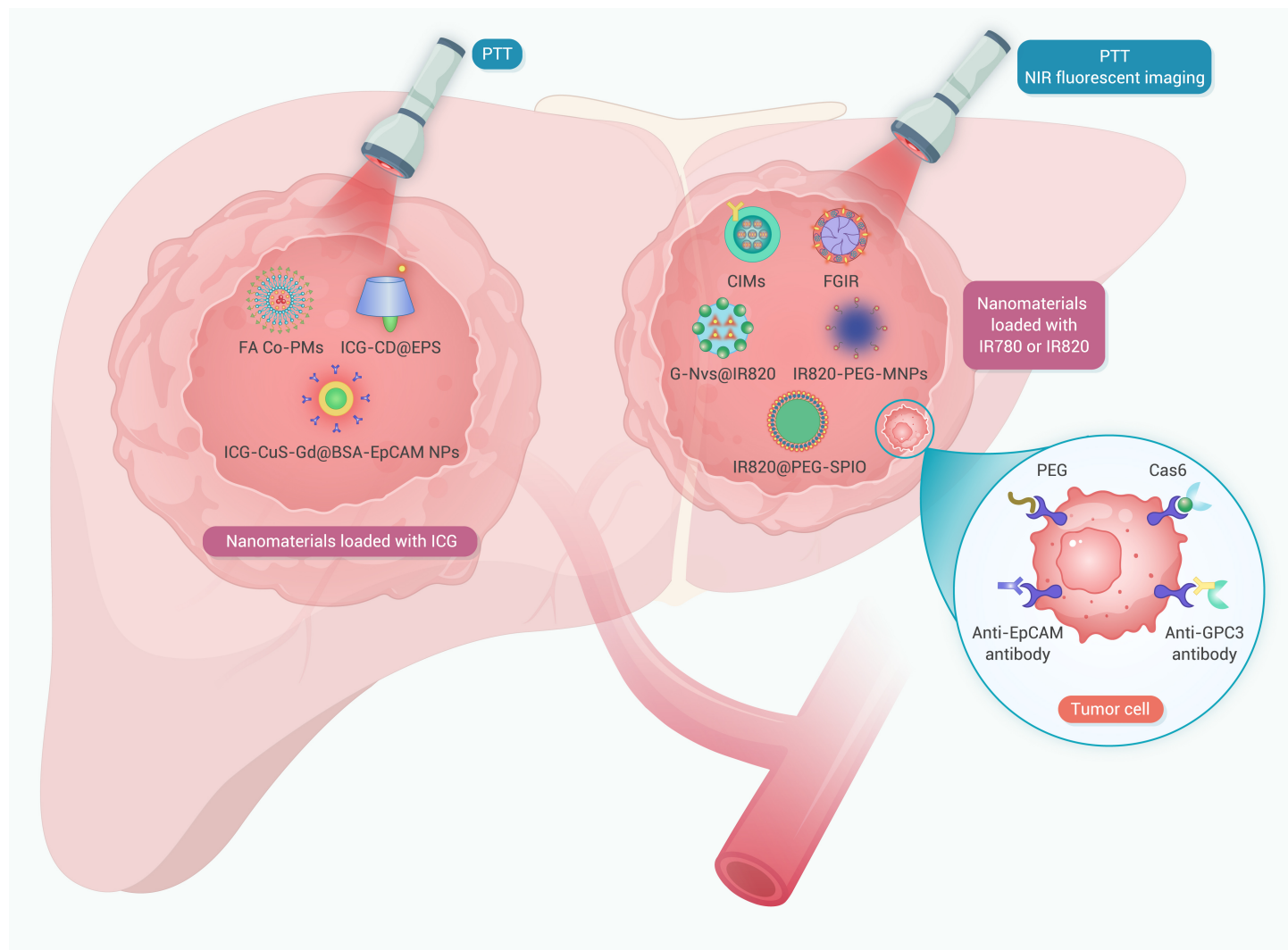


Figure 7. Nanomaterials loaded with small molecular dyes enhance PTT for HCC Nanomaterials loaded with ICG, IR780 and IR820, enhance PTT for HCC. HCC, hepatocellular carcinoma; PTT, photothermal ablation; ICG, Indocyanine green; FA Co-PMs, FA-modified polymeric micelles co-loaded with Dox and ICG; ICG-CuS-Gd@BSA-EpCAM NPs, CuS-Gd@BSA cores modified with anti-EpCAM and ICG; ICG-CD@EPS, conjugated ICG-COOH with supramolecular β -CD and co-loaded them with the chemotherapeutic drug etoposide; CIMs, mesoporous silica NPs loaded with IR780 and coated with CAR-T cell membranes; FGIR, Fe_3O_4 NPs loaded with GOx and modified with red blood cell membranes and IR780; G-Nvs@IR820, growth arrest-specific protein 6-expressing cell membrane nanovesicles encapsulating IR820; IR820@PEG-SPIO NPs, SPIO cores modified with IR820.

potentiates immune responses. Zeolitic imidazolate framework-8 (ZIF-8), a prototypical metal-organic frameworks (MOFs), exhibits ultra-high porosity, a tailorable architecture, favorable biocompatibility, and pH-triggered biodegradability.¹¹⁰ These attributes enable ZIF-8 to shield encapsulated therapeutics from premature degradation in circulation while permitting controlled drug release within the mildly acidic TME, thereby achieving high tumor-specific accumulation and cytotoxicity.¹¹¹ Consequently, ZIF-8 serves as an ideal platform for oncological applications (Figure 2, Table 1).¹¹¹ Capitalizing on this, Zhang et al. designed ZIF-8 NPs loaded with the autophagy-inducing small-molecule compound STF62247 and the PD-L1 small-molecule inhibitor BMS202, designated as STF62247-BMS202@ZIF-8/PEG-FA (SBZP) NPs.⁹¹ SBZP NPs suppressed the proliferation and induced apoptosis of residual HCC cells exposed to sublethal thermal stress in an autophagy-dependent manner.⁹¹ Further, SBZP NPs amplified autophagy in residual HCC cells and triggered ICD, thereby significantly promoting DCs maturation.⁹¹ The combination of RFA and SBZP NPs treatment effectively inhibited HCC growth and established long-term immune memory.⁹¹ Additionally, SBZP NPs markedly enhanced ICD in residual tumor cells, activated antitumor immunity, and substantially suppressed the growth of residual HCC.⁹¹ Moreover, Chen et al. incorporated As agents into ZIF-8 to fabricate As-encapsulated ZIF-8 NPs (As@ZIF-8 NPs).⁹² Following iRFA in murine HCC, intratumoral administration of As@ZIF-8 NPs led to selective accumulation within residual tumors, pH-dependent disintegration, and liberation of As^{3+} , resulting in significant inhibition of residual tumor growth, metastasis, and

epithelial-mesenchymal transition.⁹² Despite these advantages, ZIF-8 is limited by poor physiological dispersibility and an inherent lack of tumor-targeting capability, which markedly restricts its *in vivo* application.¹¹¹ To overcome these limitations, surface functionalization strategies have been developed, markedly enhancing intratumoral accumulation and improving therapeutic efficacy.¹¹¹

Tumor cells enhance their own proliferation by suppressing apoptosis.¹¹² Consequently, inducing non-apoptotic regulated cell death (nARCD) has emerged as a novel strategy for HCC immunotherapy.¹¹³ Currently, nARCD pathways—including ferroptosis, pyroptosis, cuproptosis, and necroptosis—are newly recognized forms of ICD that synergize with antitumor immunity, converting immune-“cold” tumors into immune-“hot” ones and exerting potent antitumor effects.¹¹³ Therefore, future studies should focus on developing additional nanomaterials that specifically target HCC cells to trigger diverse modes of nARCD, thereby inhibiting tumor recurrence after ablation therapy and suppressing the growth of residual lesions.

Nanomaterial-mediated DC modulation to enhance RFA in HCC. The cyclic GMP-AMP synthase (cGAS)-stimulator of Interferon Genes (STING) pathway is an innate immune signaling cascade activated by pathogen- or tumor-derived double-stranded DNA (dsDNA).¹¹⁴ This pathway participates in both the initiation and progression of HCC. DNA damage within HCC cells generates cytosolic dsDNA, which triggers and activates the cGAS-STING signaling axis, leading to the release of type I interferons (IFN-I) that are indispensable for DCs maturation.¹¹⁵ Subsequently, IFN-I-licensed DCs

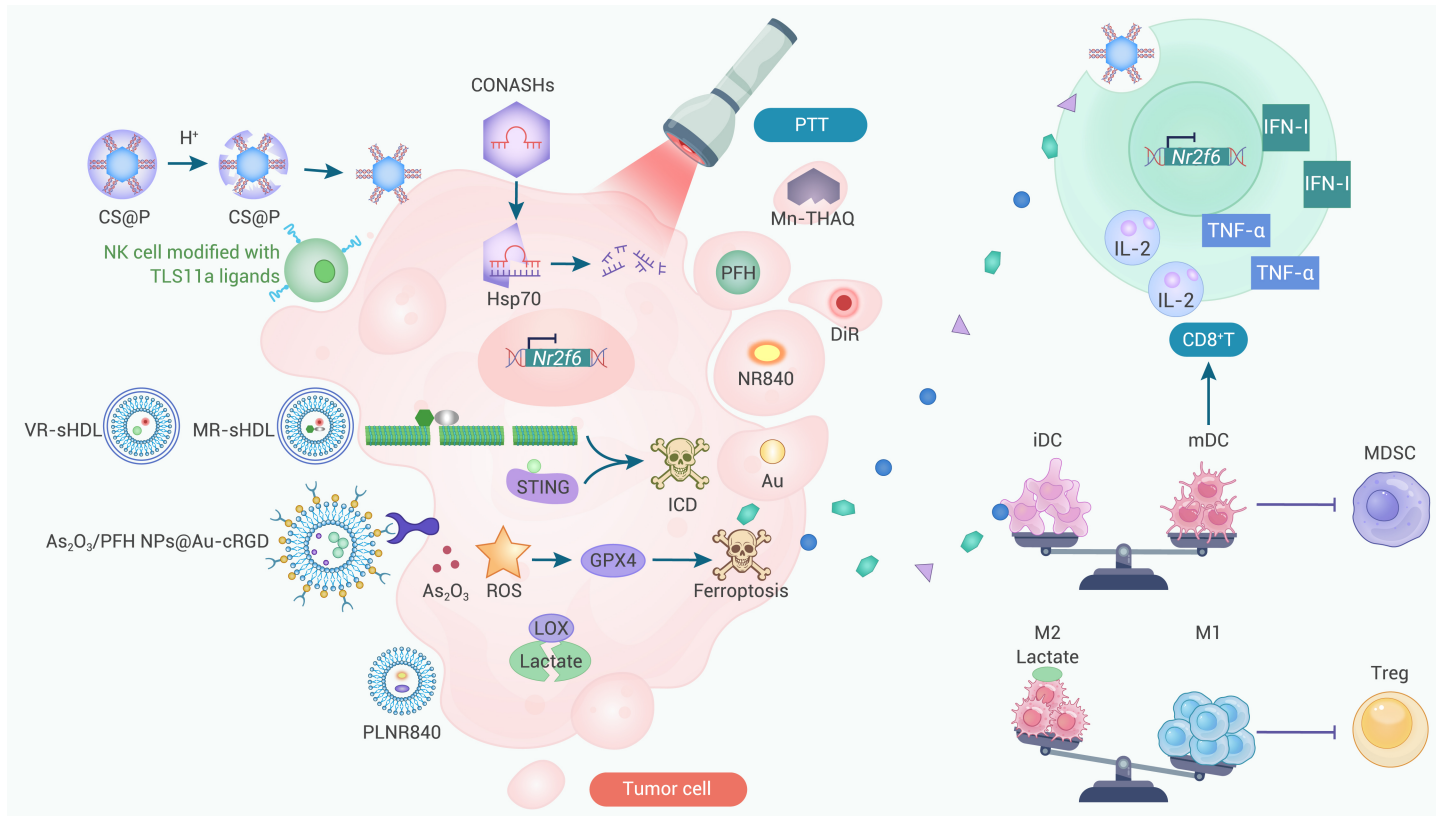


Figure 8. Nanomaterial-mediated TME modulation enhances PTT in HCC Nanomaterial-based strategies were employed to enhance PTT for HCC through multimodal immunomodulation. Specifically, the nanomaterials potentiated T-cell activity and augmented the tumor-killing capacity of NK cells. Furthermore, they modulated the secretome of tumor cells to regulate DCs and TAMs, thereby remodeling the immunosuppressive tumor microenvironment. Additionally, these nanomaterials exhibited improved photothermal conversion efficiency, enabling more effective PTT. PTT, photothermal ablation; HCC, hepatocellular carcinoma; NK cells, natural killer cells; DCs, dendritic cells; TAMs, tumor-associated macrophages; CS@P, CoCuFe-LDHs loaded with Nr2f6-siRNA and coated with PEG-dimethyl maleic anhydride; DNAzyme@Mn-CONASHs, Mn-based self-assembled nanosheets incorporating Mn²⁺ and tetrahydroxyanthraquinone and adsorbed PEI and DNA enzymes targeting Hsp70 mRNA; MR-sHDL, liposomes were loaded with microtubule stabilizer mertansine; VR-sHDL, liposomes were loaded with STING agonist vadimezan-Chol; As₂O₃/PFH NPs@Au-cRGD, liposomes loaded with As₂O₃ and PFH, modified with HAuCl₄ and cRGD-SH on the surface.

migrate to tumor-draining LNs, where they cross-prime tumor-specific CD8⁺ T cells, thereby inducing systemic antitumor immunity capable of controlling both local tumor growth and distant metastasis.¹¹⁵ Furthermore, cytosolic chromatin fragments in HCC cells can stimulate cGAS-STING activation, resulting in the induction of autophagy and apoptosis.¹¹⁶ Notably, combining RFA with the immunotherapeutic agent OK-432 enhances therapeutic efficacy in murine HCC models by exploiting the cGAS-STING pathway in DCs, resulting in improved tumor responses and prolonged survival.¹¹⁷ RFA also up-regulates Toll-like receptor 4 (TLR4) expression in HCC cells, and TLR4 may function as an upstream modulator of the cGAS-STING pathway, further potentiating OK-432-mediated activation (Figure 2, Table 1).¹¹⁷

OK-432 is a lyophilized preparation of a penicillin-killed, low-virulence *Streptococcus pyogenes* strain approved by the Japanese government for immunotherapy of HCC and other malignancies.¹¹⁸ As an immunostimulatory agent, OK-432 promotes DCs maturation and expands the conventional DC1 (cDC1) subset; these mature DCs efficiently prime antitumor CD8⁺ T-cell responses.¹¹⁹ When combined with anti-PD-1 antibodies, OK-432 markedly enhances CD8⁺ T-cell functionality and, by blocking the PD-1/PD-L1 axis, alleviates tumor-mediated T-cell suppression, producing synergistic antitumor effects against residual lesions after incomplete RFA of HCC.¹¹⁹ Moreover, patients with HCC treated with OK-432-stimulated DCs exhibit prolonged recurrence-free survival.¹²⁰

To further augment OK-432 efficacy, Cao et al. incorporated RADA16-I peptide hydrogel loading lyOK-432 and Dox to fabricate the ROD.⁹³ Following iRFA, ROD released lyOK-432 and Dox in situ.⁹³ LyOK-432 recruits and matures DCs within orthotopic murine HCC, activates the cGAS-STING/IFN-I signaling cascade, and potentiates antitumor immunity.⁹³ Dox simultaneously suppresses MDSCs and Tregs while directly killing tumor cells, further restraining residual tumor growth after iRFA.⁹³ Additionally, direct delivery of the STING agonist cGAMP has been employed to amplify immune responses

in both HCC cells and DCs during RFA.⁹⁴ Tian et al. engineered layered double hydroxide (LDH) nanodiscs loaded with cGAMP (LDHs-cGAMP) that can capture TAAs.⁹⁴ RFA-induced tumor cell death releases immunogenic material, which is adsorbed by LDHs-cGAMP.⁹⁴ The resulting LDHs-cGAMP-TAA complexes are then internalized by tumor cells and DCs, triggering the cGAS-STING pathway and producing IFN-I and C-X-C motif chemokine ligand 10(CXCL10) to eradicate malignant cells.⁹⁴ Concurrently, the nanovaccine stimulates DCs, promotes immune activation, and enhances cytotoxic T-lymphocyte infiltration into tumor tissues.⁹⁴

Nanomaterials can promote IFN-I release by HCC cells, facilitating the maturation of DCs and thereby inhibiting the growth of residual HCC after iRFA. Liu et al. utilized PDLLA-PEG-PDLLA nanocomposite hydrogel combined with self-assembled NPs of TAK-981 and bovine serum albumin (BSA) to form Bt-NPs@PLEL.⁹⁵ Sub-lethal heating in the transition zone elicits a SUMO stress response, where SUMO2/3 conjugation stabilizes HIF-1α and STAT3, thereby suppressing type I IFN induction.⁹⁵ SUMOylation upregulation in residual tumors after iRFA impairs IFN-1 production and DC-mediated antigen presentation.¹²¹ Targeting SUMOylation with TAK-981, a first-in-class SUMO E1 inhibitor, derepresses the type I IFN axis, restores MHC-I expression, and reprograms the post-ablation niche into an immunogenic state, thus promoting DC maturation and antitumor immunity.^{122,123} Bt-NPs@PLEL enables the localized and sustained release of the small molecule SUMOylation inhibitor TAK-981, acting directly on residual tumors post-iRFA.⁹⁵ This hydrogel activates the IFN-I signaling pathway by inhibiting SUMO₂-mediated SUMOylation, promoting DCs maturation, and enhancing antigen-presenting capacity.⁹⁵ The application of Bt-NPs@PLEL increased the infiltration and activation of CTLs, thereby augmenting the immune response against residual tumors.⁹⁵ Upregulation of PD-L1 expression was observed in the residual tumors.⁹⁵ Consequently, combining Bt-NPs@PLEL with anti-PD-L1 therapy demonstrated a synergistic effect, effectively eradicating residual tumors and

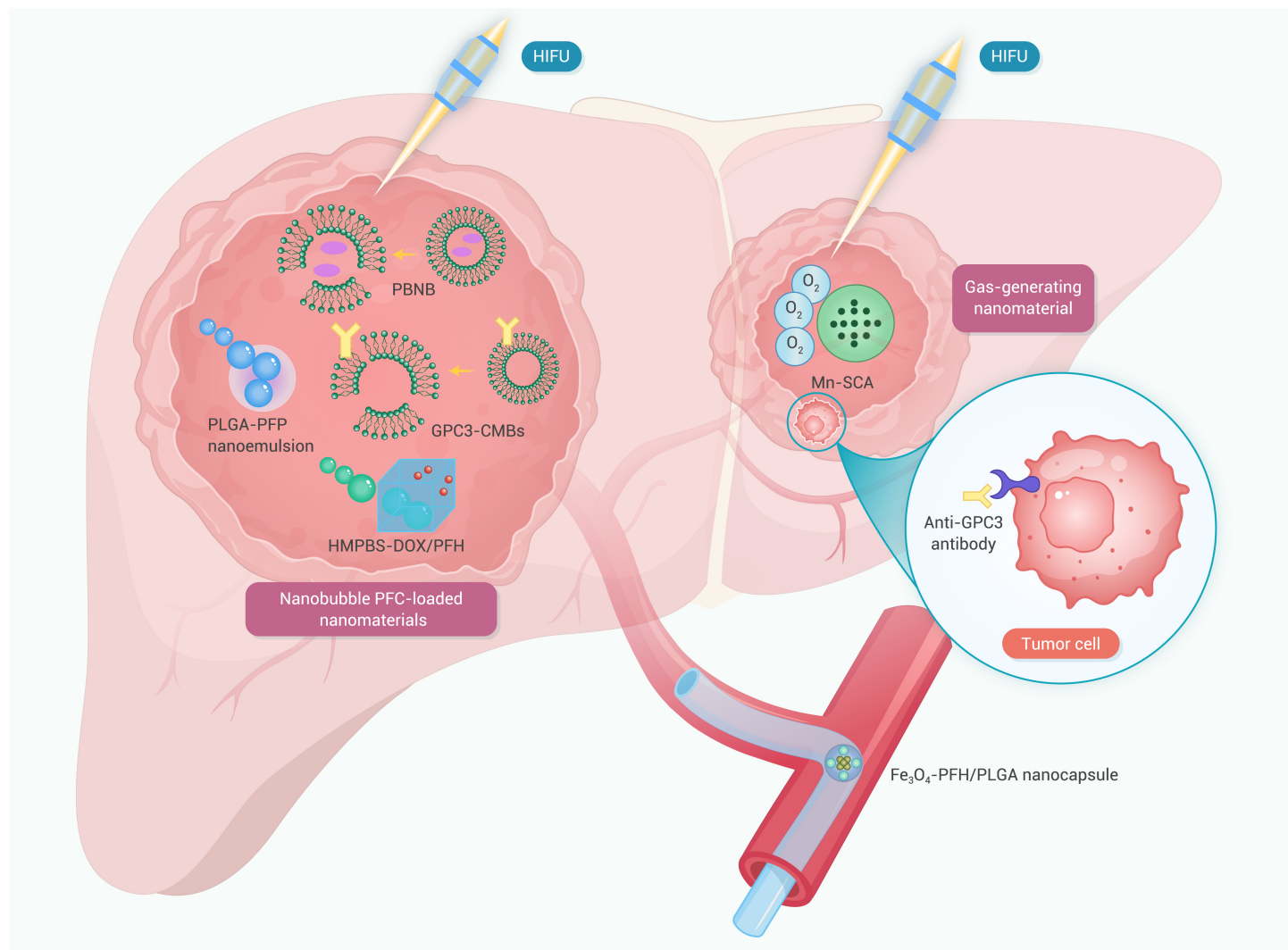


Figure 9. Nanomaterials enhance HIFU for HCC Left panel: Nanobubbles and PFC-loaded nanomaterials enhance HIFU for HCC. Right panel: Mn-SCA generate O_2 to enhance HIFU for HCC. HIFU, high-intensity focused ultrasound; HCC, hepatocellular carcinoma; ROS, reactive oxygen species; PBNBs, pro-bexarotene nanobubbles; GPC3-CMBs, cationic microbubbles conjugated with anti-GPC3 antibodies and the anticancer plasmid HSV-TK; Mn-SCA, Mn-coordinated polyphthalocyanine sonocavitation agent; PLGA-PFP nanoemulsions, PLGA to encapsulate PFP nanoemulsions; HMPBs-DOX/PFH, hollow mesoporous prussian blue nanoparticles loaded with Dox and PFH; Fe_3O_4 -PFH/PLGA nanocapsules, FH core loaded with Fe_3O_4 nanoparticles and encapsulated within a PLGA nanocapsules shell.

suppressing the growth of distant tumors.⁹⁵ Notably, the aforementioned studies primarily focus on conventional type 1 DCs, which are crucial for cross-presentation and CD8-positive T cell activation. However, the DC lineage actually encompasses several subsets: cDCs, including cDC1 and cDC2, plasmacytoid DCs (pDCs), and mature DCs enriched in immunoregulatory molecules.¹²⁴ Among these, cDC1s play a pivotal role in anti-tumor immunity by cross-presenting tumor antigens to cytotoxic CD8⁺ T cells.¹²⁵ While cDC2s promote CD4⁺ T cell responses and contribute to tumor immunogenicity, tumors can employ specific mechanisms to limit their anti-tumor activity.¹²⁴ pDCs within the TME exhibit impaired IFN-I production, potentially leading to immunosuppressive responses, and their infiltration is often associated with poorer prognosis.¹²⁶ Mature DCs, which may derive from cDC1s and cDC2s, express markers of maturation, migration, and tumor control such as CD40, CD83, CD86, CCR7, and interleukin 12 alongside markers of tolerance and immunosuppression including PD-1, PD-2, and CD200.¹²⁶ Furthermore, within the TME, LAMP3⁺ DCs exert immunosuppressive regulatory functions on various T cell subsets via the PD-L1/PD-1 axis, further contributing to dysfunctional immunity.¹²⁷ Therefore, future studies should explore the roles of the other DC phenotypes in the post-RFA immune microenvironment and design nanomaterials targeting them.

Nanomaterial-mediated MDSCs modulation to enhance RFA in HCC.

MDSCs are a heterogeneous group of immune cells originating from the bone marrow that exhibit immunosuppressive functions in various diseases,

including cancer.¹²⁸ Within the TME, MDSCs promote tumor immune escape by releasing immunosuppressive cytokines such as IL-10 and transforming growth factor-beta (TGF- β).¹²⁹ Tang et al. observed increased MDSCs infiltration within the tumor immune microenvironment (TIME) of patients following RFA, which positively correlated with the risk of post-operative HCC recurrence.⁴⁷ Animal studies demonstrated that post-irFA, MDSCs promote anti-inflammatory effects and recruit M2 phenotype TAMs by expressing high levels of PI3Ky.⁴⁷ This process regulates the critical switch between immunosuppression and immune stimulation, further facilitating tumor immune escape (Figure 2, Table 1). Consequently, Tang et al. developed a nanomaterial system with a perfluorohexane (PFH) core encapsulating the small-molecule PI3Ky-selective inhibitor IPI549 and the anti-PD-L1 antibodies, Liposome @LPE@PFH@IPI549@ α PD-L1 (LPIP).⁴⁷ Under the acidic TME and RFA conditions, LPIP expanded and released IPI549 and anti-PD-L1 antibodies.⁴⁷ This selectively inhibits MDSCs and blocks PD-L1, thereby promoting the repolarization of M2 phenotype TAMs to the M1 phenotype, activating CD8⁺ T cells, and suppressing Tregs.⁴⁷ The combined strategy of LPIP and irFA effectively eliminated residual tumor in the ablation zone by activating an immune response in the primary tumor while simultaneously inhibiting compensatory immune evasion by surviving MDSCs.⁴⁷ This approach prevented recurrence of residual tumor in incomplete ablation models after irFA. However, MDSCs levels in patients with HCC typically decrease significantly after RFA treatment. Persistently high post-treatment MDSCs levels,

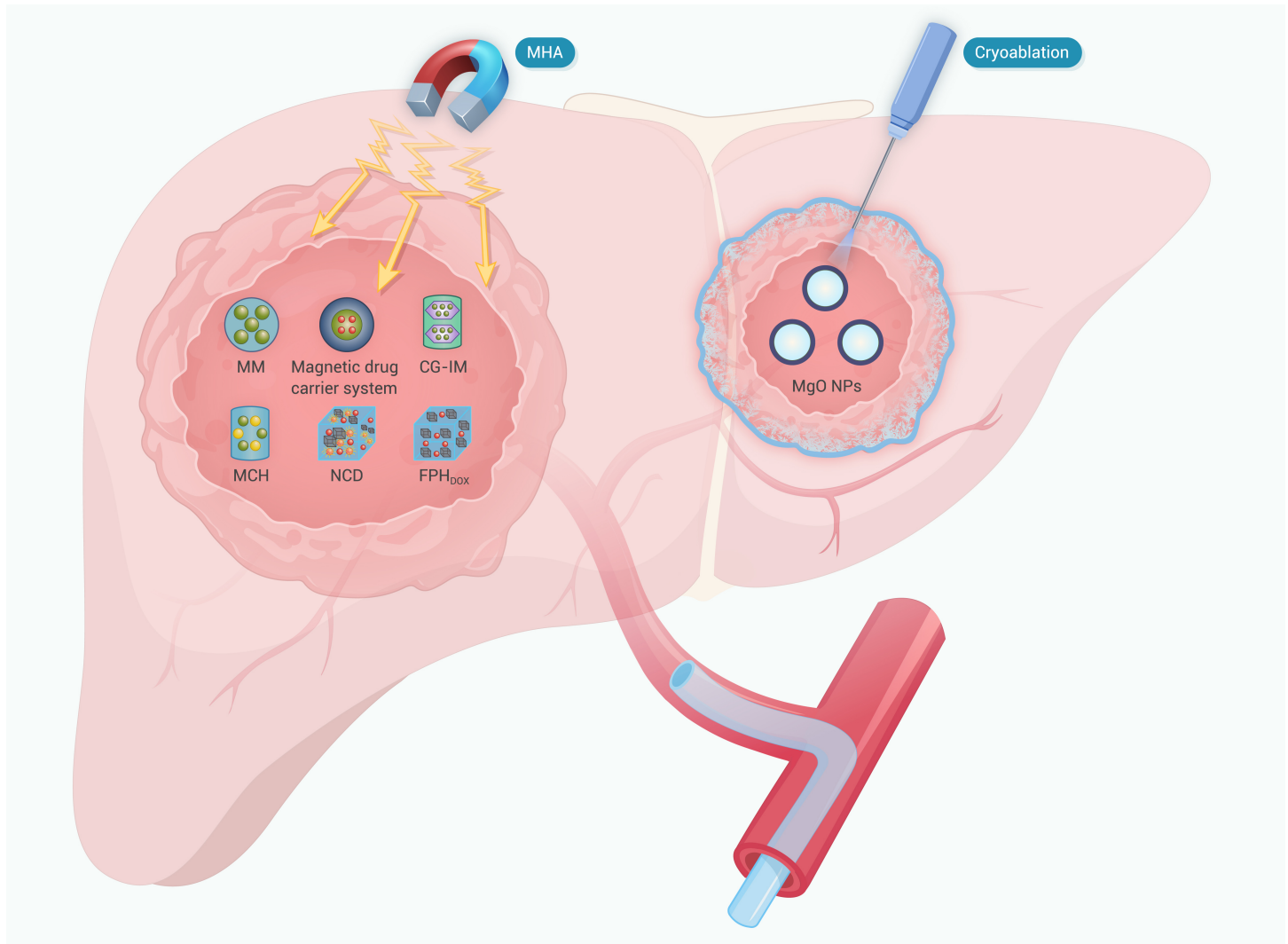


Figure 10. Nanomaterials enhance MHA and cryoablation for HCC Left panel: IONPs and hydrogels enhance MHA for HCC. Right panel: MgO NPs enhance cryoablation for HCC. MHA, hyperthermia ablation; HCC, hepatocellular carcinoma; IONPs, Iron oxide nanoparticles; PLNR840, DSPE-PEG-cRGD loaded with LOX and NR840; PLGA-magnetic microspheres; CCINs, carbon-coated iron nanocrystals; CG-IM, iron oxide nanoparticles@Mica linked with chitosan-gallic acid; MCH, magnetic colloidal hydrogels; MCH, injectable magnetic colloidal hydrogels; MgO NPs, MgO nanoparticles; NCD, NOP-CION-DOX hydrogel; FPHDOX, Dox loaded ferrimagnetic PVA Hydrogel.

however, may predict poorer recurrence-free survival.¹³⁰ Furthermore, the thermal stress conditions created by RFA promote the translation of TGF- β in MDSCs, leading to increased MDSCs accumulation and a reduction in CD8⁺ T cell numbers.¹³¹ The frequency of T cells in RFA-treated patients is inversely correlated with MDSCs levels.¹³² Therefore, future research should focus on developing nanomaterials that target MDSCs post-iRFA to modulate CD8⁺ T cell responses.

Together, Metal-based nanomaterials, including iron oxide, Au, Ag, and Sn NPs, improve the thermal efficiency of RFA and facilitate imaging, drug delivery, and combination therapies. TSLs can release chemotherapeutic agents in response to RFA-induced heating, thereby increasing local drug concentrations and therapeutic efficacy. Nanomaterials can also induce ICD mechanisms, such as ferroptosis and autophagy, modulate the TIME, and activate DCs and T cells to boost antitumor immune responses. Moreover, the combination of nanomaterials and immunotherapy can inhibit immunosuppressive cells, such as MDSCs, and reduce the risk of recurrence. Overall, nanomaterials offer new strategies to improve the efficiency, precision, and personalization of RFA for HCC, although further research and optimization are required for clinical translation.

NANOMATERIALS ENHANCE MWA FOR HCC

MWA is a percutaneous thermal ablation technique that employs high-frequency electromagnetic waves, typically at 915 or 2,450 MHz, to induce rapid oscillation of polar molecules, primarily water within biological tissues.

This process generates frictional heat, leading to coagulative necrosis of tumor cells.⁶⁰ Compared to RFA, MWA offers several advantages: consistently higher intratumoral temperatures, larger ablation volumes, faster ablation times, and lower postoperative recurrence rates.¹³³ Furthermore, MWA is less affected by the heat sink effect, enabling more uniform inactivation of tumor targets adjacent to blood vessels.¹³⁴ These features make MWA particularly suitable for treating HCCs >3 cm in diameter.^{11,134} Moreover, for HCCs <5 cm, MWA demonstrates therapeutic efficacy comparable to surgical liver resection.¹³⁵ Collectively, MWA is an effective treatment modality for HCCs measuring 3–5 cm in diameter. Despite its advantages, MWA is associated with a higher incidence of complications compared to RFA.¹³⁶ This is attributable to the larger ablation zones, which increase the risk of damage to structures, including major blood vessels and bile ducts.¹³⁶ Additionally, the complete ablation rate for MWA decreases with increasing tumor diameter. Studies report a complete ablation rate of 97.1% for HCC <3 cm treated with MWA,¹³⁷ however, rates decrease to 82.6% for HCC 3–5 cm and 64.3% for HCC 5–8 cm.¹³⁸ Therefore, to enhance ablation efficacy and reduce adverse effects, a viable method for improving MWA is currently needed.

Ionic liquids (ILs), NaCl, and non-ionic ethyl formate (EF)—polar or ionic substances acting as microwave sensitizers—can significantly enhance heat generation efficiency under the same microwave field strength by increasing dielectric loss.⁶⁰ The mechanism of action is further enhanced by the ion confinement effect, wherein microwave-sensitive materials confined within nano-scale spaces, such as those loaded onto nanocarriers, demonstrate signifi-

Table 1. Nanomaterials for enhancing ablation therapy of HCC.

Ablation technique	Nanomaterial	Nanomaterial type	Component	Drug	Size (nm)	Zeta potential (mV)	Ablation temperature (<i>in vivo</i>)	Models	Imaging	Ref.
RFA	Ferucarbotran	Fe-based nanomaterials	Fe ₃ O ₄ or γ-Fe ₂ O ₃ Carboxydextran		45–60	-	-	N1S1 orthotopic HCC rat model	MRI	52
RFA	Ferucarbotran	Fe-based nanomaterials	Fe ₃ O ₄ or γ-Fe ₂ O ₃ Carboxydextran		45–60	-	-	patients with HCC	MRI	46
RFA	Ferucarbotran	Fe-based nanomaterials	Fe ₃ O ₄ or γ-Fe ₂ O ₃ Carboxydextran		45–60	-	-	patients with HCC	MRI	53
RFA	Ferucarbotran	Fe-based nanomaterials	Fe ₃ O ₄ or γ-Fe ₂ O ₃ Carboxydextran		45–60	-	-	patients with HCC	CT and MRI	54
RFA	nCP: Fe	Fe-based nanomaterials	CaCl ₂ TSC FeCl ₃ Diammonium Hydrogen Phosphate		125 ± 60	-15	81.3 ± 1.5	N1S1 orthotopic HCC rat model	MRI	55
RFA	PEG-coated GNPs	Au-based nanomaterials	PEG HAuCl ₄					Porcine normal liver	US	61
TAE and RFA	dvGC@PNA	Au-based nanomaterials	HAuCl ₄ GSH PNTB		1.47 ± 0.5		51.5 ± 2.3	VX ₂ orthotopic hepatoma rabbit model Porcine liver	CT	62
TAE and RFA TAE and IRE TAE and PTT	Dox@PEG-HAuNS	Au-based nanomaterials	Dox PEG-SH Au(III) chloride trihydrate Cobalt(II) chloride hexahydrate ⁶⁴ Cu DOTA-LA	Dox	42.5			VX ₂ orthotopic hepatoma rabbit model	PET/CT	63
RFA	iRGD-TSL-DOX	Liposomes	DSPE-PEG ₂₀₀₀ MPPC DPPC iRGD Dox	Dox	96.05 ± 0.98			Subcutaneous H22 tumor-bearing BALB/c mice model		44
RFA	Lipo-Dox® and Mic-Qu	Liposomes and nanomicelles	PEG ₂₀₀₀ -PE Dox Quercetin	Dox	17.0 ± 2.1 (Mic-Qu)	-21.7 ± 4.3 (Min-Qu)		Normal liver of Fisher 344 female rats Fisher 344 orthotopic breast cancer rat model		76
iRFA	Fe-TPZ NPs	Fe-based nanomaterials	FeSO ₄ ·7H ₂ O TPZ	TPZ	19.23 ± 2.76			Subcutaneous Hepa1-6 tumor-bearing C57BL/6 mice model		90
iRFA	As@ZIF-8 NPs	MOF	Zn(NO ₃) ₂ 2-MeIM NaAsO ₂ COOH-PEG-COOH	As agents	75.13 ± 1.22		-20.12 ± 3.99	Subcutaneous LM3 tumor-bearing nude mice model		92
iRFA	SBZP NPs	MOF	Zn(NO ₃) ₂ ·6H ₂ O 2-MeIM STF62247 BMS202 PEG-FA	STF62247 BMS202			-10.9 ± 10.9	Subcutaneous H22 tumor-bearing mouse model		91
iRFA	ROD	Hydrogel	LyOK-432 Dox RADA16-I peptide	LyOK-432 Dox				Hepa1-6 orthotopic HCC C57BL/6 mice model		93

Table 1. (Continued)

Ablation technique	Nanomaterial	Nanomaterial type	Component	Drug	Size (nm)	Zeta potential (mV)	Ablation temperature (<i>in vivo</i>)	Models	Imaging	Ref.
RFA	LDHs-cGAMP and TAAs	Polymer nanomaterials	LDH cGAMP TAAs	cGAMP	157	41.82		Subcutaneous Hepa1-6 tumor-bearing C57BL/6 mice model Hepa1-6 C57BL/6 mice syngeneic lung metastasis model Hepa1-6 orthotopic HCC C57BL/6 mice model		94
iRFA	Bt-NPs@PLEL	Hydrogel	PLEL TAK-981 BSA	TAK-981	128			Subcutaneous Hepa1-6 tumor-bearing C57BL/6 mice model		95
RFA	LPIP	Liposome	DSPE-PEG ₂₀₀₀ PFH IPI549 Anti-PD-L1 antibody	IPI549 Anti-PD-L1 antibody	148 (LPI)			Hepa1-6 orthotopic HCC C57BL/6 mice model	MRI	47
MWA	Chitosan/Fe ₃ O ₄ @IL NPs	Polymer nanomaterials	Chitosan Fe ₃ O ₄ [Bmim][BF ₄]		6170		51.2	Subcutaneous H22 tumor-bearing ICR mice model	MRI	146
MWA	Gelatin/IL@Fe ₃ O ₄ microcapsules	Microcapsules	Gelatin [Bmim][BF ₄] FeCl ₃ Sodium citrate Ethylene glycol NaAc		5050		52 °C	Subcutaneous H22 tumor-bearing ICR mice model	MRI	147
MWA	TBP@DOX	Liposome	DSPE-PEG ₂₀₀₀ -Amine DPPC Cholesterol BML Dox Fucoidan	Dox	92.1 ± 12.5	- 15.2 ± 3.6	>50 °C	Subcutaneous H22 or HepG2 tumor-bearing nude mice model		148
MWA	LACH/PNA	Polymer nanomaterials	LA Choline carbonates PNA				70.5 °C	Subcutaneous H22 and HepG2 mice model Walker-256 orthotopic HCC rat model VX ₂ orthotopic hepatoma rabbit model		150
MWA	NaCl-LPs	Liposome	DPPC Cholesterol DSPE-PEG ₂₀₀₀ NaCl		59.7 ± 1.1	-26.21 ± 1.24	60.46 ± 1.23	Subcutaneous HepG2 tumor-bearing mice model MHHC97H orthotopic HCC mice model		154
MWA	NaCl-DOX@PLGA	Polymer nanomaterials	mPEG-PLGA NaCl Dox	Dox	100		62	HepG2-tumor-bearing nude mice		155

Table 1. (Continued)

Ablation technique	Nanomaterial	Nanomaterial type	Component	Drug	Size (nm)	Zeta potential (mV)	Ablation temperature (in vivo)	Models	Imaging	Ref.
MWA	EF-DOX-Lips	Liposome	DOPC DSPE-PEG Ethanol Dox Cholesterol EF	Ethanol Dox	80	16.9 ± 2.7		Hepa1-6 orthotopic HCC C57BL/6 mice model		159
MWA	FCMs	MOF	H ₂ BDC NH ₂ -H ₂ BDC FeCl ₃ Cu (NO ₃) ₂		225 ± 9.77	14.52 ± 0.38	63.2	Subcutaneous H22 tumor-bearing BALB/c mice model		139
MWA	Cu-Zr MOF	MOF	ZnCl ₄ CuCl ₂ H ₂ BDC PVP DMF PEG		125	-9.197	55	Subcutaneous LM3 tumor-bearing BALB/c mice model		171
MWA	PFP-Apa-MOF	MOF	H ₂ BDC NH ₂ -H ₂ BDC FeCl ₃ Fumaric acid DOPC DOPE DSPE-PEG ₂₀₀₀ PFP Apa	Apa	386.6 ± 8.3	-31.6 ± 10.6		Subcutaneous HepG2 tumor-bearing nude mice model	US	173
MWA	Mn-Ti MOFs@PEG	MOF	NH ₂ -H ₂ BDC DMF MeOH MnCl ₂ PVP TBOT PEG		353.9 ± 20.8		57.9	Subcutaneous HepG2 tumor-bearing nude mice model	MRI	170
MWA	IL@ZrO ₂ NPs	ZrO ₂ NPs	[Bmim][PF ₆] ZrO ₂		345		55	Subcutaneous H22 tumor-bearing ICR mice model Subcutaneous VX ₂ tumor-bearing rat model Swine	CT	178
TAE and MWA	mPEG-PLGA@ZrO ₂ @(DOX + ILS) microspheres	ZrO ₂ NPs	mPEG-PLGA [Bmim][PF ₆] ZrO ₂ Dox	Dox	48660		>60	VX ₂ orthotopic hepatoma rabbit model	CT	152
MWA	IL-DOX-PCM@ZrO ₂ NPs	ZrO ₂ NPs	Dox [Bmim][PF ₆] Tetradecanol ZrO ₂	Dox			58	H22 orthotopic HCC ICR mice model		180
MWA	X@BB-ZrO ₂ NPs	ZrO ₂ NPs	ZrO ₂ IL Dox Keratin Tetradecanol	Dox			64.8 ± 3.1	H22 orthotopic HCC ICR mice model VX ₂ orthotopic hepatoma rabbit model	CT	181
MWA	MZCNs	ZrO ₂ NPs	ZrO ₂ NPs [Bmim][PF ₆] TPP iRGD		216	9	56.4	Subcutaneous H22 tumor-bearing mice model		183

Table 1. (Continued)

Ablation technique	Nanomaterial	Nanomaterial type	Component	Drug	Size (nm)	Zeta potential (mV)	Ablation temperature (in vivo)	Models	Imaging	Ref.
MWA	PEG-IL-LM-ZrO ₂ SNPs	ZrO ₂ NPs	LM ZrO ₂ IL PEG				59.7	Subcutaneous H22 tumor-bearing Balb/c mice model Subcutaneous Hepa1-6 tumor-bearing C57BL/6 mice model	CT	184
TAE and MWA	MSMC	Microcapsules	Sodium Alginate MoS ₂		5600 ± 1800		60 °C	VX ₂ orthotopic hepatoma rabbit model Subcutaneous H22 tumor-bearing Balb/c mice model	CT	190
MWA	mPEG-PLGA@DMF microcapsules	Microcapsules	mPEG-PLGA DOX·HCl MoS ₂ Fe ₃ O ₄	Dox	59000		73.3	VX ₂ orthotopic hepatoma rabbit model	CT and MRI	191
MWA	DA-COD-OD-HCS hydrogel	Hydrogel	Dextran NaIO ₄ Hemin Carboxymethyl Chitosan Cholesterol oxidase Dimethylmaleic anhydride				60	Subcutaneous H22 tumor-bearing Balb/c mice model		192
MWA	ANPs-Gel	Hydrogel	mPEG-DPPE CaP As ₂ O ₃ HPMC Pluronic F127 Sodium Alginate			99.8 ± 3.5	-28.1 ± 1.1	VX ₂ orthotopic hepatoma rabbit model	CEUS	193
MWA	ALG-Ca-Mn gel	Hydrogel	ALG CaCl ₂ MnCl ₂				50	Subcutaneous H22 or CT26 tumor-bearing Balb/c mice model VX ₂ orthotopic hepatoma rabbit model		200
MWA	Man-CDs and DAMPs	CDs	Man Ethylenediamine Phosphoric acid DAMPs				60	Hepa1-6 orthotopic HCC C57BL/6 mice model Hepa1-6 HCC rechallenged C57BL/6 mice model		201
MWA	smDV-αCTLA-4	Nanobiomaterial	smDV Anti-CTLA-4 Antibody		60	-30	45.3	Subcutaneous Hepa1-6 tumor-bearing C57BL/6 mice model		202

Table 1. (Continued)

Ablation technique	Nanomaterial	Nanomaterial type	Component	Drug	Size (nm)	Zeta potential (mV)	Ablation temperature (<i>in vivo</i>)	Models	Imaging	Ref.
MWA	LOX-MnO ₂ @Gel	Hydrogel	sSiO ₂ NPs KMnO ₄ Na ₂ CO ₃ PAH LOX HA PLGA-PEG-PLGA	LOX	172.1 (LOX-MnO ₂)			Hepa1-6 orthotopic HCC C57BL/6 mice model		207
PTT	GNR70@PEG-LF	GNRs	HAuCl ₄ PEG Lactoferrin		70 (length) and 11.5 (width)	-15		Subcutaneous HepG2 tumor-bearing nude mice model		226
PTT	Adr/GNRs@PMS-antiEpCAM	Nanomicelles	GNRs Ethyl 11-(4-mercaptobenzoyl) undecanoate CTAB Dox PLGA- <i>b</i> -PEG-COOH PLGA- <i>b</i> -PEG-NH ₂ Anti-EpCAM antibody	Dox	117.1 ± 1.3	-27.4		Hepa1-6 orthotopic HCC C57BL/6 mice model	PAI	227
PTT	AFLG	GNRs	TeO ₂ H ₂ SeO ₂ N ₂ H ₄ ·H ₂ O HAuCl ₄ FeCl ₃ γ-Fe ₂ O ₃ Lenvatinib β-Glucan SH-PEG SDS PSS	Lenvatinib	195 (length) and 47 (width)	-12	79	Subcutaneous Hepa1-6 tumor-bearing C57BL/6 mice model	MRI and PAI	228
PTT	Dox@PEG-HAuNS	Au Nanospheres	Dox PEG HAuNS	Dox				N1S1 orthotopic HCC rat model	PET/CT	234
PTT	Au@PDA-RGD NPs	Au Nanostars	Au seeds PDA HS-PEG-RGD HS-PEG-COOH				> 55	Subcutaneous HepG2 tumor-bearing nude mice model		244
PTT	DOX@CAuNCs	Au nanocages	H22 cell membrane HAuCl ₄ (NH ₄) ₂ SO ₄ DOX·HCl	Dox	104.5	-30.5	52.5	Subcutaneous HepG2 tumor-bearing nude mice model		250
PTT	SO-Au-MSN	GNPs	TEOS HAuCl ₄ Sor	Sor	104.3 ± 3.7	-10.22 ± 2.4		In vitro		251
PTT	BSA-GNPs	GNPs	BSA TSC HAuCl ₄		40.5			Tumor tissue from HCC patients		252
TAE and PTT	PBNPs	Fe-based nanomaterial	Triton X-100 Hexanol Cyclohexane FeSO ₄ K ₃ [Fe(CN) ₆] Citric acid		34	-27	62.2	VX ₂ bilateral auricular tumor rabbit model		260

Table 1. (Continued)

Ablation technique	Nanomaterial	Nanomaterial type	Component	Drug	Size (nm)	Zeta potential (mV)	Ablation temperature (in vivo)	Models	Imaging	Ref.
PTT	SP94-PB-SF-Cy5.5 NPs	Fe-based nanomaterials	PBNPs PVP PEG SP94 1-tetradecanol Sor Cy5.5	Sor	90–110		48	Subcutaneous HepG2 tumor-bearing nude mice model Subcutaneous Hepa1-6 tumor-bearing C57BL/6 mice model	MRI and PAI	261
TACE and PTT	¹³¹ I-HCuSNPs-MS-PTX	Polymer nanomaterials	PLGA HCuSNPs PTX Na ¹³¹ I solution	PTX	47270		45	Walker-256 orthotopic HCC rat model	SPECT/CT and PAI	274
PTT	PEG-modified Dox-loaded MSN@CuS nanohybrids	Polymer nanomaterials	Na ₂ S CuCl ₂ Na ₃ CA CTAB APTES TEOS SH-PEG Dox	Dox	150	-16.6		In vitro		276
PTT	CuS@pda/PAA/DOX/GPC3	Polymer nanomaterials	Na ₂ S CuCl ₂ PDA Hydrochloride PAA Dox Anti-GPC3 antibody	Dox				Subcutaneous HepG2 tumor-bearing nude mice model		277
PTT	CuSNC@DOX@MCu-based nO ₂ -NS	Cu-based nanomaterials	CuSNC Dox KMnO ₄	Dox	89		50	Subcutaneous HepG2 tumor-bearing nude mice model	MRI and FI	278
PTT	CuS-SF@CMV	Cu-based nanomaterials	Macrophage Membrane Cancer Membrane CuS Sor Anti-VEGFR antibody	Sor Anti-VEGFR antibody	210		58.9	Subcutaneous H22 tumor-bearing BALB/c mice model	Infrared thermal imaging	281
PTT	CuS-ATMi@TGF-β NPs	Cu-based nanomaterials	ATM inhibitor Ku-60019 CuS NPs PEG Anti-TGF-β antibody	Ku-60019	200	-12.1	45	Subcutaneous H22 tumor-bearing BALB/c mice model		285
PTT	LMHSSs	Metal Sulfide Nanomaterials	Na ₂ MoO ₄ ·H ₂ O (NH ₂) ₂ CS		630		55	VX ₂ bilateral auricular tumor rabbit model	DSA, Infrared imaging, and CT	289
PTT	DOX@MoS ₂ NPs	Metal Sulfide Nanomaterials	Na ₂ MoO ₄ ·H ₂ O (NH ₂) ₂ CS Dox	Dox	300			Subcutaneous H22 tumor-bearing mice model		290
TAE and PTT	UiO-66/Bi ₂ S ₃ @DOX	MOF	UiO-66-NH ₂ Bi(C ₂ H ₃ O ₂) ₃ EG Na ₂ S Dox	Dox			77	N1S1 orthotopic HCC rat model	MRI	293

Table 1. (Continued)

Ablation technique	Nanomaterial	Nanomaterial type	Component	Drug	Size (nm)	Zeta potential (mV)	Ablation temperature (in vivo)	Models	Imaging	Ref.
PTT	GPMQNs	Quantum dot	Graphite EDC miR-122 InCl ₃ ZnS P-gp In(AC) ₃ ODE Myristic acid Amine		300			Subcutaneous drug-resistant HepG2/ADM tumor-bearing nude mice model	Infrared thermal imaging	297
PTT	MGO-TCA-FA@DOX nanocomposites	Polymer nanomaterials	GO Fe ₃ O ₄ -APTES TCA FA Dox	Dox				Subcutaneous Hepa1-6 tumor-bearing C57BL/6 mice model	Infrared thermal imaging	310
PTT	MnO-N/C NPs	Nanozymes	ZnO PAA Mn salt 2-MeIM Carbon		216.3	16.8		Subcutaneous HepG2 tumor-bearing BALB/c mice model	MRI	311
PTT	BPSP	BPNS	BP Mal-PEG-NH ₂ Sor Anti-PD-L1 antibody NMP PEG	Anti-PD-L1 antibody Sor	174.45 ± 3.17	-22.53 ± 1.64	51.3	Subcutaneous Hepa1-6 tumor-bearing C57BL/6 mice model	NIR fluorescent imaging	322
PTT	BATNS	BPNS	Bulk BP Thiosugar Au		158.1 ± 6.3	-19.9		Hep1-6 orthotopic HCC C57BL/6 mice model	MRI	323
PTT	SCPPI	Fe-based nanomaterials	SPIONs PDA PEG ICG		123.5		50.9	Subcutaneous HepG2 tumor-bearing nude mice model	US and MRI	328
TAE and PTT	Fe ₂ O ₃ -PDA-Dox and CA4P	Fe-based nanomaterials	Fe ₂ O ₃ Tris-HCl PDA Hydrochloride Dox	Dox CA4P			62	Mca-rh7777 orthotopic HCC rat model	MRI	329
PTT	SZP	MOF	Sor 2-MeIM PDA	Sor	200	-14.13	57.4	Subcutaneous HepG2 tumor-bearing nude mice model	NIR fluorescent imaging	331
PTT	PDA@Ag@GOx	PDA nanomaterials	PDA Ethanol AgNO ₃ Triethylamine DMF PEI-600 Go _x	Go _x	220			Subcutaneous Hepa1-6 tumor-bearing C57BL/6 mice model	NIR fluorescent imaging	332
PTT	Pt@PDA-c	PDA nanomaterials	K ₂ PtCl ₄ PDA PEG-SH Anti CXCR4 antibody	Anti-CXCR4 antibody	150	-33.5 ± 5.4	50	Subcutaneous HepG2 tumor-bearing nude mice model HepG2 orthotopic HCC nude mice model	PACT	333
PTT	PLT-PPy-DOX	Nanobiomaterials	PLT membranes Ppy Dox	Dox	10		51.2	Huh7 orthotopic HCC nude mice model		352

Table 1. (Continued)

Ablation technique	Nanomaterial	Nanomaterial type	Component	Drug	Size (nm)	Zeta potential (mV)	Ablation temperature (<i>in vivo</i>)	Models	Imaging	Ref.
PTT	CMC/CS@PPy + 5Fu NPs	Polymer nanomaterials	5Fu Chitosan CMC	5Fu	254.4	-28.4	42.5	Subcutaneous HepG2 tumor-bearing nude mice model	NIR fluorescent imaging	³⁵³
TAE and PTT	HPW@PANI Nanorods	Polymer nanomaterials	Aniline Phosphotungstic acid Ammonium Persulphate		178	15	60	VX ₂ orthotopic hepatoma rabbit model		³⁶³
PTT	FA Co-PMs	Liposomes	PCL-ss-PEG-ss-PCL PCL-acetal-PEG DSPE-PEG ₂₀₀₀ Folate Dox ICG	Dox	119.20 ± 1.11	-20.72 ± 0.32	52.7	Subcutaneous BEL-7404 tumor-bearing nude mice model	FI	³⁷¹
PTT	ICG-CuS-Gd@BSA-EpCAM NPs	Metal Sulfide Nanomaterials	CuCl ₂ ·2H ₂ O GdCl ₃ ·6H ₂ O BSA Na ₂ S·9H ₂ O ICG Anti-EpCAM antibody		800 or 830-20			Subcutaneous HepG2 tumor-bearing nude mice model HepG2 orthotopic HCC nude mice model	MRI, PAI, and FI	³⁷²
PTT	ICG-CD@EPS	Polymer nanomaterials	ICG-COOH TETA-β-CD Etoposide	Etoposide				HepG2 orthotopic HCC nude mice model		³⁷⁴
PTT	CIMs	Nanobiomaterials	Mesoporous AgNPs IR780 CAR-T Cell Membranes Polycarbonate porous membranes		135	-6.7	> 50	Subcutaneous Huh-7 tumor-bearing nude mice model	NIR fluorescent imaging and FI	³⁷⁷
PTT	FGIR	Metal Sulfide Nanomaterials	FeCl ₃ ·6H ₂ O HDA NaOAc PEI Go _x RBCMs IR780	Go _x	240	-16	52	Subcutaneous Hepa 1-6 tumor-bearing C57BL/6J mice model		³⁷⁹
PTT	G-Nvs@IR820	Nanobiomaterials	Cell membrane of HEK293T cells expressing Gas6 IR820		145	-24.3	62.86	Subcutaneous SMMC7721 tumor-bearing nude mice model	FI and PAI	³⁸⁸
PTT	IR820-PEG-MNPs	Melanin NPs	PEG-MNPs IR820		11.7	-38.5	52.1	Subcutaneous HepG2 tumor-bearing nude mice model HepG2 orthotopic HCC nude mice model	MRI and PAI	³⁸⁹
PTT	IR820@PEG-SPIO	Fe-based nanomaterials	Fe (acac) ₃ Oleic acid Oleylamine DSPE-PEG IR820		16.7		53.4	HepG2 orthotopic HCC nude mice model	MRI, PAI and FI	³⁹⁰

Table 1. (Continued)

Ablation technique	Nanomaterial	Nanomaterial type	Component	Drug	Size (nm)	Zeta potential (mV)	Ablation temperature (in vivo)	Models	Imaging	Ref.
PTT	CS@P	Polymer nanomaterials	Co (NO ₃) ₂ ·6H ₂ O Cu (NO ₃) ₂ ·3H ₂ O Fe(NO ₃) ₃ ·9H ₂ O Nr2f6 siRNA PEG-DMMA		About 100	-23.6	45	Subcutaneous H22 tumor-bearing BALB/c mice model Bilateral subcutaneous H22 tumor-bearing BALB/c mice model	MRI	405
PTT	DNAzyme@Mn-CONASHs and NK cells modified with TLS11a ligands	Polymer nanomaterials and biomaterials	Mn-THAQ PEI DNAzyme HCC-specific targeting TLS11a-aptamer-Cy3 Cy5-DBCO NK cells		78.7 ± 15.9	13.57 ± 1.01	54.7	Subcutaneous HepG2 tumor-bearing mice model	MRI	414
PTT	MR-sHDL and VR-sHDL	Liposome	Phospholipid Cholesterol oleate DiR Mertansine or Vadimezan-Chol ApoA-1 minetic peptide Hydration	Mertansine(MR- or Vadimezan-Chol	12.6 ± 1.7 12.4 ± 2.0		45	Subcutaneous Hepa 1-6 tumor-bearing C57BL/6J mice model	Bioluminescence imaging	417
PTT	As ₂ O ₃ /PFH NPs@Au-cRGD	Liposome	DSPE-PEG _{2k} -SH DOTAP DPPC Cholesterol As ₂ O ₃ PFH Ascorbic acid HAuCl ₄ RGD-SH		121 ± 5	10.47 ± 1.20	49	Subcutaneous Huh7 tumor-bearing nude mice model Hepa1-6 orthotopic HCC C57BL/6 mice model	US	419
PTT	PLNR840	Polymer nanomaterials	DSPE-PEG-cRGD LOX NR840		106	-44.3		Hepa1-6 orthotopic HCC C57BL/6 mice model	PAI and NIR fluorescent imaging	423
HIFU	PBNBs	Liposome	Lyso PC EDC Bexarotene prodrug	160 ± 20	-29 ± 1		Bexarotene prodrug	Porcine normal liver porcine-derived Kras or TP53-mutated HCC cells orthotopic HCC mouse model		439
HIFU	GPC3-CMBs	Liposome	DPPC DSPE-PEG ₂₀₀₀ Dc-Chol Anti-GPC3 antibody HSV-TK plasmid	520				Subcutaneous Hep3B tumor-bearing nude mice model		440
HIFU	PLGA-PFP nanoemulsions	Nanoemulsions	PLGA PFP	310.7	-32.7			VX ₂ orthotopic hepatoma rabbit model	MRI	448
HIFU	HMPBS-DOX/PFH	Fe-based nanomaterials	PVP K ₃ [Fe(CN) ₆] HCl PFH Dox				Dox	VX ₂ orthotopic hepatoma rabbit model	US and MRI	451

Table 1. (Continued)

Ablation technique	Nanomaterial	Nanomaterial type	Component	Drug	Size (nm)	Zeta potential (mV)	Ablation temperature (in vivo)	Models	Imaging	Ref.
TAE and HIFU	Fe ₃ O ₄ -PFH/PLGA nanocapsules	Fe-based nanomaterials	PFH Fe ₃ O ₄ PLGA	561.9 ± 207.2	-29.3	70		VX ₂ orthotopic hepatoma rabbit model US, MRI, Fresh degassed and PAI normal bovine liver		452
HIFU	Mn-SCA	Mn-based NPs	MnCl ₂ DBU	120				Subcutaneous Hepa1-6 tumor-bearing nude mice model	US	456
MHA	PLGA-MMs	Fe-based nanomaterials	PVA PLGA Fe ₃ O ₄ NPs		100000–150000			VX ₂ orthotopic hepatoma rabbit model	DSA	462
MHA	Magnetic drug carrier system	Fe-based nanomaterials	Fe BeFe ₁₂ O ₁₉ CCINs EPI	EPI			40.8–68.9	Porcine normal liver Subcutaneous Hepa1-6 tumor-bearing C57BL/6 mice model		463
MHA	CG-IM	Hydrogel	Chitosan Gallic acid Mica nanosheet Fe ₃ O ₄		48.2			VX ₂ orthotopic hepatoma rabbit model Subcutaneous HepG2 tumor-bearing nude mice model	US	469
MHA	MCH	Hydrogel	Gelatin A FeCl ₃ ·6H ₂ O DEG EG					VX ₂ orthotopic hepatoma rabbit model Subcutaneous H22 tumor-bearing BALB/c mice model	CT and US	470
MHA	NCD	Hydrogel	PNIPAM ₂₇₀ -OE- PEG CION DOX	DOX	-	~45-46		Subcutaneous HepG2 tumor-bearing nude mice; VX ₂ orthotopic hepatoma rabbit model	US, MRI	471
MHA	FPH _{DOX}	Hydrogel	PVA FCION DOX	DOX		~47		Subcutaneous H22 and HepG2 tumor-bearing mice; VX2 orthotopic hepatoma rabbit model	US, CT	472
Cryoablation	MgO NPs	Mg-based nanomaterials	MgO		20	<-40				477

Abbreviations: RFA, radiofrequency ablation; HCC, Hepatocellular Carcinoma; MRI, magnetic resonance imaging; CT, computed tomography; nCP: Fe, calcium phosphate biomineral nanoparticle; Fe; TSC, trisodium citrate, TSC; US, Ultrasound; PEG, polyethylene glycol; GNPs, Au nanoparticles; PEG-GNPs, GNPs coated with unmodified PEG molecules; TAE, transarterial embolization; PNA, poly(N-isopropylacrylamide-co-acrylic acid); dvGC@PNAs, dual-valent Au clusters coated with PNAs; GSH, glutathione; PNTb, p(NIPAM400co-tBax); IRE, irreversible electroporation; PTT, photothermal therapy; Dox, Doxorubicin; HANs, hollow Au nanoshells; Dox@PEG-HANs, Dox-loaded PEG-coated HANs; PEG-SH, Sulfhydryl polyethylene glycol; DOTA-LA, (1,4,7,10-tetraazacyclododecane-1,4,7-tris(acetic acid)-10-acetic acid-N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-lipoic acid mono amide; PET/CT, positron emission tomography/computed tomography; iRGD-TSL-DOX, Dox-loaded temperature-sensitive liposomes surface-modified with the tumor-penetrating peptide internalizing sequence: CRGDRGPDG; iRGD, internalizing sequence: CRGDRGPDG; DSPE-PEG₂₀₀₀, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(poly-ethylene-glycol)-2000; MPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; DPPC, dipalmitoylphosphatidylcholine; Lipo-Dox®, Liposome Dox; Mic-Qu, micellar quercetin; PEG2000-PE, polyethylene glycol 2000-phosphatidyl ethanolamine; iRFA, incomplete RFA; Fe-TPZ NPs, nanoparticles composed of

Fe²⁺ and tirapazamine; TPZ, tirapazamine; As@ZIF-8 NPs, As-encapsulated Zeolitic imidazolate framework-8 nanoparticles; MOF, metal-organic framework; 2-MeIm, 2-methylimidazole; COOH-PEG-COOH, polyethylene glycol dicarboxylic acid; SBZP NPs, STF62247-BMS202@ZIF-8/PEG-FA nanoparticles; PEG-FA, formylbenzoic acid-modified PEG; ROD, RADA16-I peptide hydrogel loading IyOK-432 and Dox; LDHs-cGAMP, layered double hydroxide nanodiscs loaded with cyclic GMP-AMP; TAAs, tumor-associated antigens; LDH, layered double hydroxide; cGAMP, cyclic GMP-AMP; Bt-NPs@PLEL, PDLLA-PEG-PDLLA nanocomposite hydrogel combined with self-assembled nanoparticles of TAK-981 and bovine serum albumin; PLEL, PDLLA-PEG-PDLLA; BSA, bovine serum albumin; LPIP, Liposome@LPE@PFH@IPI549@ α PD-L1; PFH, perfluorohexane; LPI, Liposome@LPE@PFH@IPI549; MWA, microwave ablation; Chitosan/Fe₃O₄@IL NPs, co-encapsulating 1-butyl-3-methylimidazolium tetrafluoroborate and Fe₃O₄ NPs within a chitosan matrix; [Bmim][BF₄], 1-butyl-3-methylimidazolium tetrafluoroborate; ICR, Institute of Cancer Research; Gelatin/IL@Fe₃O₄ microcapsules, ionic liquid and Fe₃O₄ nanoparticles in gelatin microcapsules; TBP@DOX, DOX and 1-butyl-3-methylimidazolium-L-lactate into fucoidan conjugated liposomal nanoparticles; DSPE-PEG₂₀₀₀-Amine; BML, 1-butyl-3-methylimidazolium-L-lactate; LACH/PNA, PNA, incorporating a multifunctional IL formed by α -lipoic acid and choline; LA, α -Lipoic acid; NaCl-LPs, Liposomes packed with NaCl; NaCl-DOX@PLGA, NaCl and Dox loaded into hollow PLGA NPs; mPEG-PLGA, methoxy poly(ethylene glycol)-poly(lactic-co-glycolic acid); EF-DOX-Lips, EF and Dox encapsulated within liposomes; DOPC, 1,2-dioleacyl-sn-propyl-3-choline phosphate; DSPE-PEG, 1,2-distearoyl-sn-glycero-3-phosphatidylethanolamine-N-succinyl (polyethylene glycol); EF, ethyl formate; FCMs, Fe-doped Cu bimetallic MOFs; H₂BDC, terephthalic acid; NH₂-H₂BDC, 2-Aminoterephthalic acid; Cu-Zr MOF, microwave-activated Cu-doped zirconium MOF; PVP, polyvinylpyrrolidone; DMF, N, N-dimethylformamide; PFP-Apa-MOF, MOF loading perfluoropentane and apatinib; DOPE, 1,2-dioleacyl-sn-propyl-3-phosphatidylethanolamine; PFP, perfluoropentane; Apatinib; Mn-Ti MOFs@PEG, Mn-doped Ti-based MOFs coated with PEG; MeOH, Methanol; TBOT, Tetrabutyl titanate; IL@ZrO₂ NPs, Zirconia shells with hollow and mesoporous structures, encapsulating the 1-butyl-3-methylimidazolium hexafluorophosphate; ZrO₂ NPs, Zirconia NPs; [Bmim][PF₆], 1-butyl-3-methylimidazolium hexafluorophosphate; ZrO₂, Zirconia; mPEG-PLGA@ZrO₂@(DOX + ILS) microspheres, microspheres composed of mPEG-PLGA encapsulating hollow ZrO₂ nanoparticles co-loaded with Dox and IL; IL-DOX-PCM@ZrO₂ NPs, Ionic liquid, Dox, and phase change material-loaded ZrO₂ NPs; X@BB- ZrO₂ NPs, Ball-in-ball structured ZrO₂ nanoparticles loaded with ionic liquid, Dox, keratin, and tetradecanol; MZCNs, mitochondria-targeting ZrO₂ nanoparticles; TPP, triphenylphosphonium; PEG-IL-LM-ZrO₂ SNPs, PEG-modified supernanoparticles composed of ionic liquid and liquid metal loaded into mesoporous ZrO₂ nanoparticles; LM, liquid metal; MSMC, MoS₂-loaded sodium alginate microcapsules; mPEG-PLGA@DMF microcapsules, mPEG-PLGA microcapsules to co-load Dox, MoS₂ nanosheets, and Fe₃O₄ nanoparticles; ANPs-Gel, As₂O₃-NPs encapsulated within an injectable thermoresponsive hydrogel; mPEG-DPPE, PEG-dipalmitoylphosphatidylethanolamine; HPMC, Hydroxypropyl Methylcellulose; CEUS, contrast-enhanced US; ALG-Ca-Mn gel, alginate hydrogel co-loaded with Ca²⁺ and Mn²⁺; ALG, alginate; Man-CDs, Mannose-derived carbon dots; DAMPs, damage-associated molecular patterns; CDs, carbon dots; Man, Mannose; smDV- α CTLA-4, small dendritic cell nanovesicles conjugated with anti-CTLA-4 antibody; LOX-MnO₂@Gel, Lactate oxidase-loaded hollow mesoporous MnO₂ nanoparticles embedded in a hydrogel composite system; sSiO₂NPs, solid silica nanoparticles; PAH, cationic polymer poly(allylamine hydrochloride); LOX, lactate oxidase; HA, Hyaluronic acid; PLGA-PEG-PLGA, poly(lactide-co-glycolide)-poly(ethylene glycol)-poly(lactide-co-glycolide); GNR70@PEG-LF, GNRs surface-modified with PEG and LF; GNRs, Au nanorods; ADR/GNRs@PMs-antiEpCAM, polymeric micelles loaded with Dox and surface-modified with anti-epithelial cell adhesion molecule antibody and GNRs; CTAB, Cetyltrimethyl ammonium bromide; EpCAM, epithelial cell adhesion molecule; AFLG, AuHNR@Y-Fe₂O₃@Lenvatinib@ β -Glucan; SH-PEG, thiolated polyethylene glycol; SDS, Sodium Dodecyl Sulfate; PSS, Poly(sodium-pstyrenesulfonate); Au@PDA-RGD NPs, PDA-coated GNSs conjugated with RGD peptides; PDA, polydopamine; SH-PEG-COOH, Carboxyl-poly-ethylene glycol thiol; SH-PEG-RGD, RGD-terminated polyethylene glycol thiol; DOX@CAuNCs, Au nanocages loaded with Dox and coated with HCC cell membranes; SO-Au-MSN, GNPs to coat mesoporous silica NPs loaded with sorafenib; TEOS, tetraethyl orthosilicate; Sor, sorafenib; BSA-GNPs, bovine serum albumin-conjugated GNPs; BSA, bovine serum albumin; PBNPs, Prussian Blue NPs; SP94-PB-SF-Cy5.5 NPs, PBNPs were conjugated with Sor, SP94, and Cy5.5; ¹³¹I-HCuSNPs-MS-PTX, PLGA microspheres encapsulating hollow CuS nanoparticles and PTX, labeled with radioactive iodine-131; PTX, paclitaxel; SPECT, single-photon emission computed tomography; PEG-modified Dox-loaded MSN @CuS nanohybrids, PEG-modified Dox-loaded mesoporous silica nanoparticle@CuS nanohybrids; CTAB, cetyltrimethylammonium bromide; APTES, (3-aminopropyl) triethoxysilane; CuS@pda/PAA/DOX/GPC3, CuS@PDA nanocapsules loaded with Dox, PAA and anti-GPC3 antibodies; CuSNC@DOX@MnO₂-NS, hollow mesoporous CuS nanocages encapsulating Dox and further coated with MnO₂ nanoshells; CuSNC, hollow mesoporous CuS nanocages; FI, fluorescence imaging; CuS-SF@CMV, CuS nanoparticles encapsulating Sor and coated with a cancer cell-macrophage hybrid membrane, further modified with anti-VEGFR antibodies; VEGFR, vascular endothelial growth factor receptor; CuS-ATMi@TGF- β NPs, ataxia telangiectasia mutated inhibitor-loaded hollow-structured CuS nanoparticles with surface modification with anti-TGF- β antibody; ATM, Ataxia telangiectasia mutated; TGF- β , transforming Growth Factor Beta; LMHSs, MoS₂ hollow spheres; DOX@MoS₂ NPs, MoS₂ hollow spheres loaded with Dox; UiO-66/Bi₂S₃@DOX, compositing the MOF, UiO-66, with Bi₂S₃ and loading them with Dox; EG, Ethylene Glycol; GPMQNs, graphene-P-gp loaded with miR-122-indium phosphide core and ZnS shell quantum dot nanocomposites; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; ODE, 1-Octadecene; MGO-TCA-FA@DOX nanocomposites, multifunctional hybrid material by modifying magnetic graphene oxide with trimethyl cholanolic acid and folic acid, and loading Dox; GO, graphene oxide; TCA, trimethyl cholanolic acid; FA, folic acid; MnO-N/C NPs, Mn oxide/nitrogen-doped carbon composite nanoparticles; BPSP, black phosphorus nanosheets loaded with Sor and anti-PD-L1 antibodies to form photothermal-boosted NanoBike; BPNS, BP nanosheets; BP, Black phosphorus; NMP, N-methyl-2-pyrrolidone; NIR, near-infrared; BATNS, BP-Au-thiosugar nanosheets; SCPII, SPIONs clusters@PDA-PEG@ICG; SPIONs, superparamagnetic iron oxide nanoparticles; ICG, Indocyanine green; Fe₂O₃-PDA-Dox, nanocubes of α -Fe₂O₃ coated with PDA and loaded with Dox; CA4P, combretastatin A-4 phosphate disodium; SZP, SOR@ZIF-8@PDA; PDA@Ag@GOx, PDA as the core for the in situ synthesis of AgNPs on its surface, followed by the loading of GOx; DMF, dimethylformamide; GOx, glucose oxidase; PEI, polyethylenimine; Pt@PDA-c, platinum-doped PDA nanomaterial; CXCR4, C-X-C chemokine receptor type 4; PACT, photoacoustic CT; PLT-PPy-DOX, polypyrrole nanoparticles and Dox encapsulated within a platelet membrane; PPy, polypyrrole; PLT, platelet; CMC/CS@PPy+5Fu NPs, carboxymethyl cellulose to encapsulate chitosan NPs loaded with PPy and 5-fluorouracil; 5Fu, 5-fluorouracil; CMC, carboxymethyl cellulose; HPW@PANI Nanorods, oxidatively polymerizing aniline with phosphotungstic acid as an acid catalyst and ammonium persulfate to synthesize PANI nanorods; FA Co-PMs, FA-modified polymeric micelles co-loaded with Dox and ICG; PCL-acetal-PEG, poly(ϵ -caprolactone)-acetal-poly(ethylene glycol); PCL-ss-PEG-ss-PCL,

amphiphilic copolymer poly(ϵ -caprolactone)-ss-poly(ethylene glycol)-ss-poly(ϵ -caprolactone); ICG-CuS-Gd@BSA-EpCAM NPs, CuS-Gd@BSA cores modified with anti-EpCAM and ICG; ICG-CD@EPS, conjugated ICG-COOH with supramolecular β -CD and co-loaded them with the chemotherapeutic drug etoposide; TETA- β -CD triethylenetetramine- β -CD; CIMs, mesoporous silica NPs loaded with IR780 and coated with CAR-T cell membranes; FGIR, Fe₃O₄ NPs loaded with GOx and modified with red blood cell membranes and IR780; HAD, 1,6-hexanediamine; RBCMs, red blood cell membranes; G-Nvs@IR820, growth arrest-specific protein 6-expressing cell membrane nanovesicles encapsulating IR820; Gas6, growth arrest-specific protein 6; IR820@PEG-SPIO NPs, SPIO cores modified with IR820; MNPs, melanin NPs; CS@P, CoCuFe-LDHs loaded with Nr2f6-siRNA and coated with PEG-dimethyl maleic anhydride; NR2F6, nuclear receptor subfamily 2 group f member 6; PEG-DMMA, PEG-dimethyl maleic anhydride; DNAzyme@Mn-CONASHs, Mn-based self-assembled nanosheets incorporating Mn²⁺ and tetrahydroxyanthraquinone and adsorbed PEI and DNA enzymes targeting Hsp70 mRNA; NK cells, natural killer cells; THAQ, tetrahydroxyanthraquinone; DBCO-Cy5, Cy5 conjugated dibenzocyclooctyne; MR-sHDL, liposomes were loaded with microtubule stabilizer mertansine; VR-sHDL, liposomes were loaded with STING agonist vadimezan-Chol; As₂O₃/PFH NPs@Au-cRGD, liposomes loaded with As₂O₃ and PFH, modified with HAuCl₄ and Crgd-sh on the surface; DOTAP, 2,3-Dioleoyloxy-propyl-trimethylammoniumchloride; HIFU, high-intensity focused ultrasound; PBNBs, pro-bexarotene nanobubbles; Lyso PC, 1-palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine; EDC, 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide; GPC3-CMBs, cationic microbubbles conjugated with anti-GPC3 antibodies and the anticancer plasmid HSV-TK; Dc-Chol, 3 β -[N-(N',N'-dimethylaminoethane)-carbamoyl]cholesterol; HMPBs-DOX/PFH, hollow mesoporous Prussian blue nanoparticles loaded with Dox and PFH; Fe₃O₄-PFH/PLGA nanocapsules, FH core loaded with Fe₃O₄ nanoparticles and encapsulated within a PLGA nanocapsules shell; PAI, photoacoustic imaging; Mn-SCA, Mn-coordinated polyphthalocyanine sonocavitation agent; DBU, 1,8-diazabicyclo [5.4.0] undec-7-ene; PLGA-PFP nanoemulsions, PLGA to encapsulate PFP nanoemulsions; MHA, hyperthermia ablation; DSPE-PEG-cRGD, DSPE-PEG-cyclic arginine-glycine-aspartic acid; PLNR840, DSPE-PEG-cRGD loaded with LOX and NR840; PLGA-MMs, PLGA-magnetic microspheres; PVA, polyvinyl alcohol; CCINs, carbon-coated iron nanocrystals; EPI, epirubicin hydrochloride; DSA, digital subtraction angiography; CG-IM, iron oxide nanoparticles@Mica linked with chitosan-gallic acid; MCH, magnetic colloidal hydrogels; NCD, NOP-CION-DOX hydrogel; FPH_{DOX}, Dox loaded ferrimagnetic PVA Hydrogel; NOP, poly(N-isopropylacrylamide₂₇₀)-Ortho ester-Poly(ethylene glycol); PNIPAM₂₇₀-OE-PEG, poly(N-isopropylacrylamide₂₇₀)-Ortho ester-Poly(ethylene glycol); CION, cube-shaped Iron Oxide Nanoparticles; FCION, ferrimagnetic Cube-shaped Iron Oxide Nanoparticles.

cantly stronger dipole polarization and ionic conduction than their free-state counterparts.⁶⁰ This enables more efficient conversion of microwave energy into thermal energy. This unique spatial confinement effect indicates that anchoring microwave sensitizers onto the surface of nanomaterial carriers or encapsulating them within their cavity structures can effectively regulate ionic motion spatially, ultimately yielding superior microwave-to-thermal conversion performance. Notably, novel nanomaterials—including MOFs, ZrO₂ nanosheets, and MoS₂ nanosheets—have emerged as a new generation of highly efficient microwave-sensitizing agents, owing to their tunable porous architectures and large specific surface areas.¹³⁹ These materials enable the surface functionalization required to carry traditional microwave sensitizers, and their inherent unique electronic structures can directly respond to the microwave field, generating localized hotspots (Figures 3 & 4, Table 1).

Ion-confined microwave-sensitizing nanomaterials enhance MWA for HCC

IL-loaded sensitizing nanomaterials enhance MWA for HCC. ILs are molten salts composed of organic cations and organic or inorganic anions, typically exhibiting melting points below 100 °C.¹⁴⁰ They primarily consist of organic cations paired with organic or inorganic anions that confer low melting points.¹⁴¹ Typical cations include ammonium, imidazolium, sulfonium, piperidinium, and pyridinium ions.¹⁴¹ Anions are broadly categorized into inorganic species such as Br⁻, Cl⁻, SO₄²⁻, PF₆⁻, and BF₄⁻, as well as organic species including carboxylate, phosphate, and amino acid derivatives.¹⁴² Recently, functional ILs with bioactive properties have been developed. Through structural design, the chemical and physical characteristics of these ILs can be precisely tailored, leading to their widespread application in pharmaceutical engineering and biomedicine.¹⁴³ Notably, ILs exhibit significantly enhanced electromagnetic wave absorption under microwave irradiation due to ion migration effects.¹⁴⁴ When encapsulated within nanomaterials, interfacial polarization effects further amplify their microwave absorption performance.^{144,145} Leveraging this advantage, various IL-loaded nanocomposites have emerged, demonstrating significantly enhanced therapeutic outcomes in biomedical applications such as MWA (Figure 3, Tables 1 & S1).¹⁴⁵

Research on IL-augmented nanomaterials in MWA has made significant progress. Tang et al. developed a theranostic chitosan-based microcapsule system by co-encapsulating 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF₄]) and Fe₃O₄ NPs within a chitosan matrix, chitosan/Fe₃O₄@IL NPs.¹⁴⁶ Under microwave irradiation at 1.8 W/cm² for 5 min, this material significantly increased the ablation temperature in mice HCC from 41.3 °C and 40.9 °C (MWA alone group) to 51.2 °C.¹⁴⁶ The Fe₃O₄ component served as

a hyperthermia enhancer and enabled precise pre-treatment localization and post-operative residue assessment via T₂-weighted MRI.¹⁴⁶

Employing a similar design concept, Meng et al. constructed a gelatin-based microcapsule system, gelatin/IL@Fe₃O₄ microcapsules.¹⁴⁷ After 5 min of microwave irradiation at ultra-low power density (1.8 W/cm², 450 MHz), this system elevated the ablation temperature from 42 °C (saline control group) to 52 °C, achieving complete ablation in experimental animals.¹⁴⁷ Similar to the Tang system, this material also possessed real-time MRI monitoring capability.¹⁴⁷ Xu et al. expanded the chemical diversity of ILs, selecting the microwave-sensitizing agent 1-butyl-3-methylimidazolium L-lactate (BML), structurally analogous to [Bmim][BF₄], and co-loading it with Dox into fucoidan-modified liposomal NPs (TBP@DOX).¹⁴⁸ This system achieved targeted delivery via specific binding of fucoidan to P-selectin on HCC cell surfaces.¹⁴⁸ Under the synergistic action of the acidic TME and microwave irradiation, BML enhanced ablation temperature and triggered complete Dox release.¹⁴⁸ TBP@DOX combined with microwave therapy significantly enhanced drug transport efficiency into the nucleus, maintained efficacy while reducing the Dox dose to non-toxic levels, and induced no observed acute or chronic metabolic side effects.¹⁴⁸ TBP@DOX and microwave irradiation enhanced Dox delivery into HCC cell nuclei, enabling dose reduction and toxicity mitigation without residual acute or chronic metabolic side effects *in vivo*.¹⁴⁸

In HCC, cancer-associated fibroblasts (CAFs) interact with macrophages, hindering T cell infiltration and forming an immunosuppressive barrier.¹⁴⁹ The spatial organization and molecular mechanisms underlying these CAF-macrophage immunosuppressive niches are discussed in detail in "Spatial Multi-Omics Reveal the HCC Microenvironment and Post-Ablation Immune Remodeling with Abscopal Effects." Notably, IL can kill tumor cells and inhibit the function of CAFs. Zhang et al. designed a temperature-sensitive amphiphilic polymer, PNA, incorporating a multifunctional IL formed by α -lipoic acid (LA) and choline, resulting in LACH/PNA.¹⁵⁰ LACH/PNA promotes heat and mass transfer within the tumor by disrupting the tumor stroma and killing CAFs, inducing ICD in tumor cells.¹⁵⁰ This increases the infiltration of CD8⁺ T cells in the tumor tissue, promotes the maturation of DCs, and reduces the ratios of Tregs, MDSCs, and M2 macrophages in the TME, reversing the post-MWA immunosuppressive conditions and preventing recurrence and distant metastasis. However, the specific regulatory mechanisms by which LACH/PNA reduces α -smooth muscle actin and inhibits CAFs' function remain unclear.

The use of microwave-sensitizing nanomaterials to carry ILs also demonstrates promising MWA capabilities, which will be further elaborated in "ZrO₂ NPs enhance MWA for HCC." However, ILs currently used in MWA often

Table 2. Clinical research on enhancing hepatocellular carcinoma ablative therapy using nanomaterials.

Clinical trail	Trail no.	Status	Country	Ablation and other	Drug	Treatment	Cancer type	Primary outcomes measure	Outcome
Radiofrequency-responsive layered double hydroxides for enhanced arterial embolization and thermal immunotherapy in hepatocellular carcinoma	NCT06966986	Active, not recruiting	China	TAE and RFA	Layered double hydroxides		Liver carcinoma	Changes in the proportion of different immune cell subsets were detected, especially the number and functional status of CD8+ T cells, Tregs, and NK cells	
RFA combined with recombinant human adenovirus type 5 in the treatment of hepatocellular carcinoma	NCT03790059	Unknown status	China	RFA	H101	RFA combined with H101	HCC	Tumor-free survival	
OPTIMA	NCT02112656	Completed	United States Canada China Germany Italy Korea Malaysia Philippines Singapore Spain Thailand Vietnam	RFA	ThermoDox®	ThermoDox® 50 mg/m ² start infusion over 30 minutes about 15 minutes before RFA begins.	HCC	Overall survival	Failed to significantly prolong the overall survival of patients
Phase 3 study of ThermoDox with RFA in treatment of hepatocellular carcinoma (HCC)	NCT00617981	Completed	United States Canada China Italy Japan Korea Malaysia Philippines Thailand	RFA	ThermoDox®	ThermoDox® 50 mg/m ² start infusion over 30 minutes about 15 minutes before radiofrequency ablation begins.	HCC	Progression Free Survival	Failed to significantly prolong the disease-free survival of patients
A study of ThermoDox™ in combination with RFA in primary and metastatic tumors of the liver	NCT00441376	Completed	United States	RFA	ThermoDox®	15 ml vial containing 2mg/ml Doxorubicin HCl, DPPC, MSPC, DSPE-MPEG 2000. Administered as single dose intravenously over 30 minutes. Dose is determined by dose cohort patient enters study.	HCC and Liver Neoplasms	To determine the MTD of systemically delivered, heat-activated ThermoDox® in combination with RFA of liver neoplasms. To test alternative infusion reaction prophylaxis regimens. To assess the safety of ThermoDox® plus RFA after administration of potential multiple cycles. To determine the PK of ThermoDox	No results posted

Table 2. (Continued)

Clinical trail	Trail no.	Status	Country	Ablation and other	Drug	Treatment	Cancer type	Primary outcomes measure	Outcome
HORA EST HCC	NCT03437382	Completed	Netherlands	RFA and radioembolization	Holmium-166 radioembolization microspheres	Radioembolisation as adjuvant treatment to RFA	HCC	Treatment area dose that will result in delivery of a radiation absorbed dose of 120Gy to the target area in at least 90% of patients.	No results posted
Role of perfluorobutane in lesion detection, targeting and response assessment for ablation of HCC	NCT05068076	Completed	India	RFA or MWA	Perfluorobutane	Perfluorobutane enhanced ultrasound will be done prior to ablation of HCC and after 2 hours post ablation and comparison will be done with 1 month post procedure CT/MRI	HCC	Comparison of treatment response two hours post procedure with Perfluorobutane with routine CECT/CEMRI done at 1 month post procedure using modified RECIST criteria for HCC.	No results posted

Abbreviations: RFA, radiofrequency ablation; TAE, transarterial embolization; Tregs, regulatory T cells; NK cells, natural killer cells; OPTIMA, Study of ThermoDox With Standardized Radiofrequency Ablation (RFA) for Treatment of Hepatocellular Carcinoma (HCC); HCC, Hepatocellular Carcinoma; MTD, maximum tolerated dose; PK, pharmacokinetics; DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; DSPC, 1-myristoyl-2-stearyl-sn-glycero-3-phosphocholine; DSPE-MPEG 2000, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)-2000; HORA EST HCC, Holmium Radioembolization as Adjuvant Treatment to RFA for Early Stage HCC: Dose Finding Study; CT, computed tomography; MRI, magnetic resonance imaging; CECT/CEMRI, contrast-enhanced computed tomography/magnetic resonance imaging.

contain petroleum-derived imidazolium components.^{146,151,152} Imidazolium-based ILs can exhibit toxicity under certain conditions and release deleterious decomposition products,¹⁴³ which limits the clinical translation of IL-loaded nanomaterials.

NaCl-loaded sensitizing nanomaterials enhance MWA for HCC. NaCl, as a non-toxic microwave sensitizer, can achieve efficient tumor ablation when combined with nanomaterials. Under microwave irradiation, high concentrations of NaCl ions confined within small-sized liposomes exhibit rapid heating compared to free NaCl (Figure 3, Tables 1 & S1).¹⁵³ Leveraging this property, Zhou et al. designed liposomes packed with NaCl (NaCl-LPs).¹⁵⁴ Within NaCl-LPs, chloride and sodium ions undergo intense collisions during microwave irradiation, generating heat that induces coagulative necrosis in HCC cells.¹⁵⁴ Combined treatment with NaCl-LPs and MWA demonstrated significant tumor suppression and lower recurrence rates in both subcutaneous and orthotopic HCC models.¹⁵⁴ Furthermore, Dou et al. co-loaded NaCl and Dox into hollow poly(lactic-co-glycolic acid) (PLGA) NPs, forming NaCl-DOX@PLGA, thereby integrating MWA with chemotherapy.¹⁵⁵ Under microwave irradiation, NaCl-DOX@PLGA enhanced the ablation temperature, promoted Dox release, and induced apoptosis in HCC cells.¹⁵⁵ Notably, the combination of Dox and microwave irradiation significantly increased intracellular calcium ion concentration in HCC cells, leading to mitochondrial dysfunction, promotion of apoptosis, and further inhibition of HCC.¹⁵⁵ Dox, the first nanoformulation approved by the FDA for cancer treatment,¹⁵⁶ has demonstrated favorable efficacy in HCC ablation therapy.¹⁵⁷ Additionally, the real-time monitoring of residual tumors during ablation therapy necessitates the use of contrast agents. Currently, diagnostic-capable nanomaterials such as ferumoxytol and SPIONs are also FDA-approved.¹⁵⁸ Consequently, the development of non-toxic nanomaterials co-loaded with NaCl, Dox, and contrast agents represents a promising research direction with significant clinical translation potential.

EF-loaded sensitizing nanomaterials enhance MWA for HCC. To circumvent the limitations associated with ionic sensitizers, non-ionic microwave-responsive agents have been developed. EF is a representative non-ionic compound that exhibits efficient microwave absorption while

displaying low toxicity toward normal tissues. (Figure 3, Tables 1 & S1).⁶⁰ Zhou et al. encapsulated EF and Dox within liposomes, forming EF-DOX-Lips.¹⁵⁹ EF-DOX-Lips accelerate the conversion of electromagnetic energy into thermal energy, thereby generating reinforced MWA.¹⁵⁹ Metabolites of EF include ethanol, which contributes to chemical ablation of HCC tissues, further enhancing tumor suppression.¹⁵⁹ Simultaneously, EF vaporization enhances liposome rupture and cavitation, which promotes Dox uptake into HCC cells, achieving combined MWA and chemotherapy.¹⁵⁹ Incomplete MWA activates the Ephrin type-A receptor 2 (EphA2) gene in orthotopic HCC mouse models, leading to activation of the phosphoinositide 3-kinase (PI3K)/ protein kinase B (AKT) and mitogen-activated protein kinase (MAPK) signaling pathways.¹⁵⁹ This activation promotes tumor proliferation, angiogenesis, and consequently, HCC growth, recurrence, or metastasis. In contrast, EF-DOX-Lips effectively suppresses the EphA2 gene, thereby inhibiting PI3K/AKT and MAPK pathway activation and ultimately impeding HCC progression.¹⁵⁹ However, a key limitation of this study is the use of Hepa1-6 cells orthotopically inoculated in C57BL/6 mouse models. This model's TIME exhibits anti-tumor characteristics, including high CD8⁺ T-cell and M1 macrophage infiltration, and low MDSCs infiltration.¹⁶⁰ However, it does not fully recapitulate the human liver TIME.¹⁶⁰ Therefore, the mechanism by which EF-DOX-Lips regulates incomplete MWA warrants further validation in other animal models. Furthermore, the receptor tyrosine kinase EphA2, belonging to the Eph receptor family, is highly expressed in tumor tissues but exhibits relatively low levels in most normal adult tissues.¹⁶¹ Diverse therapeutic strategies targeting EphA2 inhibition are under development, including small-molecule inhibitors, therapeutic antibodies, and peptide-drug conjugates.¹⁶² Consequently, elucidating the precise mechanism of EphA2 gene regulation by EF-DOX-Lips, as well as investigating the similarities and differences between EF-DOX-Lips and other EphA2-targeting inhibitors, deserves comparative investigation.

Microwave-absorbing nanomaterials enhance MWA for HCC

MOFs enhance MWA for HCC. MOFs are crystalline porous materials formed by the self-assembly of metal cluster nodes and organic ligands via

coordination bonds.¹⁶³ MOFs possess tunable porous structures, high specific surface area, and promote the conversion of microwave energy through ion collisions within their pores.¹⁶⁴ Furthermore, MOFs offer advantages including well-defined pore sizes, structural and functional flexibility, high drug-loading capacity, and biocompatibility;¹⁶⁵ thus, serving as excellent microwave-sensitive materials and carriers.¹⁶⁶ Microwave dynamic therapy (MDT) is a non-thermal microwave treatment modality.¹⁶⁷ It utilizes microwave irradiation to stimulate sensitizing agents to generate ROS, inducing tumor cell apoptosis or necrosis and achieving significant tumor cell killing.¹⁶⁸ Owing to their high porosity, MOF structures can be tailored by selecting appropriate metal ions and linkers.¹⁶⁹ Modification of MOFs with metal ions such as Fe, Cu, and Mn enables ROS generation upon microwave irradiation or endogenous chemical stimuli, facilitating the combination of MWA and MDT (Figure 3, Tables 1 & S1).^{164,170,171} Therefore, Lou et al. designed Fe-doped Cu bimetallic MOFs (FCMs),¹⁶⁴ whose porous structure and embedded bimetallic ions enhanced the vibration and friction of ions/polar molecules within confined spaces, generating additional heat.¹⁶⁴ Consequently, FCMs exhibited potent thermal effects under microwave radiation.¹⁶⁴ Moreover, the bimetallic doping increased the exposure of microwave-sensitive active centers and improved the separation efficiency of electron-hole pairs within the framework structure.¹⁶⁴ Therefore, FCMs reduced GSH levels and increased the generation of H₂O₂, a type of ROS.¹⁶⁴ Catalyzed by Cu²⁺, H₂O₂ underwent a Fenton reaction to produce OH[•], another type of ROS, further enhancing MDT efficacy.¹⁶⁴ FCMs effectively destroyed murine HCC tissue upon microwave irradiation, with no significant adverse effects observed in normal tissues.¹⁶⁴ Feng et al. designed a microwave-activated Cu-doped zirconium MOFs (Cu-Zr MOFs).¹⁷¹ Similar to FCMs, Cu-Zr MOF achieved combined MWA and MDT therapy.¹⁷¹ Bulk RNA sequencing analysis revealed that Cu-Zr MOFs targeted the heme oxygenase-1 (Hmox1)/GSH peroxidase 4 (Gpx4) axis, inducing ferroptosis in HCC cells and potentiating MWA.¹⁷¹ Gpx4 is a key regulator of ferroptosis. Reduction or inactivation of the selenoperoxidase Gpx4 leads to membrane lipid peroxidation, consequently triggering ferroptosis.¹⁷² Therefore, developing MOFs that inhibit Gpx4 and promote ferroptosis is beneficial for MWA in HCC (Figure 3, Table 1).

Zhang et al. developed an iron-based MOF nanomedicine by loading the US contrast agent perfluoropentane (PFP) and the antiangiogenic agent apatinib (Apa), designated PFP-Apa-MOF.¹⁷³ Following uptake by HCC cells, the Fe within PFP-Apa-MOF increased intracellular levels of ROS, subsequently inhibiting the function of Gpx4, thereby inducing ferroptosis.¹⁷³ Under microwave irradiation, PFP was activated to form microbubbles, enabling US detection of the ablation margin in HCC.¹⁷³ Concurrently, Apa inhibited residual tumor growth post-MWA in mice by suppressing tumor angiogenesis.¹⁷³ MOFs possess the advantage of functioning simultaneously as MRI contrast agents and drug carriers, enabling concurrent theranostics.¹⁶⁹ MOFs can also be loaded with T1 MRI contrast agents, such as Mn. Qin et al. designed Mn-doped Ti MOF nanosheets, designated Mn-Ti MOF@PEG.¹⁷⁰ Compared to microwave irradiation alone, Mn-Ti MOF@PEG generated significantly more heat under microwave irradiation.¹⁷⁰ The doping of Mn in Mn-Ti MOF resulted in a narrowed band gap and increased defects, facilitating greater ROS generation upon microwave triggering, thereby achieving MDT.¹⁷⁰ The Mn within Mn-Ti MOF also enhanced T1-weighted MRI contrast, allowing visualization of nanosheet accumulation within HCC and guiding subsequent microwave irradiation.¹⁷⁰ Notably, despite significant achievements leveraging the EPR of nanocarriers, their accumulation within tumors typically increases by only 20–30% compared to critical normal organs, indicating that targeting efficiency remains suboptimal.¹⁷⁴ MOFs can be functionalized with anti-CD47 antibodies, which bind to CD47 specifically overexpressed on the surface of HCC cells, thereby improving targeting efficiency.¹⁷⁵ Capitalizing on the modifiable nature of MOFs, future development should focus on creating MOFs that specifically target HCC cells. These MOFs should be co-loaded with anticancer drugs and contrast agents, facilitating integrated theranostics for MWA.

ZrO₂ NPs enhance MWA for HCC. ZrO₂ NPs are hollow spherical nanostructures exhibiting microwave sensitivity and CT imaging properties, making them ideal synergistic nanomaterials for MWA.¹⁴⁵ ZrO₂ NPs are biocompatible, disperse well under physiological conditions, and demonstrate stability within the bloodstream,¹⁷⁶ readily reaching tumor sites even under low circu-

latory flow conditions.¹⁷⁷ Furthermore, their high specific surface area enables the loading of ILs and chemotherapeutic drugs, further enhancing the efficacy of MWA (Figure 3, Tables 1 & S1).^{152,176,178} Utilizing silica microspheres as templates, Shi et al. fabricated ZrO₂ shells with hollow and mesoporous structures, encapsulating the IL 1-butyl-3-methylimidazolium hexafluorophosphate ([Bmim][PF₆]) as a core, thereby generating IL@ZrO₂ NPs.¹⁷⁸ Under microwave irradiation, IL@ZrO₂ NPs demonstrated effective ablation of murine HCC, achieving tumor suppression rates exceeding 90% and complete tumor eradication within 16 days.¹⁷⁸ CT imaging revealed concentration-dependent contrast enhancement, with HU values linearly correlated to nanoparticle concentration.¹⁷⁸ ICP-MS quantification of intratumoral Zr content confirmed tumor accumulation of >2% ID/g at 12 h post-injection.¹⁷⁸ Biodistribution studies in mini swine showed peak hepatosplenic CT signals at 12–24 h, with complete clearance by day 5, indicating favorable metabolic kinetics.¹⁷⁸ The CT imaging capability enabled real-time visualization of biodistribution, metabolic processes, and therapeutic response.¹⁷⁸ To further augment HCC suppression, Mao et al. loaded Dox into ZrO₂ NP cavities.¹⁵² These Dox-loaded particles, combined with ILs, were then encapsulated within methoxy poly(ethylene glycol)-PLGA (mPEG-PLGA) microcapsules, forming mPEG-PLGA@ZrO₂-(DOX+ILs) microspheres.¹⁵² These microspheres achieve superselective occlusion of tumor-feeding arteries, retaining the microcapsules at the tumor site via vascular blockade.¹⁵² The CT imaging functionality of the mPEG-PLGA@ZrO₂-(DOX+ILs) microspheres guided therapeutic intervention and elevated the MWA temperature beyond 60 °C.¹⁵² MWA also triggered the de-encapsulation of the mPEG-PLGA microcapsules, releasing Dox with a cumulative release of ~75% over 48 h under hyperthermic conditions.¹⁵² This strategy accomplished a triple-combination therapy integrating TAE, MWA, and chemotherapy for HCC.¹⁵²

Phase change material (PCM) Tetradecanol melts between 39 °C and 40 °C.¹⁷⁹ Encapsulating chemotherapeutic drugs and ILs within tetradecanol can increase drug loading capacity and reduce leakage during transport, further minimizing toxicity. Upon reaching the tumor site, tetradecanol melts under MWA temperatures (>45 °C), releasing the encapsulated drugs.^{180,181} Long et al. co-loaded [Bmim][PF₆] and Dox into hollow ZrO₂ NPs.¹⁸⁰ These NPs were then sealed with tetradecanol, generating IL-DOX-PCM@ZrO₂ NPs.¹⁸⁰ Under microwave irradiation, IL-DOX-PCM@ZrO₂ NPs accumulated in murine HCC significantly increased ablation efficiency, elevating the ablation temperature to 58 °C.¹⁸⁰ Concurrently, MWA-induced rearrangement of structural proteins within HCC cells enhanced transmembrane transport, leading to increased uptake of Dox, augmenting the chemotherapeutic effect.¹⁸⁰ Furthermore, Long et al. developed an intelligent triple-stimuli-responsive drug delivery system (designated X@BB-ZrO₂ NPs) based on ZrO₂ NPs (where 'X' represents the loaded components: IL, Dox, keratin, and tetradecanol).¹⁸¹ The disulfide bonds within keratin are readily cleaved under reducing conditions, while its carboxyl groups are susceptible to disruption in the mildly acidic TME.¹⁸² Therefore, keratin was selected as the pH/GSH stimulus-responsive component for X@BB-ZrO₂ NPs.¹⁸¹ X@BB-ZrO₂ NPs enhanced the efficacy of MWA under microwave irradiation and the TME, while simultaneously releasing Dox.¹⁸¹ These NPs increased ablation efficiency in animal models of HCC.¹⁸¹ The "dual protection" afforded by keratin and tetradecanol enabled precise Dox release, minimizing systemic side effects.¹⁸¹ X@BB-ZrO₂ NPs also enhanced CT imaging capability, facilitating the monitoring of orthotopic HCC growth in rabbits.¹⁸¹

In addition to Dox loading, Chen et al. designed mitochondria-targeting ZrO₂ NPs (MZCNs).¹⁸³ The MZCNs are composed of ZrO₂ NPs encapsulating [Bmim][PF₆], the mitochondrial-targeting molecule triphenylphosphonium (TPP), and the integrin-targeting peptide iRGD.¹⁸³ MZCNs target the mitochondria of HCC cells.¹⁸³ Under MWA, they induce mitochondrial dysfunction, leading to apoptosis of HCC cells and enhancing MWA efficiency.¹⁸³ Furthermore, Wu et al. loaded ROS-generating liquid metal and [Bmim][PF₆] into ZrO₂ NPs.¹⁸⁴ PEGylation was performed to enhance biocompatibility, constructing PEG-IL-LM-ZrO₂ supernanoparticles (SNPs).¹⁸⁴ IL-LM-ZrO₂ SNPs generate ROS specifically upon microwave irradiation and elevate the ablation temperature, achieving combined MWA and MDT to suppress growth in murine models of HCC.¹⁸⁴ IL-LM-ZrO₂ SNPs also enhance CT imaging capability, enabling real-time visual monitoring of therapeutic efficacy.¹⁸⁴ Notably, the IL loaded onto ZrO₂ NPs and the IL cation discussed in "IL-loaded sensitizing

nanomaterials enhance MWA for HCC" are both based on the Bmim structure. Bmim, while being an efficient sensitizer for MWA, induces cell inactivation by disrupting cellular structures, exhibiting certain biological toxicity.¹⁸⁵ Therefore, future efforts should focus on reducing the toxicity of Bmim-based ILs to facilitate their clinical translation.

MoS₂ nanosheets enhance MWA for HCC. MoS₂ nanosheets, a member of the transition metal dichalcogenide family, exhibit excellent microwave absorption properties.¹⁸⁶ This property stems from defect-induced dipole polarization generated by Mo and S vacancies, coupled with their high specific surface area.¹⁸⁷ Additionally, MoS₂ possesses superior CT imaging enhancement capabilities, enabling real-time monitoring of tumor ablation therapy.¹⁸⁸ However, their biocompatibility raises significant concerns (Figure 3, Tables 1 & S1).¹⁸⁹ To address this limitation, Fu et al. developed a unique microwave embolic agent by encapsulating MoS₂ nanosheets within sodium alginate microcapsules.¹⁹⁰ These MoS₂-loaded sodium alginate microcapsules (MSMCs) demonstrated good microwave sensitivity and exhibited strong contrast enhancement in CT imaging, achieving selective occlusion of HCC-feeding arteries.¹⁹⁰ The embolized MSMCs distribute uniformly throughout the periphery and interior of the tumor in animal models, contributing to enhanced MWA efficacy.¹⁹⁰ Owing to the dual effects of microwave sensitivity and embolization, MSMCs generate large ablation zones under microwave irradiation, resulting in significant tumor suppression.¹⁹⁰ Furthermore, Tang et al. utilized mPEG-PLGA microcapsules to co-load Dox, MoS₂ nanosheets, and the MRI contrast agent Fe₃O₄ NPs, forming mPEG-PLGA@DMF microcapsules.¹⁹¹ Delivered via catheter-mediated superselection of tumor-feeding arteries, these microcapsules effectively occluded the tumor vasculature.¹⁹¹ Under microwave irradiation, the aggregated mPEG-PLGA@DMF microcapsules exhibited potent ablation effects and promoted the release of Dox.¹⁹¹ This strategy achieved a triple-combination therapy integrating TAE, MWA, and chemotherapy for animal HCC models, increasing the average necrotic area and tumor suppression rate by 129.33% and 73.46%, respectively.¹⁹¹ mPEG-PLGA@DMF microcapsules also enhanced dual-modal MR/CT imaging capabilities, guiding synergistic treatment and predicting post-treatment tumor progression.¹⁹¹

Nanomaterial-mediated TME modulation to enhance MWA in HCC

Nanomaterial-mediated tumor cell modulation to enhance MWA in HCC. Most current studies focus on immune cells, fibroblasts, and endothelial cells in the TME, while overlooking the role of tumor cells themselves. Therefore, directly targeting tumor cells to inhibit their proliferation and metastatic behavior is an effective approach (Figure 4, Tables 1 & S1). Shen et al. synthesized an acid-responsive double-network hydrogel composed of oxidized dextran (OD) and hemin-chitosan (HCS), which was loaded with cholesterol oxidase (COD) modified with dimethylmaleic anhydride (DA), forming DA-COD-OD-HCS hydrogels.¹⁹² After MWA, HCC cells generated an acidic residual TME enriched with cholesterol-containing tumor debris.¹⁹² Upon local injection of DA-COD-OD-HCS hydrogels, DA-COD released COD under acidic conditions, degrading cholesterol in tumor debris and producing H₂O₂ and 4-cholesten-3-one.¹⁹² Based on the antitumor effects of 4-cholesten-3-one, hemin further reacted with H₂O₂ via the Fenton reaction, inducing ferroptosis in residual tumor cells and generating DAMPs.¹⁹² Among these DAMPs, HMGB1 recruited immature DCs to the residual tumor site, increasing effector T cell infiltration and promoting the secretion of tumor necrosis factor α (TNF- α) and IFN- γ cytokines, further inhibiting residual tumors and distant metastases.¹⁹²

Moreover, Duan et al. developed PEG-dipalmitoylphosphatidylethanolamine (mPEG-DPPE) calcium phosphate NPs loaded with As₂O₃, which were encapsulated in an injectable thermosensitive hydrogel, ANPs-Gel.¹⁹³ ANPs-Gel enhanced autophagy in tumor cells, induced apoptosis, and suppressed epithelial-mesenchymal transition, thereby inhibiting tumor growth and metastasis in animal models of HCC.¹⁹³ In this study, US-guided MWA was employed to precisely locate liver tumors, ensuring treatment accuracy. Furthermore, Sonovue, a sulfur hexafluoride-based microbubble contrast agent, was used in contrast-enhanced US (CEUS) to assess tumor blood flow and angiogenesis.¹⁹³ However, this study did not incorporate microbubbles or other contrast agents with US imaging enhancement capabilities into the hydrogel, which may limit the application of hydrogels for US-guided thera-

pies. In the future, integrating US contrast agents into hydrogels could simplify operational procedures and reduce trauma caused by repeated contrast agent injections, providing a more efficient and precise solution for US-guided tumor treatment.

Nanomaterial-mediated DC modulation to enhance MWA in HCC. MWA induces necrosis of HCC cells, leading to the release of TAAs and DAMPs.¹¹ This promotes the recruitment and activation of DCs into the TME, facilitating T-cell maturation and immune responses.¹¹ However, these immunogenic effects elicited by local ablation are relatively weak and insufficient to meet the requirements for sustaining antitumor effects and preventing recurrence.¹⁹⁴ Only ~30% of patients develop an immune response following MWA, achieving long-term remission and improved disease-free survival.¹⁹⁵ Clinical trials have demonstrated that MWA combined with cellular immunotherapy, including DCs, cytokine-induced killer cells, and CTLs, significantly improves the percentage of peripheral blood lymphocytes.¹⁹⁶ The combination of MWA with PD-1 blocking agents, such as nivolumab or pembrolizumab, enhances response rates and improves survival outcomes in patients with advanced HCC.¹⁹⁷ The synergistic antitumor activity achieved by combining DCs- cytokine-induced killer cell therapy with MWA markedly diminishes recurrence risk and prolongs disease-free survival.¹⁹⁸ Unlike the sequential therapies explored in basic and clinical research, the combination of nanomaterials with ablation can exert synergistic antitumor effects, yielding therapeutic outcomes that surpass the additive effects of individual treatments.¹⁹⁹ Given the pivotal role of DCs in the TME of HCC post-MWA, nanomaterial design primarily focuses on promoting DC maturation through TAAs or DAMPs (Figure 4, Table 1).

Zhu et al. designed an alginate hydrogel co-loaded with Ca²⁺ and the STING agonist Mn²⁺, termed ALG-Ca-Mn gel.²⁰⁰ The combination of ALG-Ca-Mn gel and MWA enhanced microwave heating, increased Hsp70 expression, elevated ROS levels, and induced oxidative stress.²⁰⁰ This oxidative stress led to disruption of calcium homeostasis and mitochondrial damage, resulting in ICD of HCC cells and the release of DAMPs such as CRT, high mobility group box 1 (HMGB1), and ATP.²⁰⁰ These DAMPs were taken up by immature DCs.²⁰⁰ Concurrently, ALG-Ca-Mn gel activated the cGAS/STING signaling pathway, promoting the release of IFN-I.²⁰⁰ IFN-I facilitated DCs maturation, activated CD8⁺ T cells, and induced the generation of memory T cells.²⁰⁰ IFN-I also promoted the repolarization of M2 phenotype TAMs to the M1 phenotype, further inhibiting tumor growth.²⁰⁰ Furthermore, Zhou et al. designed mannose-derived carbon dots (Man-CDs), which capture the DAMPs released by HCC cells following MWA.²⁰¹ After MWA of HCC, DAMPs released by tumor cells can be effectively captured by intratumorally administered Man-CDs.²⁰¹ Man-CDs target DCs via mannose receptors, enhancing their ability to process and present TAAs, thereby activating T cells and suppressing both primary HCC and metastases.²⁰¹ Additionally, Li et al. investigated the conjugation of small nanovesicles (smDVs) derived from mature DCs with CTLA-4 antibody, forming smDV- α CTLA-4.²⁰² Combining smDV- α CTLA-4 with tumor-infiltrating lymphocytes effectively killed residual HCC cells post-ablation.²⁰² Collectively, these nanomaterials enhance DC stimulation by DAMPs, promote DC maturation and TAA processing capacity, and activate T cells and other tumor-killing cells, suppressing HCC. Determining which specific DAMP within the post-MWA immune microenvironment contributes most significantly to DC maturation warrants further investigation to guide future nanomaterial design.

Nanomaterial-mediated metabolite modulation to enhance MWA in HCC. Lactate, as a key metabolite in the TME, shapes the TME through its effects on different cellular populations.²⁰³ In tumor cells, lactate influences signaling pathways, enhances the lactate shuttle, increases resistance to oxidative stress, and promotes lactylation.²⁰⁴ Across different cell populations, interactions between lactate and immune cells govern processes such as cell differentiation, immune responses, immune surveillance, and therapeutic efficacy.²⁰⁴ Owing to the rapid proliferation of tumor cells, the TME is characterized by hypoxia, acidity, and nutrient deprivation.²⁰⁵ These features result in metabolic reprogramming of tumor cells within the TME, promoting tumor progression.²⁰⁶ Chen et al. found that in mouse HCC tissues after incomplete microwave ablation, the increased expression of key glycolytic proteins—glucose transporter-1 (GLUT-1) and lactate dehydrogenase A (LDHA)—was driven by hypoxia-inducible factor 1 α (HIF-1 α).²⁰⁷ This led to the

accumulation of lactate in the TME, which in turn led to the polarization of macrophages toward the pro-tumoral M2 phenotype, proliferation of Tregs, and reduced infiltration of CTLs.²⁰⁷ To address this, the authors designed a nanomaterial to deplete lactate. They physically mixed hollow mesoporous MnO₂ NPs, loaded with lactate oxidase (LOX), with a precursor solution of poly (lactic acid-PEG)-poly (lactic acid-PEG) (PLGA-PEG-PLGA) to form LOX-MnO₂@Gel.²⁰⁷ Under MWA, LOX-MnO₂ NPs were gradually released from the hydrogel, and LOX catalyzed the oxidation of lactate into pyruvate and H₂O₂, while consuming O₂.²⁰⁷ MnO₂ NPs exhibited peroxidase-like activity, catalyzing the decomposition of H₂O₂ into O₂ and water, thereby providing the oxygen required for LOX and sustaining the catalytic reaction.²⁰⁷ Local lactate depletion mediated by LOX-MnO₂@Gel reduced the proportions of M2 phenotype TAMs and Tregs, restored intratumoral CTLs function, and, in combination with an anti-PD-1 antibody, suppressed HCC recurrence after incomplete microwave ablation.²⁰⁷ Future studies should further explore the specific mechanisms by which LOX-MnO₂@Gel modulates the TME, including its effects on immune cell subpopulations and tumor metabolic pathways. Notably, nanozymes have emerged as versatile tools to reshape the TME through broader metabolic interventions.²⁰⁸ By mimicking glucose oxidase, peroxidase, and glutathione oxidase activities, certain nanozymes deplete glutamine or reprogram glycine, serine, and threonine metabolism, thereby depriving tumor cells of essential amino acids and disrupting redox homeostasis.^{208,209} Meanwhile, other nanozyme platforms induce lipid peroxidation and trigger non-apoptotic cell death pathways such as ferroptosis and cuproptosis, which amplify immunogenic cell death and promote DC maturation.²¹⁰ These multi-pronged metabolic and oxidative stress interventions work synergistically to repolarize M2 macrophages toward an M1 phenotype, restore CTL effector function, and overcome the immunosuppressive barrier that limits post-ablation outcomes.^{208,209}

MWA achieves tumor ablation through high-frequency electromagnetic energy; however, its efficacy is limited by tumor size and the risk of complications. The introduction of nanomaterials has significantly enhanced the thermal effects and targeting capabilities of MWA, while improving the outcomes of combination therapies. Nanomaterials loaded with microwave sensitizers or chemotherapeutic agents have increased the ablation efficiency of MWA and optimized the therapeutic process through real-time imaging guidance. Additionally, immunomodulatory nanomaterials further enhance the anti-tumor effects of MWA by promoting DCs maturation, the death of tumor cells, and the consumption of metabolites. Despite these advancements, challenges such as material toxicity and insufficient targeting remain to be addressed. Future studies should focus on developing low-toxicity, highly targeted, and multimodal-integrated nanomaterials, aiming to enhance clinical applicability and improve outcomes for patients with HCC.

MWA, microwave ablation; HCC, hepatocellular carcinoma; DCs, dendritic cells; TAMs, tumor associated macrophages; TME, tumor microenvironment; ICD, immunogenic cell death; EMT, epithelial-mesenchymal transition; ROS, reactive oxygen species; Hsp70, heat shock protein 70; cGAS, cyclic GMP-AMP synthase; STING, stimulator of Interferon Genes; IFN- γ , type I interferon; TNF- α , tumor necrosis factor α ; DAMPs, damage-associated molecular patterns; Tregs, regulatory T cells; mDC, mature DC; iDC, immature DC; M1, M1 phenotype TAMs; M2, M2 phenotype TAMs; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; ALG-Ca-Mn gel, alginate hydrogel co-loaded with Ca²⁺ and Mn²⁺; Man-CDs, Mannose-derived carbon dots; DAMPs, damage-associated molecular patterns; smDV- α CTLA-4, small dendritic cell nanovesicles conjugated with anti-CTLA-4 antibody; LOX-MnO₂@Gel, Lactate oxidase-loaded hollow mesoporous MnO₂ nanoparticles embedded in a hydrogel composite system; sSiO₂NPs, solid silica nanoparticles; ANPs-Gel, As₂O₃-NPs encapsulated within an injectable thermo-responsive hydrogel.

NANOMATERIALS ENHANCE PTT FOR HCC

PTT is a minimally invasive ablation modality that converts near-infrared (NIR) light into localized heat, resulting in tumor cell death through coagulative necrosis or apoptosis.²¹¹ The advantages of PTT include reduced patient pain, shorter treatment duration, significant therapeutic efficacy, and the generally non-toxic and harmless nature of most photoabsorbers, resulting in minimal side effects.²¹² However, the therapeutic mechanisms underlying PTT remain unelucidated, and the penetration depth of NIR light is limited to

~1 cm, which may hinder effective irradiation of deep-seated tissues.²¹³ Moreover, the *in vivo* distribution and potential toxicity of these materials have not been thoroughly investigated.²¹³ Therefore, the photothermal conversion efficiency, selective uptake, and biosafety of PTAs remain key research focuses in the PTT treatment of HCC.²¹⁴ Given its minimally invasive nature and spatial specificity, PTA-based PTT has been widely explored in numerous preclinical studies.²¹⁵ According to their chemical composition, these NIR-absorbing PTAs can be categorized into metal-based nanomaterials, carbon-based nanomaterials, black phosphorus (BP) nanomaterials, conjugated polymers (CPs), and nanomaterials loaded with small-molecule dyes. In the following sections, we will review recent advances in the development of these PTAs for enhancing PTT for HCC ablation. Furthermore, we discuss how PTT induces ICD in HCC cells and the subsequent activation of antitumor immune responses (Figures 5–8, Table 1).

Metal nanomaterials enhance PTT for HCC

Au-based nanomaterials enhance PTT for HCC. The fundamental properties of GNPs have been introduced in "Au-Based Nanoparticles Enhance RFA for HCC." GNPs are considered ideal photothermal transducers based on their ability to strongly absorb NIR light, a property attributed to their unique structural dimensions.²¹⁶ The optical properties of GNPs depend on SPR.²¹⁷ During SPR, Au electrons resonate with incident radiation, allowing the Au electrons to absorb and scatter light.²¹⁸ This leads to the collective oscillation of free electrons within the metallic nanostructure.²¹⁹ Resonance occurs when the frequency of the external light matches the natural frequency of the free electrons, a process known as SPR.²¹⁹ Upon irradiation of GNPs with NIR light at wavelengths close to their plasmon resonance, the absorbed light energy can be converted into heat, resulting in irreversible cellular damage.²²⁰ Furthermore, certain specially shaped GNPs possess a photon capture cross-section that is four to five times larger than that of conventional photothermal dyes.²¹⁷ These properties enable GNPs to generate heat at accumulation sites under NIR irradiation, thereby facilitating cell destruction or drug release.⁵⁸ Furthermore, GNPs exhibit tunable properties, allowing for the synthesis of NPs with specific sizes and desired shapes. This flexibility allows for the adjustment of the SPR-matched external light source range from 520 nm to 800–1200 nm, optimizing their photothermal performance.²¹⁸ Various types of GNPs, such as Au nanorods (GNRs), Au nanospheres, Au nanostars (GNSSs), and Au nanocages, have been effective tools for PTT in cancer therapy.²¹⁶ In the following sections, we will discuss the roles of these materials in enhancing PTT for HCC (Figure 5, Tables 1 & S1).

GNRs are quasi-one-dimensional, rod-shaped GNPs.²²¹ Owing to their highly tunable morphology, unique anisotropic optical properties, and adjustable plasmon resonance wavelengths, GNRs have attracted significant attention in the biomedical field.²²² The structural anisotropy of GNRs results in transverse and longitudinal SPR modes.²²³ With an increasing aspect ratio, the longitudinal SPR peak can be linearly tuned from the visible to the NIR region.²²⁴ At the longitudinal dipole plasmon wavelength, the ends of GNRs exhibit significant electromagnetic field enhancement and a large extinction cross-section.²²⁴ These properties endow GNRs with high photothermal conversion efficiency, which can be further optimized through rational structural design.²²⁵

Based on the excellent PTT performance of GNRs, Li et al. developed GNRs surface-modified with PEG and the tumor-targeting protein lactoferrin (LF), designated GNR70@PEG-LF.²²⁶ Compared with unmodified GNRs, GNR70@PEG-LF exhibits a longer half-life *in vivo*, prolonged accumulation in HCC tissues, and significantly enhanced PTT sensitization effects in animal models of HCC.²²⁶ These effects may be attributed to the improved stability conferred by PEG and LF-mediated targeted uptake by HCC cells.²²⁶ Moreover, the photothermal effect of GNRs can be utilized for controlled drug release; hence, they are often designed as drug carriers to reduce toxicity and achieve precise spatiotemporal release.²²³ Locatelli et al. designed polymeric micelles loaded with Dox and surface-modified with anti-epithelial cell adhesion molecule (EpCAM) antibody and GNRs (Adr/GNRs@PMs-antiEpCAM).²²⁷ This system targets HCC via anti-EpCAM recognition of EpCAM on cancer stem cells.²²⁷ Upon laser irradiation, GNRs generate high temperatures, induce cell membrane poration, and promote selective release of Dox at the tumor site, thereby enhancing cytotoxicity.²²⁷

Furthermore, Cui et al. constructed a composite nanoplateform (AuHNR@ γ -Fe₂O₃@Lenvatinib@ β -Glucan, AFLG) consisting of Au hollow nanorods (AuHNR) as the core, coated with γ -Fe₂O₃, loaded with lenvatinib, and surface-modified with β -1,3-glucan.²²⁸ β -Glucan can be recognized by the C-type lectin receptor Dectin-1 on DCs and macrophages, achieving targeted delivery to tumor tissues.²²⁸ Lenvatinib is sustainably released at the tumor site, inhibiting tumor angiogenesis.²²⁸ Under NIR-II laser irradiation, AFLG efficiently converts light energy into heat, resulting in direct ablation of tumor cells.²²⁸ Additionally, β -glucan can enhance anti-tumor immune responses by inducing the polarization of immunosuppressive M2 phenotype TAMs to pro-inflammatory M1 phenotype. This polarization enhances T cell-mediated immune cytotoxicity, promotes DC maturation, and CLT cell activation.²²⁸ AFLG can also be used for magnetic resonance T2-weighted imaging and photoacoustic imaging (PAI), facilitating preoperative localization and intraoperative navigation.²²⁸ Despite the excellent imaging capabilities and photothermal conversion efficiency of GNRs, they have not yet entered clinical trials.²²¹ This limitation stems from the potential risk of long-term toxicity caused by *in vivo* accumulation and the fact that complex surface modifications, while reducing toxicity, may compromise their stability.^{221,229} Therefore, future research should develop GNRs with low toxicity, high water solubility, and high stability, as well as systematic studies of their biodistribution, toxicity, and pharmacokinetic profiles.

Compared to GNRs, Au nanospheres exhibit lower photothermal conversion efficiency due to their isotropic structure, resulting in limited PTT sensitization.²³⁰ Drug-loaded nanomaterials administered via the hepatic artery in combination with PTT can block tumor arterial blood supply through the EPR, increase local chemotherapeutic drug concentration, and reduce side effects, thereby achieving synergistic effects of TACE and ablation therapy.²³¹⁻²³³ This approach relies on the EPR to block tumor arterial blood supply and enhances local drug concentration and reduces side effects, compensating for the design limitations of Au nanospheres and improving the efficacy of HCC treatment. In this context, Li et al. designed hollow Au nanospheres loaded with Dox and coated with PEG, referred to as Dox@PEG-HAuNS.²³⁴ When mixed with iodized oil and administered via the hepatic artery, Dox@PEG-HAuNS can embolize tumor vessels and enhance NPs uptake and retention in the tumor.²³⁴ Subsequent PTT further suppresses HCC growth.²³⁴ In addition, Dox@PEG-HAuNS can enhance PET/CT imaging, enabling quantitative analysis of NPs uptake.²³⁴ Owing to their longer half-life, Au nanospheres possess superior imaging capabilities.²³⁵ Therefore, the combination of Au nanospheres with TACE and PTT holds promising prospects for intraoperative tumor contouring and treatment.

GNSs are Au nanomaterials with sharp tips and heterogeneous structures, resembling sea urchins.²³⁶ Their high aspect ratio and optical properties are similar to those of GNSs but with a smaller radius.²³⁷⁻²³⁹ The multiple sharp spikes of GNSs produce a "lightning rod" effect, significantly enhancing the local electromagnetic field and improving photothermal conversion efficiency.²⁴⁰⁻²⁴² The plasmon resonance wavelength of GNSs can be tuned from 700 to 1,100 nm, which falls within the "tissue optical window," facilitating deep tissue penetration of NIR light and efficient heat accumulation within tumors.²⁴³ Li et al. developed polydopamine (PDA)-coated GNSs conjugated with RGD peptides (Au@PDA-RGD NPs), which achieved HCC targeting via iRGD and, in combination with PTT, reduced mitochondrial membrane potential, increased lysosomal permeability, induced apoptosis and autophagy, and inhibited tumor growth.²⁴⁴ Although autophagy can function as both a tumor suppressor and promoter in HCC,²⁴⁵ this study did not further investigate its role in Au@PDA-RGD NPs-mediated PTT. Notably, individual nanostars are processed via the lysosomal pathway after cellular uptake.²³⁶ While aggregation may occur during this process, no evidence of endolysosomal escape has been observed.²³⁶ Future studies should focus on optimizing nanostar structures to enhance PTT ablation efficiency and regulate lysosomal responses in tumor cells.

Au nanocages are hollow Au-based nanomaterials characterized by ultra-thin porous walls.²⁴⁶ Similar to other GNPs, Au nanocages exhibit excellent photothermal conversion efficiency.²⁴⁷ Their unique structure allows precise tuning of their plasmon resonance wavelength to any desired point in the NIR region.²⁴⁸ The hollow interior and porous walls provide an ideal space for drug loading and controlled release, increasing drug payload and preventing

premature release.²⁴⁹ Therefore, Au nanocages have been applied as drug carriers and PTT sensitizers in HCC ablation therapy. Xu et al. designed Au nanocages loaded with Dox and coated with HCC cell membranes, designated DOX@CAuNCs.²⁵⁰ The cell membrane coating reduces macrophage phagocytosis, prolongs circulation time, and enhances uptake by tumor cells.²⁵⁰ Under NIR irradiation, DOX@CAuNCs convert light into heat and release Dox.²⁵⁰ Notably, the HCC cell membranes coating can also alleviate AuNCs-induced *in vivo* inflammatory responses.²⁵⁰ Overall, Au nanocages hold great translational potential; however, like other nanomaterials, their clinical application will largely depend on their *in vivo* biodistribution and pharmacokinetics.²⁴⁹ By optimizing size and surface chemistry, Au nanocages can achieve favorable biodistribution, minimal nonspecific accumulation in healthy tissues, and enhanced clearance via physiological systems.²⁴⁹

Other GNPs have also been investigated for PTT enhancement. Wang et al. utilized GNPs to coat mesoporous silica NPs loaded with Sor, termed SO-Au-MSN, which facilitated Sor accumulation in HCC cells and induced apoptosis under NIR irradiation.²⁵¹ Furthermore, BSA-conjugated GNPs (BSA-GNPs) have been reported to selectively accumulate in *ex vivo* human HCC tissues and achieve PTT upon infrared irradiation.²⁵² However, the specific type of Au nanomaterial was not specified in this study. Notably, the use of patient-derived tissues strengthens the translational relevance of these findings. Various Au nanomaterials, with their excellent photothermal conversion efficiency, drug-loading capacity, and tumor-targeting ability, significantly enhance the synergistic effect of PTT and chemotherapy, and also offer multifunctionality for imaging guidance. Nevertheless, their clinical translation still faces challenges such as biosafety, *in vivo* distribution, and long-term toxicity, necessitating further optimization and in-depth investigation.

HCC, hepatocellular carcinoma; PTT, photothermal ablation; GNR70@PEG-LF, GNRs surface-modified with PEG and LF; Adr/GNRs@PMS-antiEpCAM, polymeric micelles loaded with Dox and surface-modified with anti-epithelial cell adhesion molecule antibody and GNRs; AFLG, AuHNR@ γ -Fe₂O₃@Lenvatinib@ β -Glucan; Au@PDA-RGD NPs, polydopamine-coated GNSs conjugated with RGD peptides; DOX@CAuNCs, Au nanocages loaded with Dox and coated with HCC cell membranes; SO-Au-MSN, GNPs to coat mesoporous silica NPs loaded with sorafenib; BSA-GNPs, bovine serum albumin-conjugated GNPs; PBNPs, Prussian Blue NPs; SP94-PB-SF-Cy5.5 NPs, PBNPs were conjugated with Sor, SP94, and Cy5.5; 131I-HCuSNPs-MS-PTX, PLGA microspheres encapsulating hollow CuS nanoparticles and PTX, labeled with radioactive iodine-131; PEG-modified Dox-loaded MSN @CuS nanohybrids, PEG-modified Dox-loaded mesoporous silica nanoparticle@CuS nanohybrids; CuS@pda/PAA/DOX/GPC3, CuS@PDA nanocapsules loaded with Dox, PAA and anti-GPC3 antibodies; CuSNC@DOX/MnO₂-NS, hollow mesoporous CuS nanocages encapsulating Dox and further coated with MnO₂ nanoshells; CuSNC, hollow mesoporous CuS nanocages; CuS-SF@CMV, CuS nanoparticles encapsulating Sor and coated with a cancer cell-macrophage hybrid membrane, further modified with anti-VEGFR antibodies; CuS-ATMi@TGF- β NPs, ataxia telangiectasia mutated inhibitor-loaded hollow-structured CuS nanoparticles with surface modification with anti-TGF- β antibody; LMHSs, MoS₂ hollow spheres; DOX@ MoS₂ NPs, MoS₂ hollow spheres loaded with Dox; UiO-66/Bi₂S₃@DOX, compositing the MOF, UiO-66, with Bi₂S₃ and loading them with Dox; GPMQNs, graphene-P-gp loaded with miR-122-indium phosphide core and ZnS shell quantum dot nanocomposites.

Inorganic nonmetallic nanomaterials enhance PTT for HCC

Prussian blue nanoparticles (PBNPs) enhance PTT for HCC. PBNPs are nanomaterials composed of ferrocyanide, characterized by their unique structure and multifunctionality.²⁵³ The three-dimensional cubic porous network of Prussian blue endows it with significant application potential in fields such as chemical sensing, catalysis, gas storage, and drug delivery.²⁵⁴ Functionally, PBNPs exhibit excellent photothermal conversion efficiency and MRI properties, making them highly valuable in cancer PTT and imaging.²⁵⁵ The photothermal conversion capability of PBNPs is primarily attributed to their strong optical absorption in the NIR region, enabling efficient conversion of absorbed light into heat energy.²⁵⁶ Notably, the heat generated by PBNPs under NIR irradiation can induce localized hyperthermia, effectively destroying tumor cells while minimizing damage to surrounding healthy tissues.^{240,257} The paramagnetic properties of PBNPs enable them to enhance the contrast of MRI

images, further increasing their value in the field of imaging.²⁵⁸ Moreover, surface modification strategies allow PBNPs to achieve efficient drug-loading and controlled drug release, which significantly enhances the therapeutic efficacy of chemotherapy.²⁵⁹ Additionally, PBNPs exhibit excellent biocompatibility, low toxicity, and biodegradability (Figure 5, Tables 1 & S1).^{253,255}

Based on these properties, studies have explored the therapeutic efficacy of PBNPs administered via tumor-feeding arteries in animal models. Pang et al. demonstrated the rapid and effective delivery of PBNPs into HCC tissues in rabbits via the hepatic artery, followed by NIR irradiation to perform PTT.²⁶⁰ PBNP-mediated PTT effectively ablated primary tumors and activated CTLs, thereby suppressing the growth of distant tumors.²⁶⁰ Additionally, Zhou et al. developed SP94-PB-SF-Cy5.5 NPs, a multifunctional platform where PBNPs were conjugated with Sor, an HCC-specific targeting peptide SP94, and a NIR dye Cy5.5.²⁶¹ MRI and PAI confirmed the targeted accumulation of SP94-PB-SF-Cy5.5 NPs in HCC tissues.²⁶¹ Under NIR irradiation, this platform achieved PTT and simultaneously released Sor.²⁶¹ Moreover, the peroxidase-like activity and photothermal effects of PBNPs alleviated tumor hypoxia, improved the immunosuppressive TME, reduced M2 phenotype TAMs, promoted DCs maturation, and increased CTL tumor infiltration.²⁶¹ When combined with an anti-PD-L1 monoclonal antibody, the local antitumor effects were extended systemically, inducing long-term immune memory and inhibiting tumor metastasis and recurrence.²⁶¹

In summary, PBNPs exhibit enhanced PTT efficacy and TME modulation to improve the outcomes of immunotherapy in HCC treatment. Although PBNPs have been approved by the FDA as a clinical antidote for thallium and other radioactive element poisoning,²⁶² their biosafety still requires further optimization. High accumulation of intravenously administered PBNPs in mice may pose potential risks to the liver and lungs.²⁶³ Nevertheless, PBNPs demonstrate good biocompatibility and safety, particularly at low doses.²⁶³ Looking forward, strategies such as arterial targeted delivery, surface modification, and component optimization are expected to further enhance the biosafety of PBNPs, promoting their clinical translation in HCC therapy.

Metal sulfide nanomaterials enhance PTT for HCC. CuS NPs are p-type semiconductors and an important class of transition metal sulfides.²⁶⁴ CuS NPs exhibit excellent optical properties and photothermal conversion capabilities, with a photothermal conversion efficiency of up to 71.4%.²⁶⁵ Mechanistically, CuS NPs can absorb light in the NIR region (700–1100 nm) and convert light energy into heat through the vibrational energy of the d-d transition of Cu²⁺ ions.^{264,266} Additionally, the optical properties of CuS NPs can be modulated by altering their chemical composition.^{267,268} Specifically, the local SPR of CuS NPs can be regulated in the NIR region via redox reactions.^{267,269} Moreover, CuS NPs exhibit low toxicity, low synthesis cost, and ease of preparation.^{270,271} These features make CuS NPs highly effective in PTT, enabling the efficient ablation of tumor cells.²⁷² Furthermore, CuS NPs can be combined with other therapeutic agents to form multifunctional nanoplateforms, enhancing the synergistic effects of chemotherapy and PTT.²⁷³ This section will introduce CuS NPs loaded with antitumor drugs such as paclitaxel (PTX), Dox, Sor, and ataxia telangiectasia mutated (ATM) inhibitors to enhance PTT for HCC treatment.

PTX-loaded CuS NPs have been designed to improve the efficacy of PTT. Liu et al. developed PLGA microspheres encapsulating hollow CuS NPs (HCuSNPs) and PTX, labeled with radioactive ¹³¹I, forming ¹³¹I-HCuSNPs-MS-PTX.²⁷⁴ After intra-arterial injection, ¹³¹I-HCuSNPs-MS-PTX embolized the tumor blood vessels.²⁷⁴ Single photon emission computed tomography (SPECT)/CT and PAI confirmed the targeted delivery of microspheres to tumors, enabling preoperative PTT planning through dual imaging.²⁷⁴ Under NIR laser irradiation, ¹³¹I-HCuSNPs-MS-PTX achieved photothermal conversion and released PTX.²⁷⁴ The microspheres provided localized chemotherapy, phototherapy, and radiotherapy, effectively ablating transplanted tumors.²⁷⁴ Notably, PTX is not a first-line chemotherapy drug for HCC, whereas Dox is commonly used in TACE.²⁷⁵ Therefore, many studies have explored the combination of Dox with CuS NPs (Figure 5, Table 1).

Wu et al. designed PEG-modified Dox-loaded MSN@CuS nanohybrids.²⁷⁶ Dox was stably stored in the inner pores of MSN, while CuS NPs on the surface exhibited high photothermal conversion efficiency and heat-mediated controlled Dox.²⁷⁶ However, this study only provided *in vitro* data, and the antitumor efficacy in animal models remains unclear. To further investigate

the antitumor efficiency of Dox-loaded CuS NPs, Yang et al. developed CuS@PDA nanocapsules loaded with Dox and surface-modified with polyacrylic acid (PAA) and anti-glypican-3 (GPC3) antibodies, forming CuS@PDA/PAA/DOX/GPC3.²⁷⁷ This nanoplateform targeted HCC cells via the high expression of GPC3 on their surface and released Dox in acidic TME.²⁷⁷ PAA and CuS enhanced PTT efficacy in animal models.²⁷⁷ Additionally, Lin et al. designed hollow mesoporous CuS nanocages (CuSNC) encapsulating Dox and further coated with MnO₂ nanoshells (MnO₂-NS), forming CuSNC@DOX/MnO₂-NS.²⁷⁸ In tumor tissues, GSH and H⁺ decomposed MnO₂-NS into paramagnetic Mn²⁺, enabling dual imaging via MRI and fluorescence imaging (FI) for pre-ablation tumor localization.²⁷⁸ The acidic TME also promoted Dox release.²⁷⁸ Under NIR irradiation, CuSNC enhanced PTT, achieving guided imaging, chemotherapy, and PTT synergistically.²⁷⁸ These studies reveal that TME-triggered drug release may be more effective than ablation heat-induced release.

In addition to CuS NPs loaded with chemotherapeutics, studies have also explored their combination with targeted therapies. Sor is a small-molecule multi-kinase oral targeted drug,²⁷⁹ approved by the FDA as a first-line treatment for HCC.²⁸⁰ Ji et al. designed hollow CuS NPs encapsulating Sor and coated with a cancer cell-macrophage hybrid membrane, further modified with anti-vascular endothelial growth factor receptor (VEGFR) antibodies, forming CuS-SF@CMV.²⁸¹ The VEGFR antibodies and hybrid membrane coating enhanced the homotypic targeting capability of CuS-SF@CMV NPs toward HCC cells, enabling more efficient accumulation of NPs within tumor cells.²⁸¹ Under NIR laser irradiation, CuS NPs achieved photothermal conversion, rapidly increasing the local tumor temperature to levels sufficient to kill tumor cells.²⁸¹ The VEGFR antibodies and Sor inhibited tumor cell proliferation and angiogenesis by suppressing the Rat Sarcoma virus (Ras)/Rapidly Accelerated Fibrosarcoma (Raf)/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) and PI3K/AKT pathways.²⁸¹ CuS-SF@CMV NPs achieved a synergistic effect of PTT and targeted therapy by rapidly killing tumor cells and persistently inhibiting tumor cell growth, thereby improving therapeutic outcomes.²⁸¹ Notably, acquired resistance to Sor remains a major challenge in the management of HCC.²⁸² Therefore, future research should focus on how Sor-loaded CuS NPs can simultaneously enhance PTT and overcome Sor resistance.

CuS NPs also load small-molecule inhibitors efficiently. KU6001 is a novel and highly specific ATM kinase inhibitor,²⁸³ which effectively enhances DNA damage in HCC cells by inhibiting ATM.²⁸⁴ Cai et al. designed ATM inhibitor-loaded hollow-structured CuS NPs with surface modification using anti-TGF- β antibodies, forming CuS-ATMi@TGF- β NPs.²⁸⁵ CuS-ATMi@TGF- β NPs targeted tumor cells via anti-TGF- β antibodies.²⁸⁵ Under NIR irradiation, low-temperature PTT was achieved, causing minimal damage to normal tissues while activating CD4⁺ and CD8⁺ T cells.²⁸⁵ Moreover, PTT and ATM inhibitors downregulated the expression of Hsp70 and Hsp90, increased the transcription of tumor suppressor genes, and reduced the transcription of tumor-associated genes.²⁸⁵ Although CuS NPs are generally considered less toxic than other Cu-based NPs owing to their low solubility, they may still induce cytotoxicity at higher doses through oxidative stress and inflammation.²⁸⁶ To advance the clinical application of CuS NPs, it is necessary to optimize their design and dosage, enhance their renal clearance, improve the selectivity of delivery systems, and minimize potential toxicity.²⁷⁰

Other metal sulfide nanomaterials enhance PTT for HCC. Metal sulfide NPs are also highly efficient PTAs.²¹⁴ Their biotoxicity can be reduced through encapsulation or surface modification.²¹⁴ In addition to CuS NPs and PB NPs, MoS₂, Bi₂S₃, and ZnS are also promising metal-based nanomaterials for enhanced PTT. MoS₂ exhibits excellent photothermal conversion efficiency and can be used for both PTT and light-responsive drug release.²⁸⁷ Furthermore, MoS₂ can adsorb biomolecules and drug molecules via covalent or non-covalent interactions, thereby improving its targeting ability and drug loading capacity (Figure 5, Table 1).²⁸⁸ Tan et al. designed MoS₂ hollow spheres (LMHSs) to enhance PTT for the ablation of HCC tissues in animal models.²⁸⁹ Guided by digital subtraction angiography (DSA), infrared imaging, and CT, LMHSs were administered via the tumor artery and effectively killed tumor cells and inhibited their growth without damaging surrounding healthy tissues.²⁸⁹ Additionally, Li et al. developed MoS₂ hollow spheres loaded with Dox (DOX@MoS₂ NPs).²⁹⁰ Under NIR irradiation, DOX@MoS₂ NPs exhibited

excellent PTT effects, achieving a complete response with no recurrence in an animal HCC model.²⁹⁰ Therefore, future studies should focus on developing more MoS₂-based nanomaterials combined with PTT to explore their role in tumor ablation therapy.

As a metal sulfide, Bi₂S₃ also possesses high photothermal conversion efficiency and has shown potential for PTT in tumors.²⁹¹ It can achieve effective tumor ablation under relatively low laser intensity.²⁹² Liu et al. designed multifunctional NPs, UiO-66/Bi₂S₃@DOX, by integrating the MOF, UiO-66, with Bi₂S₃ and loading them with Dox.²⁹³ When administered via arterial pathways, these NPs accumulated in tumor tissues.²⁹³ In the acidic TME, UiO-66 degraded, releasing Bi₂S₃ and Dox.²⁹³ Bi₂S₃ demonstrated excellent photothermal conversion efficiency, converting NIR light into thermal energy to generate high temperatures and kill tumor cells.²⁹³ Furthermore, PTT enhanced the cytotoxicity of Dox, thereby improving the efficacy of chemotherapy.²⁹³

ZnS-based nanomaterials can effectively convert light energy into thermal energy under NIR irradiation, achieving efficient ablation of tumor cells.²⁹⁴⁻²⁹⁶ Based on this, Zeng et al. designed graphene-P-gp loaded with miR-122-indium phosphide core and ZnS shell quantum dot nanocomposites (GPMQNs).²⁹⁷ GPMQNs utilized P-gp antibodies for active targeting of HCC cells, enhancing tumor imaging depth and three-dimensional imaging capabilities, and improving preoperative imaging for PTT.²⁹⁷ The high concentration of GSH in tumor tissues promoted the release of miR-122, which upregulated the expression of tumor suppressor gene p53 and apoptosis-related gene Bcl, thereby inducing apoptosis in HCC cells.²⁹⁷ Under NIR irradiation, GPMQNs generated a photothermal effect, further killing HCC cells.²⁹⁷

In summary, metal nanomaterials are ideal candidates for PTT owing to their excellent optical and thermal properties. First, metal nanomaterials exhibit strong SPR effects, allowing them to effectively absorb NIR light and convert it into thermal energy. This property enables precise heating of tumor sites without damaging surrounding normal tissues, thereby achieving tumor cell ablation.^{298,299} Additionally, advancements in the synthesis and functionalization of metal nanomaterials have enabled their combination with other treatment modalities, such as TACE and chemotherapy. In practical applications, the biocompatibility and biodegradability of metal nanomaterials are critical research focuses. Surface modification of metal nanomaterials can significantly improve their stability and tumor-targeting ability *in vivo*. This reduces side effects, enhances treatment safety, and facilitates their clinical translation.^{300,301} Overall, metal nanomaterials hold great promise for PTT in HCC. With continuous technological advancements, these materials are expected to play a greater role in clinical treatments, providing safer and more effective therapeutic options for patients with HCC.³⁰²

Carbon-based nanomaterials enhance PTT for HCC. Carbon-based nanomaterials are nanoscale materials composed of carbon elements, including fullerene, CNTs, graphene, and carbon quantum dots.³⁰³ These materials exhibit remarkable properties in biological photothermal conversion, primarily due to their high surface area and excellent light absorption capabilities, enabling the absorption of a broad spectrum of light and enhancing photothermal conversion efficiency.³⁰⁴ Moreover, the structure and surface properties of carbon-based nanomaterials can be regulated through chemical modification, further improving their photothermal conversion efficiency.³⁰⁵ They also possess exceptional thermal conductivity.³⁰⁶ Represented by graphene, carbon-based nanomaterials are widely used in cancer PTT owing to their efficient photothermal conversion capabilities.^{307,308} Under NIR irradiation, these materials rapidly heat up, enabling effective PTT against tumor cells.^{307,308} They also exhibit good stability and low toxicity during photothermal conversion, making them ideal candidates for PTT.³⁰⁹ Through rational design and functionalization, carbon-based nanomaterials can be employed for PTT and integrated with other diagnostic and therapeutic modalities, such as imaging guidance and chemotherapy, to construct multifunctional therapeutic platforms.

Gong et al. successfully developed a novel multifunctional hybrid material by modifying magnetic graphene oxide (MGO) with trimethyl cholic acid (TCA) and folic acid (FA), and loading Dox, forming MGO-TCA-FA@DOX nanocomposites.³¹⁰ The modification with FA and TCA enabled MGO-TCA-FA@DOX to specifically target HCC cells, enhancing the material's accumulation at tumor sites.³¹⁰ Under NIR irradiation, MGO-TCA-FA@DOX killed HCC

cells through enhanced photothermal effects and triggered controlled release of Dox, thereby improving chemotherapy efficacy.³¹⁰ Additionally, Hu et al. developed MnO/nitrogen-doped carbon composite NPs (MnO-N/C NPs), which are nanocomposites of Mn oxide and nitrogen-doped carbon.³¹¹ MnO-N/C NPs exhibit peroxidase, oxidase, and catalase-like activities along with photothermal conversion effects and enhanced MRI T1 imaging capabilities.³¹¹ Through their multi-enzyme-like activities and photothermal conversion properties, MnO-N/C NPs demonstrated significant antitumor effects in HCC treatment.³¹¹ Their T1-weighted MRI imaging capability further improved treatment precision and real-time monitoring.³¹¹ The combined application of MnO-N/C NPs with PTT significantly enhanced tumor inhibition rates while causing minimal damage to normal tissues, indicating good biosafety.³¹¹

The clinical translation of carbon-based nanomaterials is limited by concerns of safety, efficacy, and production feasibility. The biocompatibility and potential toxicity of carbon-based nanomaterials are critical issues for clinical applications. Their distribution, clearance mechanisms, and long-term fate *in vivo* remain unclear, which may lead to potential toxicity concerns.³¹² Additionally, ensuring the stability and functionality of carbon-based nanomaterials *in vivo* remains a major challenge.³⁰⁹ Furthermore, their application in cancer treatment faces difficulties in effectively targeting the TME, necessitating precise adjustments in material design.³¹³ From a production perspective, the complexity and diversity of carbon-based nanomaterials pose challenges in achieving consistency and reproducibility during manufacturing.³¹⁴ In conclusion, the challenges of clinical translation for carbon-based nanomaterials are multifaceted, requiring comprehensive consideration and coordination in material design, biocompatibility, safety assessment, and production processes to achieve their broad application in medicine.³¹⁵

BP nanosheets (BPNSs) enhance PTT for HCC. BPNSs, also known as phosphorene, are a novel two-dimensional material and hold promise for overcoming the limitations of graphene and transition metal dichalcogenides.³¹⁶ In phosphorene, each phosphorus atom is covalently bonded to three neighboring phosphorus atoms, forming bilayer and puckered structures along the zigzag and armchair directions, respectively.³¹⁷ This structural anisotropy contributes to its unique properties, including photothermal and photodynamic performance,³¹⁸ mechanical properties,³¹⁹ and thermoelectric properties.³²⁰ Moreover, owing to their distinctive layered structure, BPNSs possess a high surface-to-volume ratio, making them suitable for drug loading and delivery,³²¹ and providing new options for PTT in tumor therapy (Figure 6, Tables 1 & S1).

Yang et al. designed a two-dimensional layered BPNS loaded with Sor and an anti-PD-L1 antibody to form a photothermal-boosted NanoBike (BPSP).³²² NIR-II-activated BPSPs can mediate PTT and remodel the extracellular matrix by depleting collagen I, thereby promoting deep penetration of therapeutic drugs and immune cells.³²² PTT facilitates the release of Sor from BPSP, exerting anti-angiogenic effects, and downregulating PD-L1 expression by inhibiting the RAS/RAF/ERK pathway, thereby enhancing the efficacy of anti-PD-L1 antibody and overcoming immune escape.³²² Anti-PD-L1 antibodies can block PD-1/PD-L1 recognition, and PTT-induced ICD further increases the response rate to anti-PD-L1 antibodies.³²² Jia et al. introduced Au-thiosugar-modified BPNS, termed BP-Au-thiosugar nanosheets (BATNS).³²³ Compared to bare BPNS, BATNS exhibited improved photostability, NIR absorption properties, and photothermal conversion efficiency under 808 nm irradiation.³²³ In addition, BATNS-enhanced PTT-induced tumor cell killing was associated with increased NK cell infiltration.³²³

Although BP nanomaterials possess good biodegradability and biocompatibility, they are still in the early stages of development compared to other well-studied two-dimensional nanomaterials.³²⁴ To achieve the clinical translation of phosphorene, the following three aspects must be studied: (1) further exploration of various biological responses upon contact with BPNS; (2) improvement of the synthesis efficiency, physiological stability, and functionality of BP nanomaterials; (3) more comprehensive studies on their long-term effects *in vivo* and their ecological impact.³²¹

Melanin-like nanomaterials enhance PTT for HCC. Melanin is a biopolymer primarily formed by the polymerization of phenolic compounds via quinone intermediates.³²⁵ Melanin and its synthetic analogs, such as PDA nanomaterials, can convert NIR light into heat, thereby selectively killing

tumor cells.³²⁶ As a synthetic melanin, PDA nanomaterials possess a tunable polymerization process, including surface coating and conjugation.³²⁷ Therefore, PDA nanomaterials can not only sensitize PTT in HCC but also be combined with other materials to further enhance therapeutic efficacy (Figure 6, Tables 1 & S1).

Wu et al. designed core-shell nanocomposites consisting of SPION clusters coated with PDA, designated SPIONs clusters@PDA.³²⁸ The surface was further modified with PEG and loaded with the PTA indocyanine green (ICG) to form SPION clusters@PDA-PEG@ICG (SCPPI).³²⁸ With a magnet implanted at the HCC site in animal models, T2-weighted MRI demonstrated the accumulation of SCPPI at the tumor site.³²⁸ Under NIR laser irradiation, SCPPI exhibited excellent PTT effects.³²⁸ Additionally, Yuan et al. developed nanocubes of α -Fe₂O₃ coated with PDA and loaded with Dox (Fe₂O₃-PDA-Dox).³²⁹ In this study, the vascular disrupting agent combretastatin A-4 phosphate disodium (CA4P) was first administered via hepatic artery injection.³²⁹ Subsequently, Fe₂O₃-PDA-Dox was injected through the artery under MRI guidance.³²⁹ Upon NIR irradiation, PTT was achieved, triggering the release of Dox.³²⁹ This strategy enabled a targeted therapy, TAE, and PTT combination, demonstrating favorable efficacy in animal models.³²⁹ However, in clinical applications, considering patient tolerance, guidelines recommend discontinuing targeted drugs three days prior to TACE treatment.³³⁰ Furthermore, Hu et al. designed SOR@ZIF-8@PDA (SZP), a kind of nanomaterial in which the Sor is encapsulated within ZIF-8 and coated with a PDA layer.³³¹ SZP releases Sor in acidic TME and under laser irradiation.³³¹ SZP also promotes apoptosis, inhibits HCC cell proliferation and migration, thereby suppressing tumor growth.³³¹

In addition to serving as a surface coating, PDA can also act as the core of nanomaterials. Yu et al. constructed PDA@Ag@GOx by using PDA as the core, *in situ* synthesizing AgNPs on the surface, and loading glucose oxidase (GOx).³³² The AgNPs in PDA@Ag@GOx enhanced the non-radiative conversion of PDA under NIR irradiation, improving photothermal conversion efficiency.³³² GOx catalyzes the production of H₂O₂ from glucose, which activates the otherwise non-toxic AgNPs to release toxic Ag⁺, enabling activated metal ion therapy.³³² Moreover, GOx interferes with glucose metabolism in tumor cells, reducing the synthesis of Hsps, which lowers the thermal resistance of tumor cells and further enhances PTT efficacy.³³² Notably, *in vivo* experiments demonstrated that PDA@Ag@GOx exhibited good biocompatibility and low toxicity.³³² This indicates that PDA@Ag@GOx accumulates in tumor tissues, and the toxic side effects of Ag⁺ on other organs are minimal. Furthermore, Qi et al. designed a platinum-doped PDA nanomaterial (Pt@PDA-c) surface-modified with anti-C-X-C chemokine receptor type 4 (CXCR4) antibodies.³³³ The anti-CXCR4 antibody targets HCC cells and exerts anti-tumor effects.³³³ EPR enhances photoacoustic CT imaging, improves the imaging of small HCC, and confirms the accumulation of nanomaterials.³³³ Under NIR irradiation, PDA exhibits high photothermal conversion efficiency, further inhibiting the growth of HCC.³³³

Although melanin-like materials represented by PDA have shown great potential in PTT and drug delivery systems, their pharmacokinetics, long-term toxicity, and degradation characteristics need to be studied further before their potential clinical application can be fully evaluated. Moreover, most current melanin and melanin-like materials are hydrophobic, necessitating chemical modification for practical use, which adds complexity to their implementation.³²⁵ Based on these issues, future research should focus on establishing standardized procedures for the synthesis of melanin-like materials, exploring the structure of PDA, and examining emerging data on the toxicity of melanin-based materials prior to their widespread application.³²⁵ Although numerous reports have demonstrated the excellent biocompatibility of PDA, studies reporting adverse effects associated with PDA exist, which may impact its clinical application.³³⁴

CPs enhance PTT for HCC. CPs are a class of hydrophobic π -conjugated backbone organic polymers with modifiable properties.³³⁵ The unpaired carbon electrons (π electrons) are located in out-of-plane pz orbitals, which are mobile and easily delocalized and excited.³³⁶ Upon excitation with photon energy, these π electrons undergo internal conversion to the lowest singlet excited state (S1) and then relax to the ground state via non-radiative pathways, generating heat.³³⁷⁻³³⁹ CPs also possess excellent photostability and biodegradability.^{340,341} As such, they have been applied in cancer PTT.^{342,343}

Additionally, CPs exhibit outstanding PAI capabilities. Reportedly, on an equal mass basis, CPs can provide stronger PA signals than GNRs and CNTs.³⁴⁴ CPs also serve as excellent drug carriers.³⁴⁵ However, traditional CPs tend to form aggregates in aqueous solutions, resulting in diminished ROS generation and aggregation-caused quenching, limiting their potential biomedical applications.³⁴⁶ The development of CP NPs has addressed these limitations. The following sections introduce the applications of polypyrrole (PPy) and polyaniline (PANI) nanomaterials in PTT for HCC (Figure 6, Tables 1 & S1).

PPy is formed by the oxidative polymerization of pyrrole using FeCl₃,³⁴⁷ and exhibits good biocompatibility.³⁴⁸ The transitions between π and π^* bonds in PPy enable strong and broad absorption in the NIR region, conferring excellent photothermal conversion ability suitable for PTT.^{349,350} However, the poor water solubility of PPy greatly limits its application.³⁵¹ To address this, Wu et al. encapsulated PPy NPs and Dox within a platelet membrane, forming PLT-PPy-DOX.³⁵² PLT-PPy-DOX demonstrated good stability, immune evasion, and tumor-targeting, accumulating in HCC tissues.³⁵² Upon 808 nm laser irradiation, PLT-PPy-DOX enhanced PTT sensitivity and increased Dox release.³⁵² This combination of localized chemotherapy and PTT exhibited excellent anti-tumor efficacy in inhibiting tumor growth and metastasis.³⁵² Similarly, Hu et al. used disulfide-crosslinked carboxymethyl cellulose (CMC) to encapsulate chitosan NPs loaded with PPy and 5-fluorouracil (5Fu), forming CMC/CS@PPy+5Fu NPs.³⁵³ In the acidic TME, the disulfide bonds in CMC/CS@PPy+5Fu NPs break, releasing CS@PPy+5Fu NPs.³⁵³ Under NIR irradiation, CS@PPy + 5Fu NPs enhance PTT and release 5Fu, achieving combined PTT and chemotherapy in animal HCC models.³⁵³

Despite the rapid progress in PPy nanomaterial research, many challenges remain. Future development of PPy derivatives should focus on the design of new monomers and improvements in synthetic methods to precisely control their structure and morphology, optimizing performance and expanding applications.³⁵⁴ Furthermore, the accuracy of role definition and experimental reproducibility needs to be improved, as these factors impact mechanistic studies.³⁵⁵ Combining PPy nanomaterials with other suitable components, such as Au, may form PPy-Au nanocomposites, which will yield materials more suitable for PTT applications.^{355,356}

PANI is a chemically stable, conductive π -conjugated polymer.³⁵⁷ In the presence of oxidizing agents or under acidic conditions, PANI undergoes oxidation state changes, shifting its absorption peak from the visible to the NIR region.^{358,359} Furthermore, PANI exhibits low toxicity and good biocompatibility,³⁶⁰ which promotes its application in tumor PTT.³⁶¹ Unlike organic dyes, PANI shows excellent photostability under irradiation, enabling multiple rounds of PTT.³³⁶ However, the NIR absorption of PANI occurs at pH < 4, which is lower than the acidity of the TME.³⁶² Therefore, it is necessary to combine PANI with other materials to enhance its PTT sensitization effect. In this context, Tian et al. designed HPW@PANI Nanorods by oxidatively polymerizing aniline with phosphotungstic acid as an acid catalyst and ammonium persulfate to synthesize PANI nanorods.³⁶³ HPW@PANI Nanorods were administered via hepatic artery into rabbit HCC tissues.³⁶³ Under NIR-II irradiation, HPW@PANI Nanorods achieved enhanced PTT effects.³⁶³ Combining PTT with HPW@PANI Nanorods increased CD8⁺ T cell infiltration, elicited a specific immune response, and subsequently inhibited distant tumor growth and peritoneal metastasis.³⁶³ However, the mechanism underlying CD8⁺ T cell infiltration was not further explored.

There is significant scope for future research on PANI. First, for clinical translation, detailed data on the long-term toxicity, biodistribution, and biodegradation of PANI are needed.³³⁶ Second, the number of studies on PANI-based PTT remains limited.³³⁶ Furthermore, PANI possesses unique pH-responsive photothermal properties, which should be further explored and utilized in the design of therapeutic nanomaterials.³³⁶

PTT, photothermal ablation; HCC, hepatocellular carcinoma; BPNSs, Black phosphorus nanosheets; CPs, conjugated polymers; MGO-TCA-FA@DOX nanocomposites, multifunctional hybrid material by modifying magnetic graphene oxide with trimethyl cholic acid and folic acid, and loading Dox; MnO-N/C NPs, MnO/nitrogen-doped carbon composite nanoparticles; BPSP, black phosphorus nanosheets loaded with Sor and anti-PD-L1 antibodies to form photothermal-boosted NanoBike; BATNS, BP-Au-thiosugar nanosheets; SCPPI, SPIONs clusters@PDA-PEG@ICG; Fe₂O₃-PDA-Dox, nanocubes of α -Fe₂O₃ coated with PDA and loaded with Dox; CA4P, combretastatin A-4 phosphate.

phate disodium; SZP, SOR@ZIF-8@PDA; PDA@Ag@GOx, PDA as the core for the in situ synthesis of AgNPs on its surface, followed by the loading of GOx; Pt@PDA-c, platinum-doped PDA nanomaterial; PLT-PPy-DOX, polypyrrole nanoparticles and Dox encapsulated within a platelet membrane; CMC/CS@PPy+5Fu NPs, carboxymethyl cellulose to encapsulate chitosan NPs loaded with PPy and 5-fluorouracil; HPW@PANI Nanorods, oxidatively polymerizing aniline with phosphotungstic acid as an acid catalyst and ammonium persulfate to synthesize PANI nanorods.

Nanomaterials loaded with small-molecule dyes enhance PTT for HCC

Nanomaterials loaded with ICG enhance PTT for HCC. ICG is a water-soluble tri-carbocyanine NIR dye.³⁶⁴ Owing to its low toxicity, ICG was approved by the FDA for clinical use as early as the 1960s.³⁶⁵ Composed of a polycyclic structure connected by long carbon chains, ICG exhibits excellent photothermal conversion efficiency.³⁶⁴ The peak absorption wavelength of ICG in plasma is ~800 nm, while its fluorescence emission wavelength is ~810 nm in water and 830 nm in blood.³⁶⁶ These wavelengths fall within the "optical window of biological tissues," allowing ICG to penetrate the skin and function in deep tissues such as the liver.³⁶⁷ Moreover, ICG has a moderate fluorescence quantum yield and serves as a contrast agent for PAI.³⁶⁸ However, ICG is limited by instability, short half-life *in vivo*, aggregation tendency, and limited tumor-targeting capability, which restrict its applications in tumor PTT.³⁶⁹ Loading ICG into NPs can enhance its stability, prolong its blood circulation time, and improve tumor accumulation.³⁷⁰ Consequently, various ICG-loaded nanomaterials have been developed to enhance PTT efficacy for HCC (Figure 7, Table 1).

Zhang et al. developed FA-modified polymeric micelles co-loaded with Dox and ICG, termed FA Co-PMs.³⁷¹ FA Co-PMs targeted HCC cells via FA and precisely released Dox and ICG in response to the acidic and reductive TME.³⁷¹ The PTT enhanced by ICG improved thermal efficiency and further boosted intracellular uptake and therapeutic efficacy of Dox.³⁷¹ This combination therapy effectively inhibited HCC growth in animal models while reducing toxicity to normal tissues.³⁷¹ In addition to FA modification, another study has employed anti-EpCAM antibodies to target HCC tissues. Huang et al. designed ICG-CuS-Gd@BSA-EpCAM NPs composed of CuS-Gd@BSA cores modified with anti-EpCAM and ICG.³⁷² These NPs exhibited FI, MRI, and PAI tri-modal functionalities, enabling the targeting and detection of HCC tumors smaller than 1 cm.³⁷² Under 808 nm NIR irradiation, ICG-CuS-Gd@BSA-EpCAM NPs enhanced PTT to eradicate HCC cells.³⁷² Notably, anti-EpCAM primarily targets epithelial cells, while human HCC tissues exhibit remarkable heterogeneity and lack EpCAM expression on their surface.³⁷³ Therefore, the application of anti-EpCAM should consider patient selection and verify its targeting efficiency using different models. Moreover, a study conjugated ICG derivatives, specifically ICG-COOH, with supramolecular β -cyclodextrin and co-loaded them with the chemotherapeutic drug etoposide, forming ICG-CD@EPS.³⁷⁴ Upon laser irradiation, ICG-CD@EPS enhanced PTT to eliminate HCC cells,³⁷⁴ while achieving localized etoposide release in HCC, strengthening chemotherapy efficacy and reducing side effects.³⁷⁴ In addition to ICG-COOH, other ICG derivatives, such as IR780 and IR820, have been explored for PTT, which will be discussed below.

Nanomaterials loaded with IR780 enhance PTT for HCC. IR780 is a lipophilic heptamethine cyanine NIR dye that exhibits higher fluorescence intensity and better stability than the clinically approved ICG.³⁷⁵ IR780's intrinsic tumor-targeting capability plays a critical role in image-guided phototherapy.³⁷⁶ However, limitations such as poor solubility, rapid clearance, acute toxicity, and low tumor uptake may restrict its applications.³⁷⁵ Nanomaterials can overcome these limitations. Based on this, Ma et al. designed mesoporous silica NPs loaded with IR780 and coated with CAR-T cell membranes to form CIMs.³⁷⁷ CIMs utilize the targeting capability of CAR-T cell membranes to specifically recognize and accumulate at GPC3-expressing HCC cells.³⁷⁷ Under 808 nm laser irradiation, CIMs effectively convert light energy into heat, leading to thermal damage and death of HCC cells, thereby inhibiting tumor growth and metastasis.³⁷⁷ Furthermore, the IR780 dye in CIMs emits fluorescence under NIR irradiation, enabling real-time monitoring of tumor imaging and therapeutic effects, which facilitates the evaluation of treatment efficacy.³⁷⁷ Notably, not all HCC tumors exhibit high GPC3 expression.³⁷⁸ Therefore, variations in GPC3 expression levels in HCC are the most

critical determinants influencing the delivery efficiency of CIMs (Figure 7, Tables 1 & S1).

Zhang et al. designed Gox-loaded Fe_3O_4 NPs, modified with red blood cell membranes and IR780, termed FGIR.³⁷⁹ The red blood cell membranes on FGIR extended NP circulation time *in vivo* and improved IR780 dispersion, enabling enhanced PTT under NIR irradiation.³⁷⁹ Upon accumulation at tumor sites, GOx consumed glucose, reducing the expression of glucose transporter 1 and further inhibiting glucose uptake in tumor cells, leading to decreased ATP production and reduced synthesis of Hsp70 and Hsp90.³⁷⁹ The reduction in Hsp70 and Hsp90 sensitized HCC cells to IR780-mediated PTT.³⁷⁹ Additionally, H_2O_2 generated during GOx catalysis and the photothermal effect of IR780 intensified the Fe_3O_4 -mediated Fenton reaction.³⁷⁹ Importantly, IR780 can act as an ICD inducer to trigger T cell-mediated anti-tumor immune responses.³⁸⁰ Future research should focus on the immune effects induced by IR780-loaded nanomaterials.

Nanomaterials loaded with IR820 enhance PTT for HCC. Similar to IR780, IR820 is a heptamethine cyanine NIR dye.³⁸¹ It is an FDA-approved analogue of ICG,³⁸² and exhibits excellent optical properties and photothermal conversion efficiency.³⁸³ Additionally, IR820 serves as an effective NIR-II FI and PAI agent for preoperative tumor imaging.³⁸¹ However, IR820 is limited by low tumor-targeting capability, photobleaching, and short half-life.³⁸⁴ Loading IR820 into nanomaterials can improve its optical properties and tumor-targeting ability (Figure 7, Tables 1 & S1).^{383,384}

Annexin A2 (AXL), a receptor tyrosine kinase, regulates the survival, invasiveness, and drug resistance of various human cancers, including HCC.³⁸⁵ Overexpression of AXL in HCC is closely associated with lower 5-year survival rates due to resistance to targeted therapy or chemotherapy.³⁸⁶ Growth arrest-specific protein 6 (Gas6) is the natural ligand of AXL.³⁸⁷ Accordingly, Zhang et al. designed Gas6-expressing cell membrane nanovesicles encapsulating IR820, termed G-Nvs@IR820.³⁸⁸ G-Nvs@IR820 targeted tumor tissues and provided high-resolution fluorescence and photoacoustic signals to guide precise ablation of cancerous tissues while sparing adjacent normal tissues during PTT.³⁸⁸ To enhance PTT efficiency, Chen et al. designed IR820-PEG-MNPs, which were self-assembled from PEG-modified melanin NPs and IR820 molecules.³⁸⁹ IR820-PEG-MNPs enabled PAI and MRI-guided imaging to detect tumors as small as 1.8 mm.³⁸⁹ Under NIR irradiation, IR820-PEG-MNPs effectively inhibited HCC.³⁸⁹ Additionally, Li et al. developed IR820@PEG-SPIO composed of superparamagnetic iron oxide (SPIO) cores modified with IR820.³⁹⁰ This combination targeted HCC and enabled FL/PAI/MRI-guided imaging to detect tumors smaller than 2 mm in diameter.³⁹⁰ Moreover, IR820@PEG-SPIO exhibited excellent photothermal conversion efficiency, improving laparoscopic PTT efficacy.³⁹⁰ Currently, clinical studies of ICG-enhanced PTT primarily focus on inflammatory diseases such as periodontitis and peri-implant mucositis.³⁹¹ The therapeutic efficacy of ICG-enhanced PTT in patients with metastatic melanoma and breast cancer has been reported.³⁹² Future clinical trials are needed to explore the potential of ICG and its derivatives in combined PTT for HCC.

Nanomaterial-mediated TME modulation to enhance PTT in HCC

Nanomaterial-mediated T/NK-cell modulation to enhance PTT in HCC. T cell-mediated cytotoxicity is critical in immunotherapy for HCC.³⁹³ T cells primarily include CD8⁺ T cells and CD4⁺ T cells.³⁹⁴ CD8⁺ T cells kill HCC cells by secreting cytokines such as granzyme-B, CXCL10, TNF- α , and IFN- γ .³⁹⁴ HCC cells or other cells can suppress CD8⁺ T cell infiltration and anti-tumor activity by expressing PD-1 or PD-L1.³⁹⁵ Therefore, immunotherapy for HCC often employs PD-1 or PD-L1 monoclonal antibodies.⁶ Similarly, immune checkpoints such as CTLA-4 and lymphocyte-activation gene 3 also regulate CD8⁺ T cells in HCC.³⁹⁶ CD4⁺ T cells can enhance the activation of CD8⁺ T cells, killing HCC cells.³⁹⁷ Moreover, a subset of CD4⁺ T cells, Tregs, suppresses cancer immunosurveillance and promotes HCC progression and metastasis.³⁹⁸ Single-cell RNA sequencing has confirmed reduced infiltration and increased proportion of exhausted CD8⁺ T cells in HCC tissues from patients.³⁹⁹ Exhausted T cells exhibit reduced activity and efficacy under chronic antigen stimulation, limiting their tumor response and contributing to disease progression.⁴⁰⁰ Furthermore, Treg infiltration among CD4⁺ T cells is increased.³⁹⁹ Thus, reactivating T cell immune cytotoxicity and promoting T cell infiltration are crucial for killing HCC cells and reversing the immunosuppressive TME.

Nuclear Receptor Subfamily 2 Group F Member 6 (NR2F6) is an orphan nuclear receptor that inhibits the transcription of cytokines such as IL-2, IL-17, and IFN- γ in T cells.⁴⁰¹ As an emerging immune checkpoint inhibitor,⁴⁰² NR2F6 regulates immune function by suppressing T cell cytotoxicity and promoting tumor progression. Additionally, its inhibition can enhance the anti-tumor effects of PD-L1 blockade.⁴⁰³ Therefore, silencing the immunosuppressive NR2F6 is an attractive strategy to overcome tumor-associated immune suppression (Figure 8, Tables 1 & S1).⁴⁰⁴ In this context, Lu et al. developed CoCuFe-LDHs loaded with Nr2f6-siRNA and coated with PEG-dimethyl maleic anhydride, forming CS@P.⁴⁰⁵ In the acidic TME, PEG-dimethyl maleic anhydride separates from the positively charged LDHs.⁴⁰⁵ Leveraging the property of positively charged substances being absorbed by tumor cells, LDHs carrying Nr2f6-siRNA enhanced tumor accumulation and cellular uptake.⁴⁰⁵ Under NIR laser irradiation, CS@P sensitized PTT,⁴⁰⁵ Nr2f6-siRNA inhibited HCC cell proliferation and metastasis by promoting the release of TNF- α , IL-2, and IFN- γ from T cells.⁴⁰⁵ Combined with an anti-PD-L1 antibody, CS@P suppressed both primary and distant tumors, preventing metastasis.⁴⁰⁵ The clinical success of immunotherapy demonstrates the advantages of regulating T cell responses in HCC treatment; however, many patients still develop resistance.⁴⁰⁶ Gene editing therapies can target virtually any T cell gene to improve T cell function and overcome immune suppression in the TME.⁴⁰⁶ Compared to RNA editing, DNA editing technologies such as CRISPR/Cas9 offer higher specificity and sustained therapeutic benefits for cellular regulation.⁴⁰⁷ Nanomaterials loaded with CRISPR/Cas9 have been widely applied in HCC treatment, although no studies have yet explored their use in PTT.⁴⁰⁸

NK cells share a common origin with T cells, exhibit similar functions, and complement T cells in tumor immunity.⁴⁰⁹ NK cells recognize HCC cells through membrane topology, forming lytic immune synapses to exert cytotoxic effects.⁴¹⁰ NK cells also kill tumor cells by secreting IFN- γ and TNF- α .⁴¹¹ However, studies have shown that cytotoxic NK cell subsets are deficient in HCC tissues compared to peripheral tissues.⁴¹² This may be attributed to the hypoxic TME of HCC, which induces mitochondrial fragmentation in NK cells, suppressing their survival and anti-tumor capabilities.⁴¹³ Therefore, adoptive cell therapy to promote NK cell targeting of tumor tissues represents an effective strategy.

To prevent recurrence after ablation, Zhang et al. designed NK cells modified with TLS11a ligands targeting HCC specifically.⁴¹⁴ They also developed novel Mn-based self-assembled nanosheets (CONASHs) composed of Mn²⁺ and tetrahydroxyanthraquinone (THAQ) and adsorbed polyether-imide (PEI) and DNazymes targeting Hsp70 mRNA, forming DNzyme@Mn-CONASHs to enhance intraoperative imaging and therapeutic efficacy of PTT.⁴¹⁴ By integrating adoptive NK cell therapy with anti-thermal resistance PTT, this approach achieved significantly improved anti-tumor effectiveness *in vivo*.

Nanomaterial-mediated myeloid cell modulation to enhance PTT in HCC. Myeloid cells are key regulators of tumor progression, primarily including DCs, macrophages, monocytes, and mast cells.⁴¹⁵ DCs migrate from HCC tissues to LNs and recruit T and NK cells to HCC tissues to exert anti-tumor effects (Figure 8, Tables 1 & S1).⁴¹⁶ To activate DCs in LNs, Wang et al. designed liposomes assembled from ApoA-1 mimetic peptides, lipids, and DiR with FI and photothermal conversion capabilities.⁴¹⁷ These liposomes were loaded with microtubule stabilizer mertansine or STING agonist vadimezan-Chol, forming MR-sHDL or VR-sHDL.⁴¹⁷ SHDL was selectively absorbed by HCC cells, enabling imaging and enhancing PTT sensitivity.⁴¹⁷ Mertansine and vadimezan-Chol further induced ICD in HCC cells, releasing DAMPs.⁴¹⁷ This stimulated DC maturation in LNs and subsequently activated CTLs to kill HCC cells in both primary and distant tumors.⁴¹⁷ Combined with anti-PD-1 therapy, tumor growth inhibition in animal models was further enhanced.⁴¹⁷ Additionally, promoting DC maturation in the immunosuppressive microenvironment can enhance CD8⁺ T cell infiltration.⁴¹⁸ Building on this, Qiu et al. designed liposomes loaded with As₂O₃ and PFH, modified with HAuCl₄ and Crgd-sh on the surface, forming As₂O₃/PFH NPs@Au-CRGD.⁴¹⁹ As₂O₃/PFH NPs@Au-CRGD targeted HCC, sensitized PTT, and induced ferroptosis in tumor cells.⁴¹⁹ They also promoted the maturation of DCs and M1 macrophage polarization in the TME, activating naive T cells into CTLs.⁴¹⁹ Combined with anti-PD-1 therapy, tumor growth inhibition in animals was further enhanced, and lung metastasis was significantly reduced.⁴¹⁹

TAMs, in addition to DCs, play a critical role in the immune microenvironment of HCC. In addition to tumor-suppressive M1 phenotype TAMs, immunosuppressive M2 phenotype TAMs are present.⁴²⁰ M2 macrophages are enriched in HCC tissues and promote tumor invasion and metastasis through angiogenesis activation, maintaining the stemness of HCC cells.⁴²¹ Notably, lactate produced by tumors induces histone H3K18la lactylation in macrophages, activating transcription and enhancing M2 phenotype TAMs activity.⁴²² Therefore, LDH depletion can inhibit M2 phenotype TAMs. Lu et al. designed 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-PEG-cyclic arginine-glycine-aspartic acid loaded with LOX and PTA NR840, termed PLNR840.⁴²³ PLNR840 sensitized PTT and induced ICD in tumor cells.⁴²³ LOX promoted lactate depletion, thereby reducing M2 macrophage activity.⁴²³ Combined with anti-PD-L1 therapy, PLNR840 enhanced CD8⁺ T cell activity, suppressed Tregs and MDSCs, and reversed the immunosuppressive TME.⁴²³ In summary, nanomaterials indirectly or directly regulate myeloid cells to promote T cell activity when combined with anti-PD-1 or anti-PD-L1 antibodies, representing an effective anti-tumor strategy for enhanced PTT.

Currently, clinical studies have explored PTT sensitizers for HCC treatment. However, challenges such as preoperative sensitizer hypersensitivity, intraoperative dosage dependence, and prolonged postoperative photoprotection remain. Therefore, future advancements in nanotechnology are required to optimize PTT sensitizers. In practice, NIR irradiation also induces photodynamic conversion for tumor ablation. Since photodynamic therapy is not recommended by clinical guidelines in the treatment of HCC, it is not discussed in this study.

NANOMATERIALS ENHANCE HIFU FOR HCC

HIFU is a non-invasive ablation technique that utilizes acoustic energy to induce thermal tissue necrosis.⁴²⁴ HIFU generates high-intensity US beams (0.8–3.5 MHz) through a piezoelectric transducer embedded in a US scanner, which are then focused on the target area.⁴²⁵ At the focal point, the temperature rapidly rises above 60 °C within seconds, leading to irreversible cell death via coagulative necrosis, while causing minimal damage to surrounding tissues with significantly lower energy density.⁴²⁶ Owing to the highly precise focusing of US beams, this technique allows for accurate and safe thermal ablation of target tissues without causing significant damage to adjacent anatomical structures.⁴²⁷ HIFU has demonstrated potential value in treating small HCC, particularly in patients with advanced liver cirrhosis and massive ascites.⁴²⁸ Reportedly, HIFU exhibits high safety and significant short- to mid-term efficacy.⁴²⁹ Compared with other local ablation therapies, the primary advantage of HIFU lies in its completely extracorporeal nature, eliminating the need for inserting ablation needles into the target lesion.⁴³⁰ HIFU is described as a novel ablation strategy for small HCC in the clinical practice guidelines of the European Association for the Study of the Liver (EASL).⁴³¹ Additionally, HIFU has been recognized as a key method of ablation therapy in the "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer" issued by the National Health Commission of the People's Republic of China (2019 edition).⁴³² However, major HCC treatment guidelines, such as the "Guideline for the Diagnosis and Treatment of Primary Liver Cancer (2024 edition)" and the "BCLC Strategy for Prognosis Prediction and Treatment Recommendation: The 2022 Update," have not yet recommended HIFU as a standard treatment approach. This is likely because HIFU remains in its early stages of development, and its efficacy and long-term safety require further investigation.

Although a phase II clinical trial demonstrated that HIFU is safe and effective for patients who are ineligible for liver resection or RFA,⁴³³ the prolonged treatment time required for complete tumor ablation remains a limitation.⁶⁰ This limitation contributes to complications primarily associated with thermal damage induced by focused US, such as first-degree skin burns and post-treatment pain.⁴³⁴ To enhance the therapeutic efficiency of HIFU and reduce ablation time, current research has focused on combining HIFU with other technologies to improve its efficacy. As US signal enhancers, conventional microbubbles can amplify the cavitation effect and thereby augment HIFU treatment outcomes.⁴³⁵ However, owing to their limited stability and inability to penetrate vascular endothelium and accumulate effectively within tumor tissues, the application of micron-sized microbubbles is restricted.⁴³⁵ In contrast, gas-loaded Nanomaterials, with superior stability and tumor-targeting capabilities, overcome these limitations. They not only enhance the effi-

cacy of HIFU but also serve as carriers for drugs and imaging agents, achieving synergistic tumor suppression. Furthermore, nanomaterials capable of generating O₂ directly at the tumor site can significantly enhance the therapeutic effects of HIFU (Figure 9, Table 1). This section reviews recent advances in the application of nanomaterials to enhance HIFU ablation for HCC. Gas-loaded nanomaterials can possess multimodal imaging capabilities and improve the ablation efficacy of HIFU.

Gas-loaded nanomaterials enhance HIFU for HCC

Nanobubbles enhance HIFU for HCC. Nanobubbles, serving as US contrast agents, are composed of a gas-filled core such as air, oxygen, hydrogen, or carbon dioxide, encapsulated by a stable shell made of lipids, polymers, or proteins.⁴³⁶ This structure allows nanobubbles to encapsulate drugs and release them under HIFU stimulation, enhancing local drug concentration while reducing systemic side effects.⁴³⁷ Among these, lipid-based shells are particularly advantageous owing to their ease of preparation, biocompatibility, biodegradability, and non-toxicity.⁴³⁸ Recent studies have explored the use of drug-loaded nanoliposome bubbles to enhance HIFU ablation of HCC (Figure 9, Table 1).

Misra et al. designed pro-bexarotene nanobubbles (PBNBs), which encapsulate the anticancer prodrug bexarotene.⁴³⁹ Under HIFU stimulation, PBNBs rupture, allowing the prodrug to insert into the HCCs membrane and subsequently be enzymatically cleaved to release the active drug, effectively inhibiting HCC growth in mice.⁴³⁹ Similarly, Liu et al. developed cationic microbubbles (CMBs) conjugated with anti-GPC3 antibodies and the anticancer plasmid HSV-TK, forming GPC3-CMBs.⁴⁴⁰ These nanobubbles target HCC tissues owing to the high expression of GPC3 on HCC cell surfaces. Under HIFU activation, GPC3-CMBs kill tumor cells and enhance the transfection efficiency of the HSV-TK plasmid, thereby improving HIFU's therapeutic efficacy against HCC.⁴⁴⁰ The clinical translation of nanobubble technology is hindered by the absence of standardized protocols for characterizing physical properties, drug release, and acoustic instrumentation, including US parameters and experimental setups.⁴⁴¹ Establishing uniform guidelines for nanobubbles characterization, evaluation, and detailed reporting of US device specifications and parameters is essential to improve reproducibility and facilitate regulatory approval.⁴⁴¹

Perfluorocarbon (PFC)-loaded nanomaterials enhance HIFU for HCC.

PFC is a class of small synthetic molecules composed of linear or cyclic carbon backbones substituted with fluorine and other halogens.⁴⁴² This substitution fundamentally alters the physical properties of these organic compounds. Compared with carbon-containing organic substances, PFCs exhibit higher gas solubility, volatility, density, compressibility, and stability.⁴⁴³ Clinically, microbubbles containing PFCs are commonly used as US contrast agents.⁴⁴³ PFCs can stabilize the gas within microbubbles, allowing them to persist longer in the bloodstream, improving both the quality and duration of US imaging.⁴⁴⁴ Additionally, PFCs can efficiently dissolve O₂ and deliver it to tissues, alleviating tissue hypoxia.⁴⁴⁵ However, direct intravenous injection of PFCs can cause fatal vascular embolism.⁴⁴⁶ Use of PFC nanoemulsions can address this issue by preventing rapid clearance from the bloodstream and prolonging organ retention time.⁴⁴⁶ Therefore, nanomaterials loaded with PFCs can accumulate in HCC tissues, enhance US imaging capabilities, and improve the cavitation effect of HIFU (Figure 9, Table 1).

PFP is a biocompatible PFC.⁴⁴⁷ Zhao et al. utilized PLGA to encapsulate PFP, forming PLGA-PFP nanoemulsions.⁴⁴⁸ These nanoemulsions enhanced the ablation effect of HIFU on an *ex vivo* rabbit HCC model, increased the volume of necrosis, and reduced the US energy required for effective ablation.⁴⁴⁸ Given their excellent ablation enhancement potentials, tumor-targeted PFP-loaded nanomaterials combined with HIFU have also demonstrated favorable therapeutic outcomes in animal models.⁴⁴⁹ PFH is another PFC with good biocompatibility, high O₂ affinity, and large oxygen storage capacity.⁴⁵⁰ Zhang et al. designed hollow mesoporous prussian blue NPs (HMPBs) loaded with Dox and PFH, termed HMPBs-DOX/PFH.⁴⁵¹ The HMPBs demonstrated enhanced MRI T2-weighted imaging capabilities.⁴⁵¹ Therefore, HMPBs-DOX/PFH can facilitate dual-modal US and MRI, enabling the monitoring and assessment of deep tumor ablation while improving the efficacy of HIFU.⁴⁵¹ Therefore, HMPBs-DOX/PFH can facilitate dual-modal US and MRI, enabling the monitoring and assessment of deep tumor ablation while

improving the efficacy of HIFU.⁴⁵¹ Moreover, You et al. developed Fe₃O₄-PFH/PLGA nanocapsules, consisting of an Fe₃O₄ NP-loaded PFH core and encapsulated within a PLGA shell.⁴⁵² These Fe₃O₄-PFH/PLGA nanocapsules exhibited enhanced US, magnetic resonance, and PAI capabilities, which can be used to guide TAE therapy and the planning of ablation boundaries.⁴⁵² Combined with TAE, Fe₃O₄-PFH/PLGA nanocapsules further improve the efficacy of local treatment.⁴⁵² However, PFC NPs are unstable and degradable.⁴⁵³ Currently, modification of PFC NPs with biocompatible proteins and lipids can improve their stability and reduce toxicity, which is advantageous for future clinical translation.⁴⁵³

Gas-generating nanomaterials enhance HIFU for HCC

Hypoxia drives multiple malignant processes in HCC, including metabolic reprogramming, metastasis, angiogenesis, and immune evasion.⁴⁵⁴ Designing nanomaterials capable of generating O₂ can alleviate tumor hypoxia, reverse the immunosuppressive microenvironment, and subsequently inhibit HCC progression.⁴⁵⁵ In situ formation of O₂ bubbles can assist in pre-ablation tumor localization, improve the imaging quality of HIFU ablation, and enhance the therapeutic efficacy of HIFU (Figure 9, Tables 1 & S1).⁶⁰ In this context, Liao et al. designed a sonocavitation agent (SCA) composed of Mn-coordinated phthalocyanine as catalytic sites and a conjugated-layer-stacked phthalocyanine network, Mn-SCA.⁴⁵⁶ Mn-SCA features a large d-π conjugated network and atomic Mn-N sites.⁴⁵⁶ Mn-SCA catalyzes the production of O₂ cavitation nuclei from H₂O₂ within the TME. Under the action of HIFU, these O₂ cavitation nuclei release O₂, thereby promoting the generation of ROS and inhibiting tumor growth.⁴⁵⁶ However, this study did not investigate the changes in the TIME. Furthermore, the activation of HIF-1α and HIF-2α signaling pathways following HIFU ablation contributes to residual tumor recurrence.⁴⁵⁷ Sub-lethal thermal stress and residual hypoxia in the HIFU transition zone cooperatively stabilize HIF-1α, which engages a protective autophagy program co-regulated by m6A-dependent and FOXO3-mediated transcriptional networks, allowing surviving cells to clear damaged organelles and re-enter proliferation.⁴⁵⁸ By collapsing the hypoxic substrate that sustains this HIF-driven autophagy axis, O₂-generating platforms such as Mn-SCA could eliminate the metabolic refuge on which thermo-tolerant cells depend.⁴⁵⁸ Therefore, future studies should focus on the ablation process and evaluate whether O₂-generating nanomaterials can prevent postoperative recurrence.

Nanomaterials capable of generating oxygen in situ can alleviate tumor hypoxia and enhance ablation efficiency. Overall, nanomaterials offer new strategies to improve the safety and efficacy of HIFU in the treatment of HCC.

NANOMATERIALS ENHANCE MHA FOR HCC

Magnetic hyperthermia relies on the ability of magnetic nanoparticles to generate heat under an alternating magnetic field.⁴⁵⁹ Compared with PTT, MHA enables highly precise temperature control by adjusting the magnetic field intensity and magnetic medium concentration, inducing irreversible necrosis of tissues while avoiding the limitations of light penetration depth.⁴⁶⁰ Given its advantages of high biocompatibility, deep tissue penetration, and targeted tumor-killing effects, MHA has been extensively explored in preclinical studies of various tumors, including glioblastoma.⁴⁶¹ Furthermore, the accumulation of magnetic nanomaterials in tumor sites can be achieved through TACE. Therefore, the combination of TACE and MHA holds great potential for clinical applications in HCC. Currently, conventional IONPs and novel hydrogel nanomaterials have been developed to enhance MHA. The following sections will elaborate on the roles of these two materials in MHA for HCC (Figure 10, Table 1).

IONPs enhance MHA for HCC

The role of IONPs in enhancing MRI imaging and RFA has been introduced in "Iron Oxide Nanoparticles Enhance RFA for HCC." IONPs exhibit unique dynamic magnetization effects under alternating magnetic fields and can generate heat. Additionally, their high surface area allows for the loading of antitumor drugs. Based on these properties, PLGA-magnetic microspheres (PLGA-MMs) have been synthesized to enhance MHA.⁴⁶² When combined with TACE, PLGA-MMs disrupt the vasculature of HCC, leading to tumor necrosis.⁴⁶² Furthermore, a magnetic drug delivery system has been developed using micron-sized iron powder, BaFe₁₂O₁₉, and carbon-coated iron

nanocrystals (CCINs), which are loaded with epirubicin hydrochloride.⁴⁶³ After intra-arterial or intratumoral injection, this system aggregates under the influence of a magnetic field, enhancing the embolization effect on tumor vasculature and further suppressing HCC growth through MHA.⁴⁶³ Currently, TACE faces challenges in addressing the immunosuppressive TME post-treatment, which often leads to recurrence. The secondary killing effect of MHA can further inhibit tumor growth.⁴⁶⁴ Therefore, investigating how MHA regulates the TME after TACE is of significant interest for future research.

Hydrogel-enhanced MHA for HCC

Hydrogels are three-dimensional hydrophilic polymer networks capable of absorbing large amounts of biological fluids and water while maintaining structural stability.⁴⁶⁵ They possess high solvent content, porosity/permeability, and controlled-release properties for molecules.⁴⁶⁶ Hydrogels can respond to changes in stimuli such as temperature, alternating magnetic fields, and pH, exhibiting notable alterations in network structure, swelling behavior, and mechanical strength.⁴⁶⁷ Owing to their excellent biocompatibility and carrier properties, researchers have combined hydrogels with nanomaterials to form hydrogel-nanocomposite systems.⁴⁶⁸ These systems integrate the properties of hydrogels with those of the loaded nanomaterials, creating unique materials with synergistic performance. In the biomedical field, hydrogels are primarily used for wound healing, drug delivery, and PTT.⁴⁶⁸

In HCC treatment, a study designed iron oxide NPs-modified mica nanosheets linked with chitosan-gallic acid to form CG-IM hydrogels.⁴⁶⁹ This material possesses excellent mechanical properties and is suitable as an injectable.⁴⁶⁹ After minimally invasive hepatectomy for HCC, CG-IM hydrogels can be conveniently applied to seal the bleeding liver edge, followed by MHA to effectively prevent recurrence.⁴⁶⁹ Additionally, CG-IM hydrogels can be directly injected into tumors under US guidance to sensitize MHA for treating unresectable HCC.⁴⁶⁹ Another study developed injectable magnetic colloidal hydrogels (MCH) composed of superparamagnetic Fe₃O₄ NPs and gelatin NPs.⁴⁷⁰ Under CT and US guidance, MCH was injected into HCC sites in animal models, sensitizing MHA and inhibiting HCC growth.⁴⁷⁰

To specifically evaluate the clinical translation potential of these magnetothermal responsive platforms, the following study reports detailed key experimental parameters and therapeutic outcomes in animal models. Furthermore, Yang et al. developed an acid-labile thermoresponsive magnetic hydrogel (NCD) by incorporating cube-shaped iron oxide nanoparticles (CION) and DOX into a poly(N-isopropylacrylamide)-ortho ester-PEG matrix.⁴⁷¹ The acid-cleavable ortho-ester backbone drove cumulative Dox release of $77.4 \pm 2.1\%$ at pH 6.5 over 72 h – far exceeding the $25.5 \pm 2.0\%$ release at pH 7.4 – and the storage modulus fell correspondingly from $\sim 84,500$ Pa to ~ 8 Pa, reflecting progressive hydrogel disintegration.⁴⁷¹ Under AMF (30 kA/m, 312 kHz), the tumor temperature reached $\sim 46^\circ\text{C}$ within 15 min in HepG2 xenografts, and US-, MRI-, and CT-guided percutaneous delivery in orthotopic VX₂ rabbit liver tumors reduced intratumoral nuclear density from $3,087.7 \pm 235.5$ to 295.5 ± 60.7 nuclei/mm²; at the same time, NCD achieved a $57.8 \pm 1.8\%$ volume reduction in HepG2 multicellular spheroids versus only $5.8 \pm 1.1\%$ for the pH-insensitive PCD control.⁴⁷¹ Complementing this acid-responsive strategy, Chen et al. constructed a Dox-loaded ferrimagnetic polyvinyl alcohol hydrogel (FPH_{DOX}) whose hydrogen-bond crosslink density, and hence disintegration temperature, could be precisely tuned to $\sim 47^\circ\text{C}$ by adjusting PVA content to 6 wt%.⁴⁷² AMF exposure (15 kA/m) drove the tumor site to this threshold within 2 min, boosting DOX release from $\sim 8\%$ to $\sim 45\%$ within 1 h, and US-guided percutaneous injection in VX₂ rabbit models yielded substantial tumor suppression confirmed by CT monitoring and histological analysis.⁴⁷² Notably, FPH_{DOX} retained full disintegration efficacy through 3 mm of ex vivo porcine tissue under AMF, whereas near-infrared irradiation under identical conditions failed to achieve disintegration, directly demonstrating the depth-independent advantage of magnetothermal triggering for deep-seated HCC.⁴⁷²

However, in clinical applications, percutaneous injection-based ablation remains challenging for treating tumors located deep within the body or in special regions such as the portal vein. Furthermore, percutaneous injection often results in uneven nanomaterial distribution, limiting complete tumor coverage. In contrast, TACE delivers materials via blood vessels, ensuring more uniform deposition and effective embolization of tumor-feeding

vessels. Thus, combining TACE with MHA offers a more efficient and targeted therapeutic strategy.

NANOMATERIALS ENHANCE CRYOABLATION FOR HCC

Cryoablation is a technique that alternates freezing and thawing to destroy tumor tissues.¹⁹⁹ Extremely low temperatures induced by liquid nitrogen or argon gas lead to the formation of intracellular ice crystals, which disrupt cell membranes and mechanically damage critical cellular structures.⁴⁷³ During the rewarming process, ice crystals melt from larger crystals, causing additional damage to cellular structures.¹⁹⁹ Furthermore, when ice crystals melt, the extracellular fluid transitions to a low-energy state, leading to water influx into damaged cells, exacerbating cell membrane destruction.⁴⁷⁴ Additionally, the alternating freezing and thawing cycles induce small blood vessel occlusion, resulting in tumor tissue necrosis.⁴⁷⁴

Compared with thermal ablation techniques commonly used in clinical practice, such as RFA and MWA, cryoablation offers the significant advantage of “visualized ablation.” During the procedure, CT scans can be utilized to monitor the formation of the ice ball and dynamically adjust its shape and size to ensure adequate tumor coverage while avoiding excessive ablation volume or ice ball propagation to adjacent critical structures.⁴⁷⁵ Moreover, cryoablation causes minimal damage to surrounding organs and is associated with reduced intraoperative and postoperative pain. Notably, cryoablation theoretically avoids an increase in intratumoral pressure, which may prevent the spread of tumors around the portal vein.⁴⁷⁶ As a novel technique, cryoablation has been widely applied in the treatment of HCC (Figure 10, Table 1).

Currently, research on nanomaterial-enhanced cryoablation is limited. Xu et al. designed MgO NPs,⁴⁷⁷ and established a three-dimensional numerical model based on realistic geometric anatomy to characterize nanomaterial-assisted cryoablation of HCC.⁴⁷⁷ Both the ablation and freezing zones expanded with increased loading rates and ranges of MgO NPs.⁴⁷⁷ Additionally, NPs attenuated the thermal effects of blood vessels.⁴⁷⁷ Notably, cryoablation may cause bleeding and lead to hypothermic shock.⁴⁷⁸ Whether the attenuation of vascular thermal effects by MgO NPs aligns with clinical needs warrants further investigation. The limited research on nanomaterial-enhanced cryoablation for HCC may be attributed to the challenges in optimizing cryoablation parameters and establishing postoperative evaluation criteria, both requiring extensive preliminary studies and validation. Furthermore, achieving the clinically standard temperature of below -100°C during experiments is challenging. Owing to equipment limitations, controlling the ablation range during *in situ* cryoablation of HCC is difficult, resulting in a higher mortality rate. Currently, strategies for nanomaterial-enhanced cryoablation in other solid tumors include Fe₃O₄ NPs for sensitizing tumor edge capillaries,⁴⁷⁹ chemotherapy drugs targeting tumor tissues combined with cryoablation to inhibit tumor growth,⁴⁸⁰ and chemotherapy drugs targeting tumor tissues combined with cryoablation to reverse the immunosuppressive microenvironment.⁴⁸¹ These approaches may provide valuable insights for the treatment of HCC.

THE PROTEIN CORONA AT THE NANO-BIO INTERFACE UNDER ABLATION CONDITIONS

From systemic interface to ablation-relevant biology

The nano-bio interface continuously reshapes administered nanomaterials through protein corona formation, opsonization, endothelial transcytosis and stromal sieving, with the consequence that fewer than 1% of an injected dose typically reaches the tumor bed.²⁷ For HCC ablation, this systemic constraint translates into an underappreciated problem: the GNPs, IONPs, CuS, BP nanosheets, MOFs and thermosensitive liposomes surveyed throughout this review never reach an HCC lesion in their as-synthesized form, since their synthetic identity is rapidly overwritten by an adsorbed biomolecular layer before encountering endothelium, hepatic sinusoids or tumor-cell receptors.⁴⁸² A corona-aware reading of these data is therefore essential before clinical translation can be expected.⁴⁸²

Functional consequences for HCC-targeted ablation nanomaterials

The corona governs three outcome-determining behaviors that are particularly consequential for HCC.⁴⁸³ Opsonin-rich coronas dominated by IgG, C3b and C1q facilitate Kupffer cell recognition and shorten circulation half-life,⁴⁸⁴

whereas dysopsonin-rich coronas enriched in albumin, clusterin and apolipoproteins promote stealth-like behavior and prolong circulation.⁴⁸² Tumor penetration is also affected: corona formation increases the hydrodynamic diameter, sometimes exceeding HCC vascular fenestrae and attenuating EPR-mediated extravasation,⁴⁸⁵ while corona-induced charge inversion and ligand burial can abolish active targeting in the dense fibrotic HCC stroma – most strikingly, transferrin-functionalized particles lose their receptor-targeting capability outright once a corona assembles.⁴⁸⁶ Macrophage clearance is the third axis: complement deposition and IgG opsonization on the corona are the proximate triggers of Kupffer cell and TAM capture,⁴⁸⁷ a particularly punishing effect for HCC because the liver is the very compartment in which mononuclear phagocyte system sequestration is densest.⁴⁸³

Although none of the studies surveyed in the preceding sections explicitly invoke the protein corona, the receptor–ligand and surface-modification strategies depicted across our schematic illustrations of RFA (Figure 1), MWA (Figure 3), PTT (Figures 5–7) and HIFU (Figure 9) platforms reflect, in retrospect, an implicit response to the same biological constraints.⁴⁸⁸ Short, charge-neutral peptides such as iRGD on iRGD-TSL-DOX (Figure 1) and MWA platforms (Figure 3), and SP94 on SP94-PB-SF-Cy5.5 NP (Figure 5), intrinsically limit non-specific opsonin recruitment relative to bulkier antibody constructs.⁴⁸⁷ Lactoferrin decoration of GNR70@PEG-LF and AFLG (Figure 5) engages hepatic asialoglycoprotein receptors while functioning as a dysopsonin-like surface, mirroring the *in vivo* recruitment of apolipoproteins onto stealth nanoparticles.⁴⁸⁵ Antibody motifs – anti-EpCAM on ADR/GNRs@PMs-antiEpCAM (Figure 5) and ICG-CuS-Gd@BSA-EpCAM NPs (Figure 7), anti-GPC3 on CuS@pda/PAA/DOX/GPC3 (Figure 5) and GPC3-CMBs (Figure 9), anti-TGF- β on CuS-ATMi@TGF- β NP (Figure 5), and anti-PD-L1 and anti-CXCR4 on BP and CP-based platforms (Figure 6) – together with folate-mediated delivery on MGO-TCA-FA@DOX and FA Co-PMs (Figure 6), Gas6-based GPC3 co-targeting (Figure 7) and fucoidan-based P-selectin engagement (Figure 3), were each selected for tumor-cell affinity, yet their *in vivo* efficacy depends on whether the corona preserves or buries the recognition motif. Strikingly, every platform is co-functionalized with PEG, as in PEG-coated GNP (Figure 1), GNR70@PEG-LF (Figure 5), mPEG-PLGA@DMF (Figure 3), PEG-modified Dox-loaded MSN@CuS (Figure 5) and IR820@PEG-SPIO (Figure 7), and several adopt tumor-cell-membrane cloaking such as CuS-SF@CMV (Figure 5) – strategies that act not by abolishing protein adsorption but by reshaping the corona toward a dysopsonin-rich, low-immunogenicity composition. Recasting these established choices through a corona-aware lens does not invalidate them; rather, it provides a unifying framework that explains why some HCC-targeted nanomaterials translate well *in vivo* while others, despite high *in vitro* affinity, underperform after intravenous administration.⁴⁸⁸

Dynamic remodeling under ablation heating, and the case for intra-arterial delivery

A consideration of unique relevance to ablation, yet largely absent from the HCC literature, is that the corona is not static under thermal conditions.⁴⁸⁹ Photothermal heating with GNPs, CuS, BP or carbon-based agents and magnetothermal heating with IONPs and SPIONs both impose temperature excursions that frequently exceed the 60–80 °C denaturation threshold of plasma proteins, causing corona constituents to unfold, aggregate and expose cryptic epitopes.⁴⁸⁹ The downstream effects map directly onto the three axes above: the unfolded corona acquires complement-activating motifs that shorten circulation,⁴⁸² heat-induced aggregation enlarges the effective particle size and impairs penetration,²⁷ and stealth-like coronas convert into pro-phagocytic ones that accelerate macrophage clearance within the lesion itself.⁴⁸⁷ Conversely, mild hyperthermia at approximately 41–43 °C – characteristic of the ablation periphery and many sensitization protocols – can shed the soft corona, transiently re-expose buried ligands such as transferrin, anti-GPC3 or RGD, and re-engage receptor-mediated uptake.⁴⁹⁰ The thermally remodeled corona must therefore be treated as a defining design parameter, validated by quantitative proteomics, dynamic light scattering and circular dichroism across the ablation cycle.⁴⁹⁰

A complementary route to mitigate corona burden is hepatic intra-arterial delivery, exemplified by TAE and TACE. By introducing agents directly into the hepatic artery feeding the HCC nodule, this approach bypasses the prolonged

systemic circulation in which the corona accrues and matures.⁴⁸⁵ Because nanomaterials reach the tumor bed within seconds rather than circulating for hours, opsonin adsorption, IgG and complement deposition and Kupffer cell recognition are all sharply curtailed, while the short transit window also limits the ligand-burial effects highlighted above.⁴⁹¹ Combining ablation-augmenting nanomaterials with such locoregional administration therefore offers a pragmatic clinical strategy to preserve the as-designed surface chemistry – including the iRGD, SP94, anti-GPC3, anti-EpCAM, lactoferrin and folate motifs catalogued above.

SPATIAL MULTI-OMICS REVEAL THE HCC MICROENVIRONMENT AND POST-ABLATION IMMUNE REMODELING WITH ABSCOPAL EFFECTS

Spatial transcriptomics and single-cell RNA sequencing have overturned the view of tumors as solid masses. They enable precise mapping of exhausted T cells and CAFs in HCC. They also reveal spatiotemporal TME remodeling after ablation. In untreated HCC, SPP1⁺ macrophages and CAFs form a “tumor immune barrier” at the tumor boundary. This barrier restricts CD8⁺ T cell infiltration.⁴⁹² POSTN⁺ CAFs at the invasive front physically and molecularly suppress immunity.⁴⁹² Another subset, CD90⁺ extracellular matrix CAFs, are located at the distal tumor nest. Their spatial distribution overlaps with CD8⁺ T cell areas. These CAFs directly suppress the antitumor activity of CD8⁺ T cells by secreting LAMA4. They can also induce T cell senescence through DNA damage signaling pathways.⁴⁹³ Hypoxia-metabolic myofibroblasts are also enriched at the invasive front.⁴⁹² They exclude CD8⁺ T cells via a collagen-rich physical barrier.⁴⁹² They also secrete POSTN to inhibit T cell function and drive glycolytic metabolic reprogramming.⁴⁹² TREM2⁺ macrophages enriched in non-responders recruit CD8⁺ T cells via CXCL12 and promote exhaustion.⁴⁹⁴ Thus, exhausted CD8⁺ T cells, specific CAF subsets, and immune barriers co-localize to form a complex immune evasion network.

HCC ablation induces global cellular activation in distant liver.⁴⁹⁵ After RFA, ligand-receptor interactions increase among ten cell populations. Hepatic stellate cells, cholangiocytes, and endothelial cells are the most active.⁴⁹⁵ RFA also raises liver SWE values. This phenomenon is linked to iNOS⁺ neutrophils that exert distant antitumor effects.⁴⁹⁶ Ablation disrupts the SPP1⁺ macrophage and POSTN⁺ CAF barrier.⁴⁹⁷ It reduces immunosuppressive CAFs, and reactivates type I IFN signaling.⁴⁹⁷ After MWA, distant tumors show fewer CD8⁺ T cells and more MDSCs.⁴⁹⁸ CD36 is upregulated in tumor-infiltrating immune cells.⁴⁹⁸ CD36 inhibition restores T cell function.⁴⁹⁸ MTPA, a tumor-specific thermal ablation modality, spares the adjacent normal liver parenchyma by generating hyperthermia exclusively within the tumor.⁴⁹⁷ This specificity reduces the systemic release of pro-oncogenic cytokines and promotes intratumoral infiltration of CD8⁺ T cells and M1-type macrophages.^{497,499} Furthermore, combining MTPA with PD-1 blockade further enhances antitumor immunity. Targeting TACC3 in combination with PD-1 blockade significantly increases intratumoral CD8⁺ T cell infiltration, reduces the frequency of PD-1⁺ CD8⁺ T cells, elevates the percentage of IFN- γ ⁺ CD8⁺ T cells, and thereby converts immunologically “cold” tumors into “hot” ones.⁵⁰⁰

However, the true value of these spatial omics insights lies not only in constructing high-resolution cellular maps, but also in mining key molecular pathways that drive systemic anti-tumor immunity and abscopal effects. As discussed earlier, the cGAS-STING pathway can be activated during both RFA and MWA, eliciting systemic anti-tumor immunity. Single-cell sequencing has further revealed the dynamics of cellular heterogeneity during cryoablation: dsDNA released by dying tumor cells is taken up by macrophages and dendritic cells, activating the cGAS-STING pathway and IFN-I responses in these cells. At single-cell resolution, studies have precisely identified a CXCL10⁺ macrophage subset that expands specifically during this process, which recruits CXCR3⁺ CD8⁺ T cells to distant lesions via the CXCL10-CXCR3 axis.^{501,502}

Importantly, although these immunogenic effects—including endogenous dsDNA release and STING activation—are engaged during ablation, they are relatively weak and insufficient to clear pre-existing micrometastases.⁵⁰³ Therefore, multiple nanomaterial-based strategies should be designed to amplify the cGAS-STING cascade and potentiate abscopal effects. Tumor-targeted nanoparticles loaded with STING agonists or polymers that protect

dsDNA can enhance STING activation and IFN-I production. TSLs and MOFs enable spatiotemporally controlled release of STING agonists, ensuring local activation under the heat generated by thermal ablation.⁵⁰⁴ For cryoablation, cold-responsive nanocarriers or dsDNA-capturing nanoparticles can be designed to augment cryo-induced delivery of dsDNA and targeted release of STING agonists. Moreover, based on the CXCL10⁺ macrophage subset identified by single-cell sequencing, nanocarriers that specifically target this subset can be further engineered to precisely regulate its immune-recruitment function. Collectively, these strategies synergistically enhance type I interferons, expand CXCL10⁺ macrophages, and drive the migration of CXCR3⁺ CD8⁺ T cells toward distant micrometastases, thereby eradicating residual tumor cells left behind after local ablation.

Spatial multi-omics have deciphered the immune evasion network in the HCC microenvironment and revealed how ablation disrupts these barriers while activating the cGAS-STING pathway. Based on these molecular mechanisms, designing nanomaterials that target specific cell subsets not only overcomes the traditional materials science limitation of focusing solely on material design, but also provides optimized gene editing or drug delivery strategies for basic research. Therefore, identifying clinical challenges through multi-omics sequencing and then rationally designing nanomaterials to address them should be considered a valuable research paradigm.

CONCLUSIONS AND PERSPECTIVES

Although current clinical studies on nanomaterial-assisted ablation therapy for HCC have produced limited or inconclusive results, researchers remain committed to exploring its potential and advancing this therapeutic approach (Table 2). Notably, the types of ablations primarily focus on RFA and MWA, which were introduced earlier in clinical practice, as well as their combination with embolization therapy. However, ferucarbotran, which has demonstrated promising results in RFA, has yet to be applied in clinical studies. Cryoablation has gradually gained popularity in current clinical practice owing to its advantages, such as intraoperative imaging assistance, minimal damage to surrounding organs, and reduced postoperative pain.⁴⁵⁹ Therefore, nanomaterials for enhanced cryoablation represent a promising direction for future clinical research. Efforts should not focus solely on improving the ablation efficacy itself but also on developing supportive materials, such as hydrogels, to minimize postoperative bleeding and adjuvants to boost immune responses. Inspired by NCT05068076, future clinical trials should also consider nanomaterials that assist ablation imaging, such as IONPs, nanomaterials carrying PFC, and nanomaterials loaded with small molecular dyes. Inspired by NCT05068076, future clinical trials should also consider nanomaterials that assist ablation imaging, such as IONPs, nanomaterials carrying PFC, and nanomaterials loaded with small molecular dyes. The size of nanomaterials plays a decisive role in their therapeutic performance and biological fate (Table 1). Ultrasmall particles below 10 nm offer advantages in renal clearance and tumor penetration but generate insufficient heat for sustained ablation, whereas intermediate-sized platforms ranging from 10 to 100 nm strike a balance between prolonged circulation, EPR-mediated tumor accumulation, and effective magnetic heating, though their tendency for hepatosplenic retention underscores the need for biodegradable formulations.^{505,506} Larger constructs exceeding 100 nm, particularly those with membrane coatings, demonstrate extended blood half-life and homologous tumor targeting capabilities but face limitations in extravasation and deep tissue penetration, making them more suitable for intra-arterial delivery approaches such as TACE combination strategies.⁵⁰⁷

The present review focuses on ablation therapies recommended by guidelines and commonly applied in clinical practice, including RFA, MWA, PTT, HIFU, MHA, and cryoablation. Other ablation methods, such as percutaneous ethanol ablation, sonodynamic therapy, and photodynamic therapy, are excluded because of limited clinical application or insufficient studies involving nanomaterials. Additionally, both TACE and ablation therapy for HCC offer distinct therapeutic advantages. Their combination can achieve complementary benefits, improving local tumor control and patient survival rates.⁵⁰⁸ Given the multifunctional properties of nanomaterials, they are expected to play an important role in TACE combined with ablation therapy. Therefore, preclinical studies in this area should be explored. A particularly compelling translational rationale is that HCC is supplied predominantly by the hepatic

artery, whereas normal liver parenchyma derives most of its inflow from the portal vein, an anatomical asymmetry that has long underpinned transarterial locoregional therapy.³² Coupling ablation-augmenting nanomaterials with the established intra-arterial delivery infrastructure of TACE can therefore concentrate nanomaterials within the tumor bed and integrate sensitization, embolization, and ablation within a single image-guided session. Notably, the ablation site should not be limited to the primary tumor itself. Sympathetic nerves promote HCC progression, metastasis, and immune suppression.⁵⁰⁹ Currently, the use of intravascular sympathetic nerve RFA for treating HCC (NCT06694636) has been studied clinically. However, nerve ablation is limited by non-neuronal cell damage and reinnervation of nerve plexuses after ablation.⁵¹⁰ Nanomaterial-enhanced HCC nerve ablation is also an intriguing direction for future research. Beyond these technical hurdles, the potential toxicity of nanomaterials represents a critical barrier to clinical translation that warrants systematic consideration. The nanomaterials reviewed herein have incorporated various design principles to mitigate adverse effects, which can be broadly categorized into surface modification and biodegradable engineering strategies. Surface functionalization approaches include PEGylation to prolong circulation time and reduce reticuloendothelial system clearance, as demonstrated by PEG-IL-LM-ZrO₂ suprananoparticles for MWA and Mn-Ti MOFs@PEG for combined imaging and therapy.⁵¹¹ Active targeting moieties such as RGD peptides further minimize off-target distribution, with Au@PDA-RGD nanoparticles showing 40-60% reduction in non-specific hepatic accumulation compared to unmodified counterparts.⁵¹² Biomimetic membrane coating represents an emerging paradigm, exemplified by CIMs that exploit CD47 "don't eat me" signals to evade macrophage recognition while extending blood half-life.⁵¹³ Complementing these surface strategies, biodegradable designs enable spatiotemporal control of toxicity through stimuli-responsive degradation. pH-responsive systems such as DNAzyme@Mn-CONASHs leverage the acidic TME to trigger calcium carbonate shell dissolution and manganese ion release, confining cytotoxic effects to malignant tissue while maintaining stability in normal physiological pH.⁵¹⁴ Hypoxia-activated platforms like Fe-TPZ nanoparticles selectively target post-ablation residual disease by releasing tirapazamine only under oxygen-depleted conditions created by incomplete RFA.⁵¹³ Intrinsic biodegradability further reduces long-term accumulation risks, as seen with black phosphorus nanomaterials that oxidize to endogenous phosphates within 48-72 hours and iron-based AFLG nanocomposites degraded by myeloperoxidase in lysosomes.⁵¹² Hydrogel-based localized delivery systems, including ALG-Ca-Mn gel for peritumoral injection, provide an additional layer of safety by restricting systemic exposure while maintaining therapeutic concentrations at the ablation site.⁵¹¹ Despite these advances, systematic head-to-head comparisons of toxicity mitigation strategies in orthotopic HCC models remain limited, and the integration of multi-omics profiling to identify predictive biomarkers for patient-specific toxicity risk represents an important direction for future research.

Ablation therapies are crucial for the local treatment of HCC. However, several challenges remain, including unclear intraoperative imaging that hampers complete coverage of tumor margins, changes in the postoperative immune microenvironment leading to poor efficacy or recurrence, and the inability to complete combined treatments within a single procedure. Bringing nanomaterial-enhanced ablation therapy to the clinic requires systematic efforts to overcome three major obstacles: biological gaps, manufacturing hurdles, and regulatory challenges.⁵¹⁵ Most preclinical data still come from subcutaneous xenograft models that fail to capture the human tumor stroma, metabolic context, or immune microenvironment of HCC.⁵¹⁶ A staged validation strategy is needed: first, use patient-derived organoids and liver-on-a-chip platforms to screen candidate nanomaterials.⁵¹⁷ Then evaluate efficacy and immune remodeling in humanized and orthotopic HCC models, combined with multi-omics to identify predictive biomarkers for patient stratification.⁵¹⁸ Batch-to-batch variability is a major manufacturing bottleneck.⁵¹⁹ Good manufacturing practice-compliant synthetic processes must be developed, along with orthogonal quality control methods.⁵²⁰ Early collaboration with contract development and manufacturing organizations is advisable.⁵²⁰ On the regulatory and clinical side, early dialogue with regulatory agencies is essential to define the approval pathway.⁵²¹ Clinical trial design should adopt biomarker-driven enrichment, enrolling only patients positive for predictive

markers.⁵²² A non-inferiority design with “reduced toxicity” as the primary endpoint, as successfully used for Abraxane, is a practical option.⁵²³ Pharmacokinetic modeling should guide dosing to bridge the gap between small-animal data and human responses.⁵²⁴ A deeper limitation is that most preclinical data still rely on 2D cultures and subcutaneous xenografts, which cannot recapitulate the human tumor stroma, hepatic metabolic context, or 3D architecture.⁵²⁵ This gap helps explain why many nanomaterials that perform well in animals yield limited clinical success.⁵¹⁸ Integrating next-generation models — patient-derived organoids, 3D microtumor spheroids, and liver-on-a-chip platforms — into the evaluation pipeline is therefore essential for rational thermal dosing and for assessing post-ablation immune remodeling.⁵¹⁷ The current review summarizes the roles of nanomaterials, including GNPs, liposomes, nanobubbles, carbon-based nanomaterials, BP nanomaterials, CPs, and hydrogels, in sensitizing HCC ablation therapy. It discusses the advantages and disadvantages of different materials and the challenges of clinical translation (Table 2). Furthermore, it summarizes changes in the TIME after ablation therapy and how nanomaterials regulate immune cells, such as DCs, T cells, and TAMs, to enhance ablation therapy (Table S1). These findings are expected to provide new insights and directions for improving anti-tumor therapy based on ablation treatment for patients with HCC.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Data are available from the corresponding author upon reasonable request.

SUPPLEMENTAL INFORMATION

It can be found online at <https://doi.org/10.59717/j.xinn-oncol.2026.100029>