

Advances in Engineered Nano-sensitizers for Chemoradiotherapy of Cancer: Overcoming Microenvironmental Barriers

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Abstract Conventional chemotherapy and radiotherapy damage normal tissues due to off-target toxicity, impairing patient prognosis. Chemoradiotherapy (CRT)—the concurrent use of chemotherapy and radiotherapy—has gained considerable attention, as it suppresses primary tumors and reduces metastasis. However, dose-limiting drug toxicity remains a major barrier to clinical CRT. To mitigate adverse effects and improve drug bioavailability, nano-sensitizer (NS)-mediated CRT has become a research focus. Nonetheless, unique tumor microenvironmental features, including hypoxia, abnormal vasculature, elevated reactive oxygen species, mild acidity, dense extracellular matrix, and immunosuppression, severely compromise NS efficacy. Accordingly, smart NS designed to surmount these microenvironmental barriers represent a key direction in drug development. This review summarizes recent advances in tumor microenvironment-targeted NS and their preclinical and clinical applications, aiming to deepen understanding of microenvironmental challenges in CRT and facilitate the development of potent NS.

Keywords Cancer treatment; Chemoradiotherapy; Nano-sensitizer; Radio sensitization; Microenvironmental barriers

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1 INTRODUCTION

Cancer causes approximately 10 million global deaths in 2022, ranking as the leading cause of mortality worldwide.^[1] While screening enables the early detection of some cancers, most malignancies are asymptomatic at the initial diagnosis.^[2] Thus, intensive research has focused on the development of effective anticancer therapies. Currently, surgery, chemotherapy, radiotherapy, cell therapy, and immunotherapy are the primary clinical strategies for cancer management.^[3]

Chemoradiotherapy (CRT) combines chemotherapy and radiotherapy, and is widely used to treat advanced malignancies such as gastrointestinal, cervicofacial, lung, and gynecologic cancers^[4] CRT not only enhances the killing effect on primary tumors but also significantly reduces metastasis.^[5] Multiple frameworks, including normal tissue protection, spatial cooperation, biological synergy, temporal optimization,

and cytotoxic enhancement, have been applied to analyze drug-radiation interactions across preclinical and clinical stages. Theoretically, radiosensitization by CRT involves six mechanisms (Fig. 1): (i) direct deoxyribonucleic acid (DNA) damage via drug-DNA binding, (ii) reduction of hypoxic cell fractions, (iii) enrichment of cells in radiosensitive cell cycle phases, (iv) inhibition of DNA repair, (v) limiting tumor repopulation,^[6,7] and (vi) boosting immunity via immunogenic cell death.^[4] Chemotherapy potentiates radiotherapy by sensitizing cancer cells to ionizing radiation through these pathways.^[8]

However, conventional poorly soluble drugs and their excipients exhibit cytotoxicity^[9] damaging normal tissues, and impair hepatic and renal function.^[10] Thus, there is an urgent need for agents with minimal off-target toxicity to enable safe and effective dosing. Driven by rapid tumor cell proliferation, tumor tissues display a loose architecture and irregular porous vasculature. Based on these characteristics, nanosensitizers (NS) have been developed. By incorporating chemosensitizing components into nanoparticles (NPs), multiple biological mechanisms are regulated to exert radiosensitizing effects. Moreover, these NPs can be co-loaded with chemotherapeutic agents to achieve combined chemoradiotherapy, thereby further enhancing the efficacy of radiotherapy.^[11] Benefiting from their size in the range of 20–200 nm, these NS are not readily cleared by the kidneys, which prolongs their circulation time and enhances their accumulation and penetration in tumor tissues.^[12] Based on these advantages, the rational integration of NS with radiotherapy can maintain efficacy at reduced doses, thereby mitigating normal tissue injury.

In recent decades, rapid advances in nanomedicine have enabled the development of versatile NPs with tunable sizes, morphologies, and functions,^[13] creating new opportunities for NS-mediated cancer CRT. However, the key hallmarks of

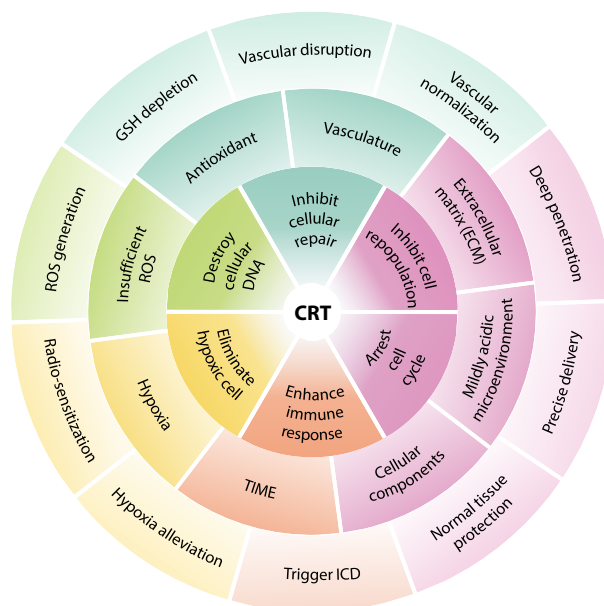


Fig. 1 Summary of the key features of tumor microenvironment (TME)-directed nanotherapeutics and the underlying pathways of cell killing.

the solid TME, including dense extracellular matrix (ECM), hypoxia, high ROS levels, mild acidity, immunosuppression, and protein overexpression, markedly impair CRT efficacy.^[14] These TME features not only hinder treatment, but also serve as actionable targets for designing actively targeted or stimulus-responsive nanocarriers (Table 1). Such targeted NPs enhance tumor accumulation and cellular internalization, accelerate on-demand drug release, and boost CRT sensitivity.^[15]

This review outlines the key TME barriers to CRT and summarizes recent advances in TME-responsive NS for overcoming

Table 1 Examples of nanomedicine in CRT.

No.	Nanoparticles	TME	Mouse model
1	Au@SA-QBA ^[16]	Vasculature	H22 s.c. tumor
2	AuHQ ^[17]	Vasculature	H22 s.c. tumor
3	NGM ^[18]	Hypoxia, iRGD	4T1 s.c. tumor
4	RDPP(Met)/ TMZ/ siMGMT ^[19]	Hypoxia	GBM
5	⁵⁵ CM ₆ NPs ^[20]	GGT/GSH/hypoxia	BxPC-3 s.c. tumor, orthotopic pancreas
6	PFCE@ cisPt(iv)-Lip ^[21]	Hypoxia	4T1 s.c. tumor
7	O ₂ @PFOB@Gel ^[22]	Hypoxia	4T1 s.c. tumor
8	O ₃ -PFD@Pt ^[23]	Hypoxia, ROS	4T1 s.c. tumor, lung metastatic tumor
9	Mn ₁₂ clusters ^[24]	Hypoxia, low pH	4T1 s.c. tumor
10	FA-Fht ^[25]	Hypoxia	CT26 s.c. tumor
11	GE11-PDA-Pt@USPIOs ^[26]	Hypoxia, low pH	H1299 s.c. tumor
12	AID nanomedicine ^[27]	Hypoxia	4T1 s.c. tumor
13	Pt@mPDA/MnO ₂ /PDA-Z _{Her2} NPs ^[28]	Hypoxia	SKOV-3 s.c. tumor
14	VCT vesicle ^[29]	Hypoxia	Orthotopic breast tumor
15	V-M-K-T vesicle ^[30]	Hypoxia	PAN-02 s.c. tumor, orthotopic pancreatic tumor
16	Fe-Pt-Cys NPs ^[31]	ROS	LLC s.c. tumor
17	NP@PVP ^[32]	ROS	EMT-6 s.c. tumor
18	Bi-PFA ^[33]	ROS, GSH, Hypoxia	4T1 s.c. tumor
19	Sc-D@Lip/Pt ^[34]	ROS	4T1 s.c. tumor
20	CNL@miPA ^[35]	Hypoxia, ROS	GBM
21	STNA ^[36]	ROS	Hepa 1-6 s.c. tumor
22	IRnR-40 ^[37]	MMP-9, ROS	Collagen-induced arthritis

Table 1 Continued.

No.	Nanoparticles	TME	Mouse model
23	CeO ₂ -MnO ₂ ^[38]	ROS, GSH	HeLa s.c. tumor
24	MPL _(SS) P@SIS ^[39]	GSH, PROTAC	GBM
25	SS _{TPTX} ^[40]	GSH	4T1 s.c. tumor
26	CA4-DNBS@ICG ^[41]	GSH, ROS	4T1 s.c. tumor
27	Bi ₂ S ₃ @mBi _x Mn _y O _z ^[42]	GSH, ROS	4T1 s.c. tumor
28	AuNPs-D-P-DA ^[43]	Low pH	KYSE-510 s.c. tumor
29	DOX@Gel-DEVD-AuNR ^[44]	Low pH, GSH, ROS	CT26 s.c. tumor
30	OPM ^[45]	Low pH	SaOS-2 s.c. tumor
31	Au-Dox@ PO-ANG ^[46]	Low pH, ANG	GBM
32	Au-NNP(RTX) ^[47]	Low pH	CT-26 s.c. tumor
33	Pt@Ce-MOF-RGD/FA ^[48]	RGD, FA, ROS	Orthotopic breast tumor
34	5-FU loaded magnetite/PEG-PCL-PEG-FA ^[49]	FA, ROS	/
35	AuNPs@MSNs-5FU-CPBA-HA ^[50]	HA, ROS	/
36	DCNP@P(Se-Dox)@ANG ^[51]	ANG, ROS	GBM
37	ALG-ATP-Aapt/CpG-cApt hydrogels ^[52]	TIME, ATP	CT-26 s.c. tumor, orthotopic breast tumor
38	PPS-SeNPs@Dox ^[53]	TIME, Temperature	Orthotopic Hepa1-6 tumor
39	MG-HOC@Rux ^[54]	TIME, MMP-2, GSH	SCC7 s.c. tumor
40	AuDAP ^[55]	TIME	4T1 s.c. tumor
41	αPDL1@MnO ₂ ^[56]	TIME, ROS	CT-26 s.c. tumor

ing these obstacles. We begin by characterizing the TME, then discuss multifaceted design strategies for NS to mitigate TME-related resistance, highlight representative studies, and conclude with the current challenges facing NS in CRT.

2 THE INTERPLAY BETWEEN CRT AND TME

2.1 Hypoxia

Most solid tumors exhibit hypoxia because aberrant vasculature fails to deliver sufficient oxygen (O₂) to meet the demands of rapidly proliferating cancer cells. Tumor hypoxia arises through three main mechanisms: anemic hypoxia, diffusion-limited O₂ delivery, and perfusion-limited O₂ delivery.^[57] These pathways generate substantial spatial and temporal heterogeneity in intratumoral oxygenation.

Hypoxic tumors undergo metabolic reprogramming to adapt to their microenvironment and alter cellular behavior. Hypoxia-inducible factor (HIF), a key mediator of this adaptation, promotes tumor survival by upregulating genes involved in metabolic adaptation, pH control, vascular remodeling, and cell death regulation.^[58,59] Severe hypoxia further drives immune evasion by suppressing T cell expansion, impairing immune cell function, and reducing antigen presentation.^[60] Radiotherapy relies on reactive oxygen species (ROS) overproduction to damage DNA/proteins and induce apoptosis^[61] but hypoxia drastically lowers ROS yield, rendering hypoxic cells three-fold more radioresistant.^[62] Hypoxic regions are poorly accessible to chemotherapeutics and display elevated expression of drug resistance genes. Collectively, these factors severely compromise both chemotherapy and radiotherapy, limiting the efficacy of CRT in most solid tumors.

2.2 Vasculature

The tumor vasculature and endothelial cells are the best-characterized radiation-sensitive components of the TME.^[63] Dysfunction of these vascular structures acts as a dose-limiting factor in CRT, triggering post-irradiation inflammation and fibrosis that manifests as elevated permeability and detachment from

the basement membrane.^[64] Relative to normal counterparts, tumor vessels exhibit greater permeability and radiosensitivity, largely due to the absence of an intact basement membrane and pericyte coverage.^[65,66]

HIF-1α overexpression triggers downstream signaling and upregulates vascular endothelial growth factor (VEGF), which drives rapid, disorganized angiogenesis. This process consumes excessive oxygen and nutrients, worsens hypoxia in deep tumor regions,^[67] and inhibits dendritic cell (DC) maturation and antitumor immunity.^[68] Absent pericyte coverage causes vascular leakage, elevates interstitial matrix pressure, and intensifies tumor hypoxia. A discontinuous basement membrane facilitates macromolecule/particle entry *via* the EPR effect or barrier penetration.^[69] Notably, structurally incomplete tumor vessels enable cancer cell intravasation and metastasis.

2.3 ROS

NS-mediated radiosensitisation relies on four core mechanisms: enhancing IR energy deposition, boosting ROS generation, remodeling the TME, and regulating intracellular signaling, among which ROS production is the best characterized.^[70] ROS are composed of oxygen-derived free radicals and non-radical species.^[71] Endogenous ROS physiologically regulate vital cellular functions primarily *via* mitochondrial or oxidase-dependent production. Tumor cells exhibit moderately elevated intracellular ROS levels compared to normal cells.^[72] Above a critical threshold, excess ROS oxidatively damages biomolecules and triggers diverse cell death programs,^[73] including intrinsic/extrinsic apoptosis, autophagy, ferroptosis, pyroptosis, and apoptosis.^[74]

While CRT-generated ROS eliminates cancer cells, those derived from aberrant cells can promote malignant progression and metastasis. ROS released by damaged or activated immune cells also triggers excessive proinflammatory and proliferative factor secretion, further driving cancer development and systemic spread. Although ROS participate in immune recognition, antigen presentation, and phagocytosis,

their overproduction impairs T-cell and natural killer (NK)-cell functions.^[75] To counteract oxidative stress, cancer cells overexpress antioxidants, primarily thioredoxin and glutathione (GSH), which mediate intrinsic radioresistance.^[76] Their synthesis relies on glutathione reductase and thioredoxin reductase.^[77] Thus, these antioxidants and their biosynthetic pathways represent promising targets for CRT-related drug development.

2.4 Mildly Acidic Environment

Tumor acidity, a hallmark of cancer, is caused by enhanced glycolysis and glutaminolysis.^[78] This disturbed intracellular pH homeostasis promotes tumor proliferation, invasion, metastasis, therapy resistance, and evasion of apoptosis.^[79–81] In the mildly acidic extracellular tumor milieu, weak-base drugs undergo “ion trapping,” which markedly reduces cellular uptake and therapeutic efficacy.^[82] The acidic TME also upregulates p-glycoprotein and SRY-box transcription factor 2, further driving drug resistance.^[83–85] Conversely, intracellular alkaline pH inhibits radiotherapy-induced mitotic arrest, conferring radioresistance synergistically with hypoxia.^[78,86] Moreover, excess lactic acid also promotes immune escape by activating regulatory T cells (Tregs), impairing effector T cells, and elevating programmed cell death protein 1 expression.^[87,88]

In addition to mediating therapeutic resistance, reversed pH gradients represent a cancer vulnerability that enables the development of pH-triggered strategies, including pH-sensitive antibodies^[89] and pH-responsive nanoparticles for anticancer drug delivery.^[90,91] These approaches are safe because they require no external energy for activation.^[92] Given the impairment of immunotherapy by extracellular acidity, the pharmacological normalization of tumor pH has become a promising anticancer strategy. Representative methods include targeting glucose metabolism,^[93] inhibiting lactate dehydrogenase A,^[94] and suppressing intracellular pH-regulating proteins or mitochondrial function.^[79,95] Buffer-mediated tumor pH modulation also suppresses tumor growth and enhances treatment efficacy.^[96]

2.5 Cellular Components and ECM in TME

The TME profoundly drives tumorigenesis, progression, metastasis, and therapeutic resistance. Functioning as a specialized ecological niche, it comprises neoplastic cells, stromal fibroblasts, vascular networks, infiltrating leukocytes, endothelial cells, and supportive ECM.^[97] Among these components, dense ECM is a major obstacle to effective CRT, as it impairs vascular oxygen and drug delivery.^[98] Additionally, severe fibrosis and water-binding components (e.g., hyaluronic acid^[99]) form a physical barrier, elevate interstitial fluid pressure, and severely reduce CRT efficacy. In addition to disrupting blood, oxygen, and drug transport, an abnormal ECM also distorts TME-associated molecular signaling.^[100]

Apart from the physical drug transport barrier imposed by the TME, intercellular crosstalk critically drives therapeutic resistance.^[101] TME-resident cells secrete diverse signaling factors, including growth factors, ECM components, and cytokines.^[102] These soluble mediators promote therapy resistance *via* pro-survival signaling, immune evasion, and ECM remodeling. For example, colorectal cancer progression is driven by transcription factor 7-like 2-mediated Wnt/ β -catenin activation.^[103] While CRT eradicates cancer cells, off-target ef-

fects damage the TME stromal cells, leaving abundant senescent stromal and cancer cells. Senescent stromal cells drive proliferation, angiogenesis, migration, and invasion *via* a senescence-associated secretory phenotype, which severely compromises therapeutic efficacy.^[104–107]

2.6 Tumor Immune Microenvironment (TIME)

The TIME consists of lymphoid and myeloid immune cells, together with their secreted cytokines.^[108] Immune cell function depends on growth factors, cytokines, chemokines, and microRNAs. Tumors evade immune surveillance by activating immunosuppressive pathways and recruiting pro-tumor immune subsets. Specifically, T helper 2 (Th2) cells, Tregs, and M2-type tumor-associated macrophages promote tumorigenesis, whereas NK cells, M1 macrophages, cytotoxic T lymphocytes, and APCs exert antitumor effects.^[109]

Accumulating evidence indicates that CRT elicits both anti-tumor and pro-tumor immune responses.^[110] CRT upregulates major histocompatibility complex class I molecule expression, stimulates type I interferon secretion, and enhances antigen cross-presentation.^[111] In contrast, it induces immunosuppressive effects, including Treg recruitment, increased circulating myeloid-derived suppressor cells (MDSCs), decreased CD8⁺ T cells, and impaired T-cell activity.^[112–114] Given these mixed immunomodulatory effects, remodeling the tumor immune milieu *via* immunotherapy represents a promising strategy to restore effective antitumor immunity against solid tumors.^[115]

3 NANOTECHNOLOGICAL STRATEGIES FOR OVERCOMING TME BARRIER OF CRT

3.1 Vasculature

The tumor vasculature supplies oxygen and nutrients to cancer cells, while facilitating metastatic dissemination. Vascular targeting thus represents a key strategy for cancer therapy,^[116] with two main approaches: (1) using angiogenesis inhibitors (AIs) and vascular disrupting agents (VDAs) to occlude tumor vessels and induce necrosis and (2) normalizing abnormal vasculature to alleviate hypoxia, thereby enhancing radiotherapy efficacy.

3.1.1 Destruction of the vascular system

Vascular-targeting agents mainly include VDAs and AIs, which modulate TME parameters such as pH and oxygenation to influence therapeutic outcomes. However, these agents fail to suppress tumor growth as monotherapy, and thus require combination therapy with radiotherapy or other modalities.^[117] In a preclinical study, Iversen *et al.* combined two VDAs (5,6-dimethylxanthone-4-acetic acid and flavone acetic acid) with radiotherapy.^[118] Results showed markedly reduced tumor oxygenation across all the VDA-treated groups. Furthermore, the therapeutic sequence determined the VDA-radiotherapy interactions, with radiosensitization only achieved when VDAs were administered concurrently with or after irradiation.

Beyond VDAs and AIs, targeting proangiogenic factors represents another promising vascular-directed strategy for radiosensitization. VEGF is an endothelial mitogen and permeability factor that promotes angiogenesis and protects endothelial cells against radiation. Therefore, targeting the VEGF pathway has become an important strategy in nanodrug de-

livery systems to enhance the efficacy of radiotherapy.^[119]

3.1.2 Normalization of vessels

Vascular normalization enhances tumor perfusion and oxygenation, thereby overcoming hypoxia-related resistance to immunotherapy, chemotherapy, and radiotherapy.^[120] Wang *et al.* functionalized AuNPs with sodium alginate (SA) and 8-quinoline boronic acid (QBA)^[16] or 8-hydroxyquinoline (HQ)^[17] to generate Au@SA-QBA and AuHQ. This nanosystem boosted pericyte coverage and downregulated VEGF, bFGF, and Ang-2, triggering vascular remodeling, improving nanomedicine accumulation, and enhancing the efficacy of radiotherapy. Treatment reduced vessel density while increasing pericyte coverage, and lowered vascular permeability further improved blood flow and oxygen delivery, thereby increasing radiosensitivity.^[121] Bevacizumab transiently elevated tumor oxygenation in mice, improving radiotherapy outcomes compared to radiation alone.^[122] Likewise, antiangiogenic pretreatment delayed tumor growth during chemotherapy by enhancing perfusion and reducing vascular permeability, thus improving drug delivery and benefiting CRT.

Normalized vasculature relieves hypoxia, promotes immune cell infiltration, and strengthens antitumor immunity.^[123] Conversely, interferon- γ secreted by CD4⁺/CD8⁺ T cells facilitates vascular normalization, expanding the functions of immunotherapy in cancer treatment.^[65]

3.2 Hypoxia

Three core strategies can overcome hypoxia-related limitations: using hypoxia as a trigger for responsive drug delivery, improving tumor oxygenation via nanotechnology, and elevating peripheral hypoxia to directly activate hypoxia-targeted sensitizers without deep penetration.

3.2.1 Hypoxia responsive drug delivery

Unlike small-molecule radiosensitizers (*e.g.*, sodium glycididazole and nimorazole) that poorly penetrate tumor hypoxic regions, well-designed nanoparticles with suitable physicochemical properties, especially small size, can achieve deep tumor infiltration and stronger radiosensitization.^[124] Nitroimidazoles and metronidazole (Met), classic hypoxic radiosensitizers, are widely used to construct hypoxia-responsive tumor-targeted delivery systems owing to their hypoxia-triggered reducibility.^[18] Under hypoxia, the hydrophobic nitro groups are bio-reduced to hydrophilic amino groups, causing polymer-based self-assembled nanoparticles to disassemble and release encapsulated hydrophobic drugs. Xie *et al.* developed amphiphilic polymers (PEG-Met) to co-encapsulate temozolomide (TMZ) and siMGMTs. Hypoxia triggers nanoparticle disassembly and payload release and synergistically sensitizes glioblastoma to CRT.^[19]

Our group has also designed a multiple hypoxia-responsive prodrug NS. Qian *et al.* synthesized a gambogic acid-metronidazole (GM) prodrug, further modifying Met on the encapsulating polymer to form GM prodrug nanoparticles, enabling targeted drug delivery to hypoxic cells and intratumoral enrichment.^[18] Tang *et al.* established γ -glutamyl transpeptidase/GSH/hypoxia-triple-responsive nanoparticles to overcome physiological and TME barriers in resectable pancreatic ductal adenocarcinoma, achieving deep tumor penetration and enhanced CRT sensitization.^[20]

3.2.2 Reoxygenation of tumor tissue

Tumor reoxygenation can relieve hypoxia, boost radiotherapy-required ROS levels, and enhance tumor cell death. Direct delivery of exogenous oxygen is the most straightforward approach. Perfluorocarbons (PFCs) are widely used for this purpose because of their high oxygen-loading capacity and good biocompatibility. Yao *et al.* developed perfluoro-15-crown-5-ether (PFCE) nanodroplets modified with cisPt(IV)-conjugated phospholipids for targeted oxygen delivery. Under X-ray irradiation, these nanodroplets induced severe DNA damage and inhibited tumor growth without obvious normal tissue toxicity.^[21] To prevent PFC leakage in circulation, Yang *et al.* fabricated an injectable thermosensitive hydrogel by encapsulating perfluorooctyl bromide (PFOB) within PFOA-modified mPEG-PLGA. This system normalized intratumoral oxygenation, downregulated HIF-1 α , and enhanced radiosensitization.^[22] Similarly, Xu *et al.* designed a cisplatin prodrug-based nanosystem for ozone delivery.^[23] Ozone decomposes to generate oxygen, thereby alleviating tumor hypoxia and remodeling the tumor microenvironment into an immune-favorable state, which holds promise for combination immunotherapy. Moreover, this nanosystem features a high drug-loading capacity and a simple synthesis process, which are advantageous for the large-scale production and quality control of nanoformulations.

Another approach to tumor reoxygenation is *in situ* decomposition of endogenous hydrogen peroxide (H₂O₂) to elevate intratumoral oxygen levels. Nanozymes with catalase-like activity, including manganese dioxide (MnO₂),^[125] Mn clusters,^[24] ferric oxide,^[25] and iridium NPs,^[126] have been widely explored for this purpose. Compared to natural enzymes, nanozymes achieve comparable hypoxia-alleviating efficacy, with greater structural stability and lower toxicity from excess oxygen generation.^[25] A polydopamine- and GE-11-modified, cisplatin-loaded ultrasmall superparamagnetic iron oxide nanozymewith dual catalase and peroxidase activity-integrated multi-stimuli responsiveness to boost CRT in hypoxic tumors.^[26] Zhang *et al.* further identified surface hydroxyl groups as critical for iron oxide nanozyme activity; ferrihydrite's abundant hydroxyls confer superior peroxidase-like performance across a broad biological pH range.^[25]

In addition to increasing the oxygen supply, reducing oxygen consumption represents an alternative strategy to alleviate tumor hypoxia. Zhang *et al.* developed an AID-based nanomedicine that disrupts the mitochondrial respiratory chain, thereby decreasing oxygen consumption, alleviating tumor hypoxia, and directly inducing ROS generation.^[27] Notably, in the design of radiosensitizers, achieving both "hypoxia relief" and "ROS elevation" is a common and effective strategy, with the two functions acting synergistically to enhance radiotherapy efficacy.

Tumor hypoxia upregulates HIF-1 α , which enhances endothelial cell survival and enzyme secretion, to drive CRT resistance. Targeting HIF-1 α for radiotherapy, Wang *et al.* fabricated Her2-specific affibody (Z_{Her2})-modified cisplatin-loaded mesoporous polydopamine/MnO₂/polydopamine nanoparticles (Pt@mPDA/MnO₂/PDA-Z_{Her2}). These nanoparticles degrade intracellularly and rapidly release cisplatin. MnO₂ catalyzes intratumoral H₂O₂ decomposition to elevate oxygen levels and reduce HIF-1 α expression, avoiding off-target toxic

city of MnO_2 -based radiosensitizers. By boosting ROS generation, this system effectively enhanced CRT sensitivity.^[28]

3.2.3 Normalizing the heterogeneous hypoxic environment in the tumor

Hypoxic regions distant from tumor vessels are poorly perfused, limiting access by hypoxia-targeted radiosensitizers, oxygen carriers, or generators and compromising efficacy. To address this barrier, we developed a strategy distinct from conventional reoxygenation or hypoxia sensitization. Chlorin e6 (Ce6) and tirapazamine were co-encapsulated in an amphiphilic cisplatin–metronidazole conjugate to form a multifunctional nanosystem.^[29] Passively accumulating near tumor vessels, this nanosystem uses Ce6-mediated sonodynamic therapy (SDT) to deplete peripheral oxygen, normalizing hypoxia distribution across the entire tumor. This enables efficient activation of hypoxia-responsive radiosensitizers without deep tissue penetration, whereas SDT directly kills peripheral cancer cells, accelerates drug release, and boosts radiosensitization. We further reported an NAD(P)H quinone oxidoreductase 1 (NQO1)-triggered hypoxia-normalization strategy. The nanosystem's co-loaded NQO1 substrate depletes peripheral oxygen in primary and metastatic tumors to sensitize hypoxia-activated CRT without exogenous stimuli, supporting clinical translation.^[30]

3.3 ROS

ROS levels directly determine CRT efficacy, making ROS elevation a key therapeutic strategy. High-Z elements are widely used to boost ROS by promoting radiation-induced Haber–Weiss and Fenton reactions; they enhance photon absorption and secondary electron emission, thereby generating more ROS with oxygen-containing substrates.^[74,127] Common high-Z components in radiosensitizing nanoparticles include platinum (Pt),^[31] gold (Au),^[128] cerium (Ce),^[129] bismuth (Bi),^[32–33] etc. Zwiehoff *et al.* confirmed that ROS production mainly depends on the high-Z element type and surface area rather than particle size or mass.^[130] Building on this mechanistic insight, Cheng *et al.* developed a nanoplatform (Sc-D@Lip/Pt) that enabled sustained ROS release upon X-ray irradiation.^[34] The system simultaneously achieved radiosensitization via persistent ROS production and enabled the effective delivery of a cisplatin prodrug. Our group has also used Au nanoclusters carrying miR-593-5p to achieve synergistic gene silencing and radiotherapy.^[35] Collectively, these studies demonstrate that rational selection of high-Z elements and engineering of nanoparticle surface properties are critical for maximizing ROS generation, whereas the integration of additional therapeutic modalities further potentiates the antitumor efficacy of NS-mediated CRT.

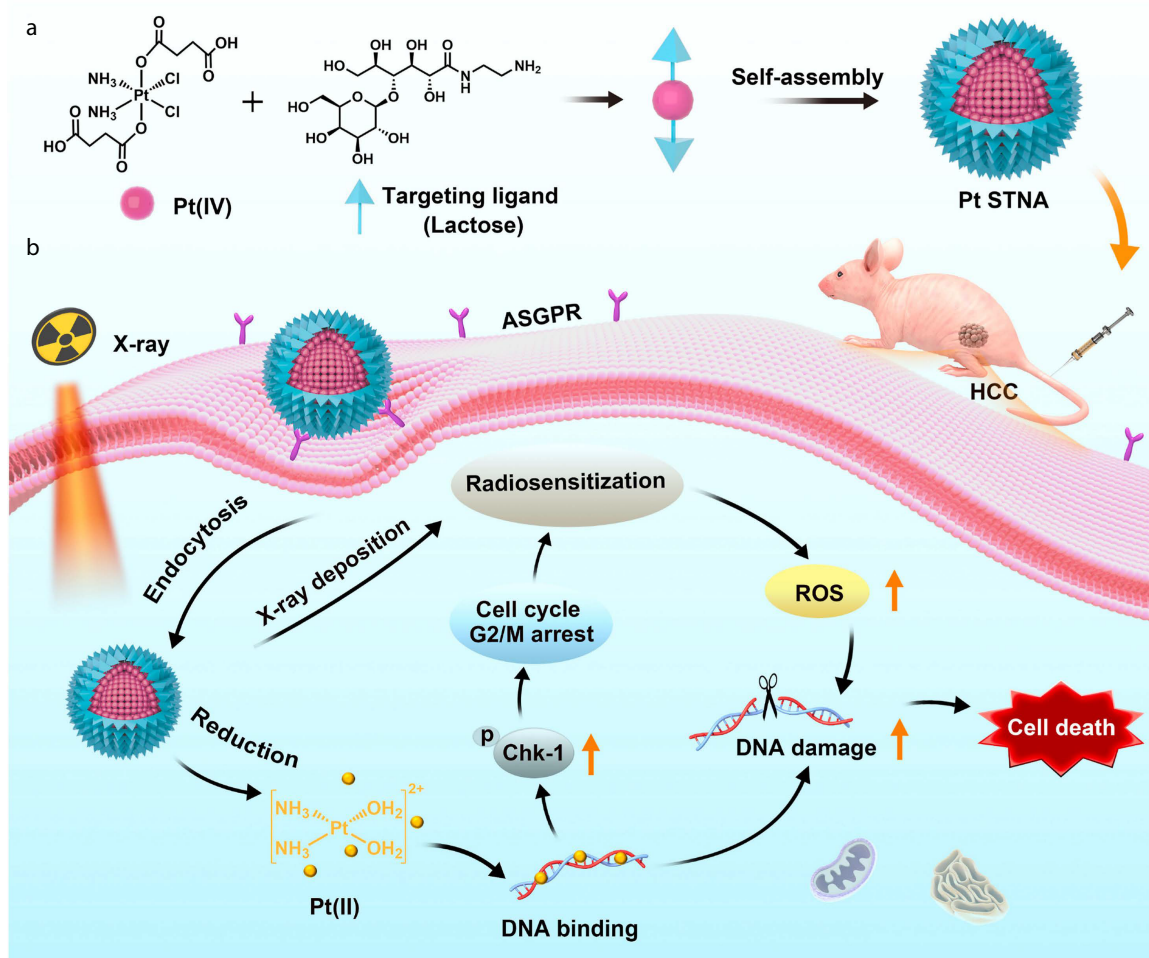


Fig. 2 (a) Pt STNA-based schematic representation of the nano-assembly mechanism; (b) Method of Pt STNA for effective chemoradiotherapy of hepatocellular carcinoma (HCC). (Reproduced with permission from Ref. [36]; Copyright (2022), Elsevier Ltd.)

The ionization energy and density govern proton radiation-induced ionization and ROS generation. Pt offers lower ionization energy and higher density than Au, yielding superior radiosensitization.^[130] Xiao *et al.* synthesized lactose-conjugated amphiphilic Pt(IV) prodrug nanoparticles (Pt STNA) that target liver cancer cells. Cisplatin (II) damages DNA and generates ROS to eliminate gap2 phase/mitosis phase-phase cells, strengthening the therapeutic outcomes (Fig. 2).^[36] To further amplify DNA damage, Ma *et al.* constructed a Pt–Bi coordination platform (NP@PVP) *via* a facile route; Bi enhanced ROS-mediated DNA damage, whereas cisplatin inhibited DNA repair, acting in spatial synchrony to boost CRT efficacy.^[32] In addition to DNA-targeting strategies, Jin *et al.* co-encapsulated cisplatin and indocyanine green (ICG) in gelatin shells for synergistic CRT, thereby adding a phototherapeutic dimension.^[37] Expanding the material scope beyond Pt, Pi *et al.* designed a cerium dioxide (CeO₂)-MnO₂ core-shell nanocomposite, where CeO₂ generated ROS and Mn²⁺ reacted with H₂O₂ to produce ROS while depleting GSH. Notably, the degraded Mn ions also enabled magnetic resonance imaging (MRI), achieving dual therapeutic and imaging functionalities (Fig. 3).^[38]

Collectively, these examples demonstrate the evolution of metal-based radiosensitizers, from single-metal Pt nanoparticles to multi-metal synergistic systems and multimodal platforms. A key advantage of such metal-based nanosystems is their inherent theranostic potential. Their metal components not only boost ROS generation for radiotherapy enhancement, but also serve as imaging contrast agents. This dual functionality enables image-guided personalized CRT with re-

al-time treatment monitoring.

3.4 GSH

As an endogenous antioxidant, GSH scavenges excess ROS and protects cells from oxidative stress, thereby significantly compromising the efficacy of CRT.^[131] Thus, designing GSH-depleting nanomedicines or suppressing tumor GSH expression represents a promising strategy to boost the effectiveness of CRT.

3.4.1 GSH responsive drug delivery

Owing to their synthetic flexibility and rapid cleavage in the high-GSH tumor microenvironment, disulfide bonds have been widely employed in GSH-responsive drug delivery systems. Guo *et al.* utilized disulfide bonds to encapsulate a proteolysis targeting chimera (PROTAC) molecule within a nanocapsule shell, generating a nanoplatfrom termed MPL_(SS)P@SIS.^[39] In animal models, when combined with TMZ and radiotherapy, this nanocapsule enhances DNA damage and oxidative stress, thereby potentiating both chemotherapy and radiotherapy. Our group also constructed a theranostic nanoplatfrom by conjugating 2,3,5-triiodobenzoic acid to paclitaxel (PTX) and a polymeric carrier *via* disulfide linkages, thereby improving PTX encapsulation.^[40]

In addition to disulfide bonds, other GSH-responsive moieties have also been explored. Hu *et al.* designed a nanoplatfrom (CA4-DNBS@ICG) based on a sulfonate ester bond, which is another GSH-cleavable linkage.^[41] Upon exposure to high GSH levels, this system releases both the anticancer drug CA4 and sulfur dioxide (SO₂). SO₂ not only exerts direct antitumor effects, but also consumes GSH, further amplifying oxidative stress.

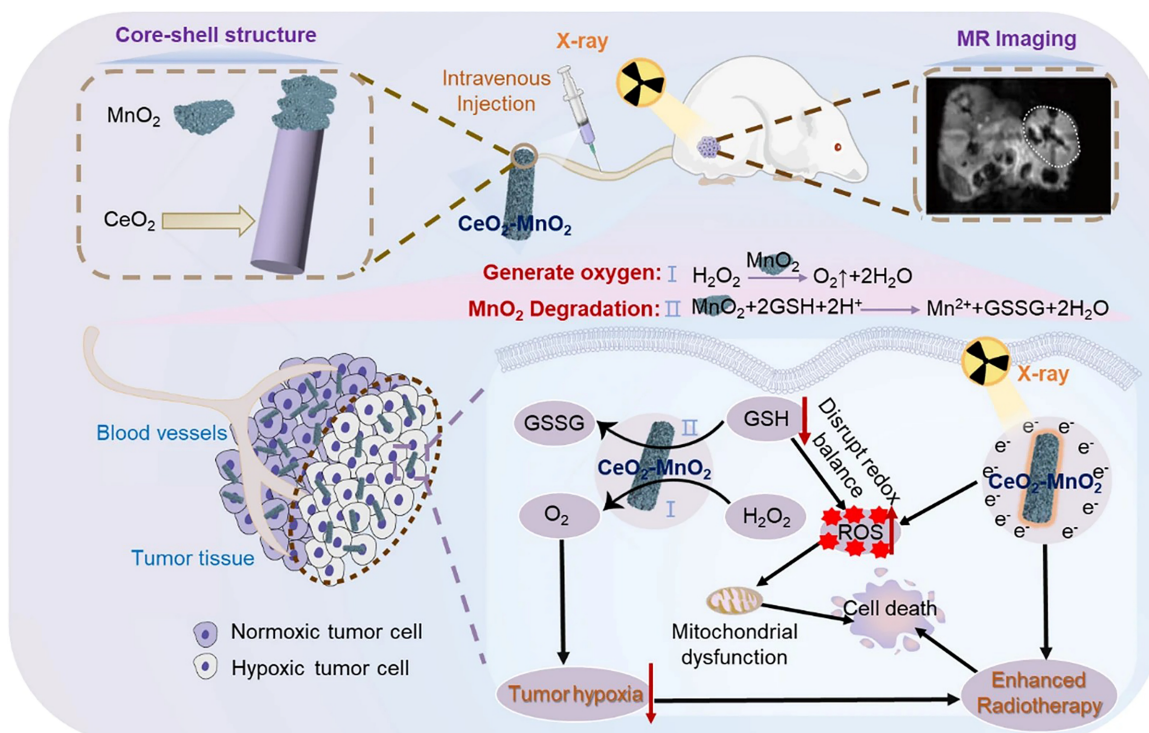


Fig. 3 Schematic structure of CeO₂-MnO₂ and its mechanism of action in radiotherapy and MRI *in vivo*. While Ce produces ROS, Mn²⁺ can also consume GSH and produce oxygen, alleviating the tumor's anoxic environment. (Reproduced with permission from Ref. [38]; Copyright (2023), The Author(s), Springer Nature.)

3.4.2 GSH consumption

Hou *et al.* fabricated a yolk-shell $\text{Bi}_2\text{S}_3@\text{mBixMnyOz}$ nanosystem using bismuth sulfide (Bi_2S_3) nanorods as the etching template for doxorubicin (Dox) loading.^[42] Mn-containing shells deplete tumor GSH, relieve hypoxia, downregulate glutathione peroxidase 4, and induce ferroptosis, whereas the Bi_2S_3 core enhances radiation deposition to synergize CRT. Similarly, Zhang *et al.* developed a biodegradable BiPt nanocomposite modified with folate-PEG (PFA) (Fig. 4).^[33] The Bi moiety consumes GSH, and Pt catalyzes H_2O_2 decomposition to generate oxygen, alleviating hypoxia and boosting the efficacy of radiotherapy. In both systems, GSH depletion serves as a core strategy to compromise the antioxidant defenses of cancer cells, rendering them more susceptible to radiation-induced oxidative damage. Moreover, GSH consumption can be readily integrated with other therapeutic modalities such as ferroptosis induction or hypoxia relief, to further amplify CRT efficacy.

3.5 Mildly Acidic Environment

pH-responsive nanomedicines represent a typical strategy to overcome the limitations imposed by a mildly acidic TME. Luan *et al.* developed a pH-sensitive AuNP system (AuNPs-D-P-DA) for targeted CRT delivery. When modified with acid-cleavable 2,3-dimethylmaleic anhydride (DA), the negatively charged

nanoparticles undergo surface charge reversal in the acidic tumor milieu, promoting tumor accumulation and effective radiosensitization (Fig. 5).^[43] Acid-triggered drug release elevates ROS levels and induces mitochondrial injury and gap 1 phase arrest, thereby enhancing CRT efficacy. Similarly, Xiao *et al.* designed a Dox@Gel-DEVD-AuNR delivery system that released Dox and simultaneously generated photoacoustic signals from AuNP aggregates to determine the optimal timing for radiotherapy, enabling precise image-guided irradiation.^[44]

Compared to Luan's system, Xiao's design adds real-time imaging. This highlights the growing trend of integrating drug delivery with diagnostic imaging to achieve theranostic precision in CRT.

Acidity can also trigger the structural transformation of nanomedicines. By leveraging the pH-responsiveness of zeolitic imidazolate framework-8 (ZIF-8), Du *et al.* constructed a dual-functional delivery system with both pH sensitivity and radiosensitizing activity.^[45] ZIF-8 enables high-capacity^[132] loading of Dox and Dbait, which were further coated with osteosarcoma-platelet hybrid membranes (OPM) to enhance tumor targeting and CRT efficacy. In metal-organic frameworks, pH-responsive organic nanomaterials have also been extensively explored. He *et al.* fabricated pH-responsive polymerosomes from amphiphilic polycaprolactone-poly(2-ethyl-2-ox-

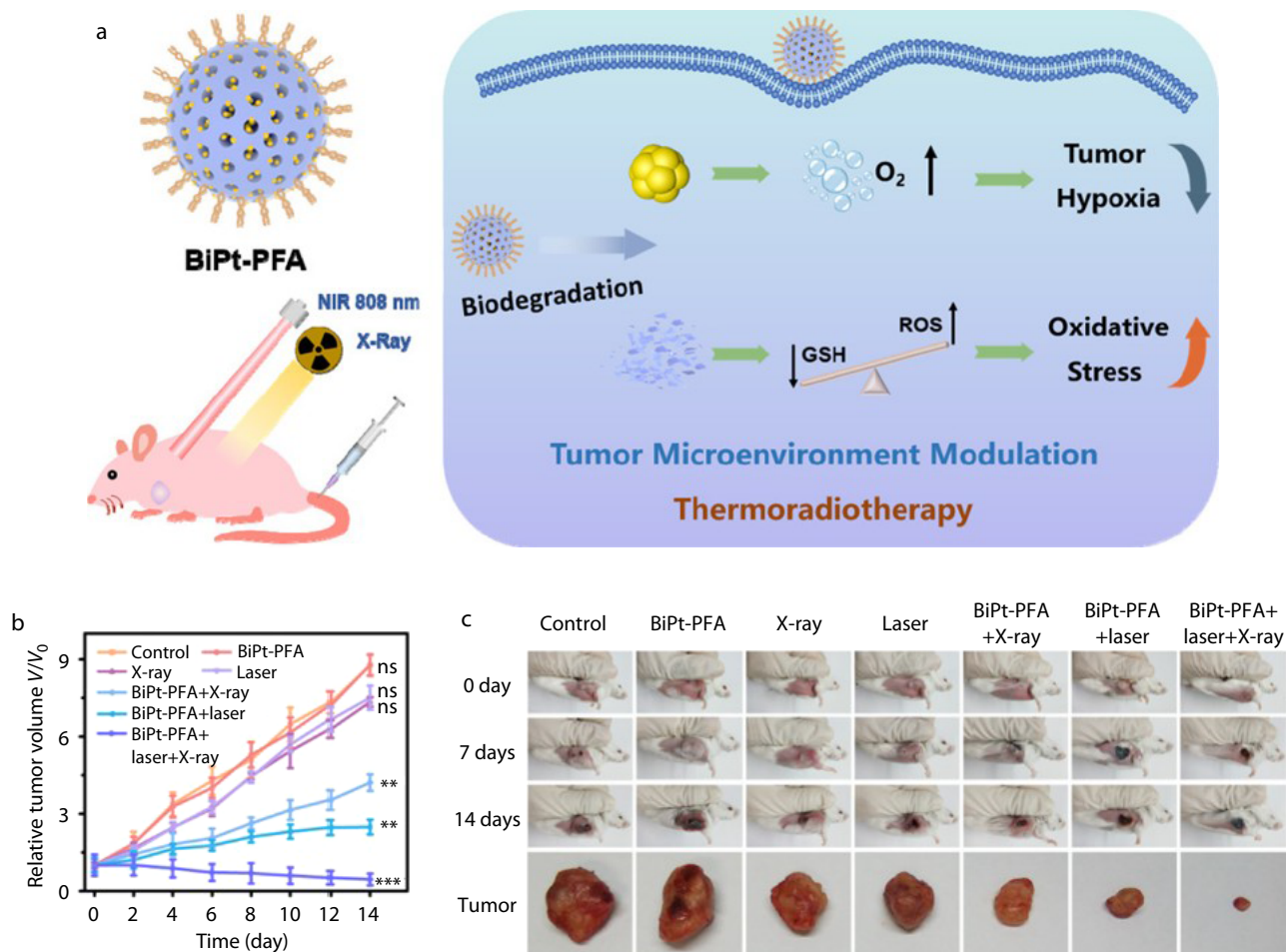


Fig. 4 (a) Illustration of BiPt-PFA NPs used in synergistic thermoradiotherapy; (b, c) BiPt-PFA used for the treatment of solid tumors (b) tumor volume curve, (c) photos of mice and tumors. (Reproduced with permission from Ref. [33]; Copyright (2020), American Chemical Society.)

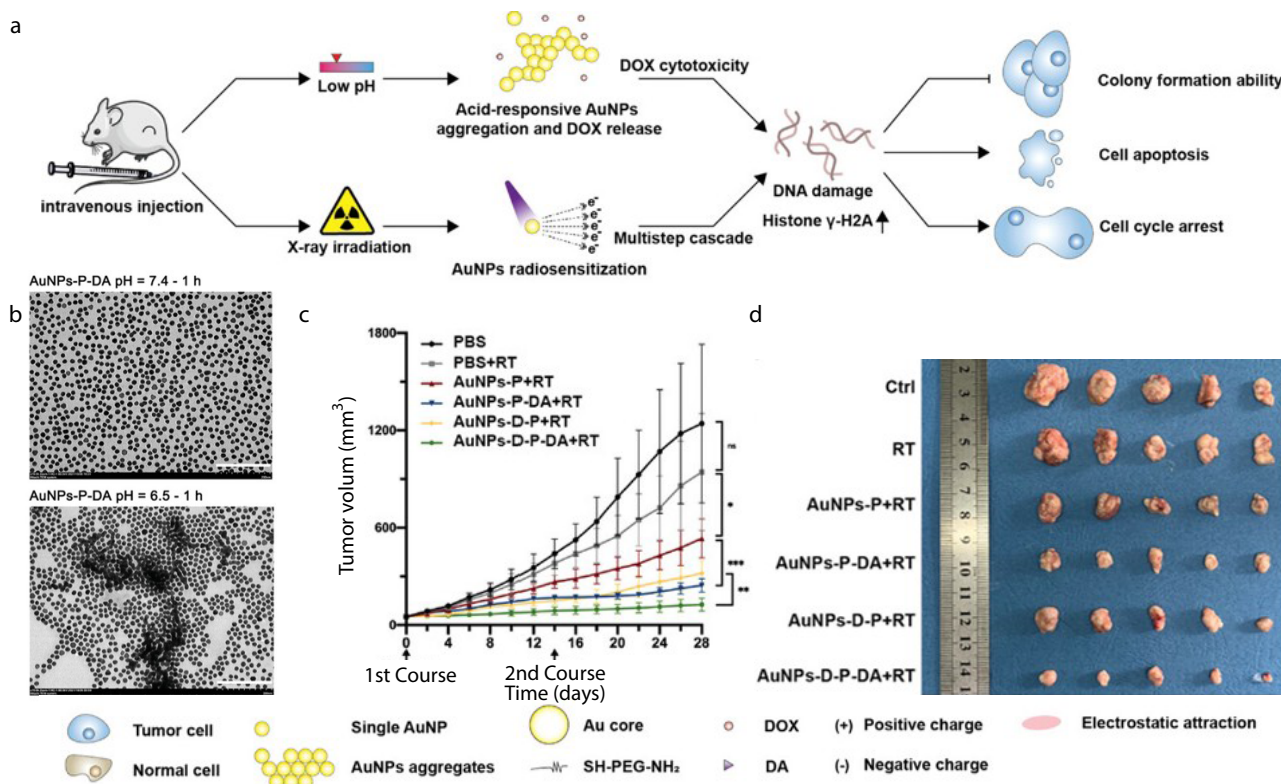


Fig. 5 (a) Schematic representation of the mechanism of action and structure of AuNPs-D-P-DA in different cells. AuNPs-D-P-DA aggregates in the weakly acidic microenvironment and deposits at the tumor site. It maintains its original structure in normal cells. (b) TEM pictures of AuNPs-P-DA at various pH levels (Scale bar: 200 nm). (c) Tumor growth curves treated with AuNPs-D-P-DA. (d) Pictures of tumors in groups treated with different methods. ($n=5$). (Reproduced with permission from Ref. [43]; Copyright (2022), Wiley-VCH GmbH.)

azoline) (PCL-PEOz), encapsulated Au NP–Dox conjugates, and modified the surface with Angiopep-2 (ANG).^[46] pH responsiveness is mediated by the tertiary amide groups of PEOz, which become protonated in an acidic environment, destabilize the polymersomes, and trigger drug release. Similarly, Li *et al.* developed a pH-responsive gold nanoassembly by modifying Au NPs with raltitrexed (RTX)-PEG and two tertiary amine moieties. At a blood pH (7.4), the assembly remains at about 160 nm; in the acidic tumor milieu, protonation of tertiary amines dissociates it into 6 nm Au NPs,^[47] which deeply diffuse into tumors and markedly enhance CRT. Collectively, these three pH-responsive systems demonstrate that protonation is the central driving force for acid-triggered structural transformation. Whether through protonation of acid-labile coordination bonds in ZIF-8 or tertiary amino groups in polymersomes and gold nanoassemblies, the resulting structural changes include degradation, destabilization, or size reduction. These changes enable tailored drug release and tumor penetration. This protonation-centered design principle underscores the versatility of pH-responsive nanocarriers in CRT applications.

3.6 Targeting Specific Cellular Component

Folate receptors (FRs) mediate cellular folate uptake and promote malignant tumor progression.^[133] Upon folate binding, FRs activate the janus kinase (JAK)/signal transducer and activator of transcription3 (STAT3) pathway *via* coreceptor gp130, driving proliferation, suppressing apoptosis, and facilitating ma-

lignant transformation.^[134,135] FRs are overexpressed in cervical, breast, colon, lung, and renal cancer.^[136–138]

Integrins mediate the connection between the ECM and cytoskeleton.^[139] Through signal transduction, they activate protein kinases, trigger intracellular pH and Ca²⁺ fluctuations, and regulate cell proliferation and adhesion.^[140] Integrin $\alpha_v\beta_3$ is critical for vascular survival, maturation, and tumor cell proliferation.^[141,142] Arginine–glycine–aspartic acid (RGD) peptides bind to approximately half of the 20 known integrins,^[143] making them ideal for nanoparticle surface modification to target $\alpha_v\beta_3$.

By leveraging both FR and integrin $\alpha_v\beta_3$ as targets, Wang *et al.* developed an inorganic nanosystem (Pt@Ce-MOF-RGD/FA) with dual RGD/folate (FA)-targeting functionality.^[48] This system enables precise targeting of breast cancer cells while enhancing ROS generation to achieve radiosensitization. Notably, the dual-targeting strategy exhibited superior tumor accumulation compared to single-ligand modification.

Various targeting strategies have also been employed to improve the delivery of radiosensitizing chemotherapeutics such as 5-fluorouracil (5-FU). Although 5-FU is an established radiosensitizing chemotherapeutic agent,^[144] its short half-life and propensity for drug resistance limit its clinical utility.^[145,146] To overcome these limitations, Mirzaghavami *et al.* developed an FA-modified triblock magnetic nanocarrier for targeted 5-FU delivery, which selectively radiosensitized HT29 cancer cells. The incorporated superparamagnetic iron oxide also enabled magnetic hyperthermia in deep tumors

under an alternating magnetic field, integrating thermotherapy with chemoradiotherapy.^[49] In another targeting approach for 5-FU delivery, Shi *et al.* utilized a hyaluronic acid shell to endow the nanoplatform with CD44 receptor-mediated tumor targeting capability (Fig. 6).^[50]

The targeting peptide ANG has been widely employed for glioblastoma (GBM) therapy. Its binding site, lipoprotein receptor-related protein-1, is a key component of the blood–brain barrier (BBB) and is highly expressed in GBM cells.

Therefore, modification with ANG enables nanoparticles to cross the BBB and specifically target GBM. Using this strategy, Su *et al.* developed an ANG-functionalized nanoparticle (DC-NP@P(Se-Dox)@ANG) for precise GBM targeting and CRT (Fig. 7).^[51] Upon X-ray irradiation, this system triggered the release of Dox while simultaneously enabling second near-infrared window (NIR-II) fluorescence imaging, thereby achieving theranostic integration.

These approaches not only help overcome major biological barriers, including the blood-brain barrier, but also improve cellular uptake and reduce off-target effects. Consequently, such functionalized NS can amplify the efficacy of chemoradiotherapy while minimizing systemic toxicity. Given their versatility and specificity, these targeting strategies hold great promise for advancing next-generation chemoradiotherapy applications.

3.7 TIME

TIME is highly heterogeneous across cancer types and patient populations, and is closely correlated with clinical prognosis.^[147] Radiation reshapes the ratio of effector T cells to Tregs,^[148] partly because ROS preferentially induce apoptosis in effector T cells rather than Tregs through a thioredoxin-dependent

pathway.^[149] Meanwhile, chemotherapeutics such as gemcitabine and 5-FU, exert cytotoxicity toward MDSCs, further contributing to immune regulation by CRT.^[150,151] On the other hand, growing evidence indicates that CRT triggers immunogenic cell death (ICD), enhances DC-mediated antigen uptake and presentation, elicits antigen-specific cytotoxic T lymphocyte responses, and promotes an immunogenic tumor phenotype.^[152–156]

Given the immune response heterogeneity across cancer types and patient populations, immunotherapeutic strategies that remodel TIME and restore immune cell cytotoxicity have gained extensive attention in CRT.^[157,158] Sun *et al.* developed an *in situ* hydrogel for CRT combined with immune checkpoint inhibition. Sodium alginate-ATP aptamer (Aapt) conjugates crosslink with Ca^{2+} at the tumor site to form a hydrogel, where Aapt competes with ATP to trigger CpG oligodeoxynucleotide release and induce ICD (Fig. 8).^[52] *In vivo* studies have shown enhanced DC maturation in draining lymph nodes; this hydrogel system boosted antitumor immunity, lowered drug dosage, and enabled sustained adjuvant delivery during CRT. Similarly, Liu *et al.* fabricated an injectable thermosensitive hydrogel (PPS-SeNPs@Dox) co-loaded with selenium nanoparticles and Dox for localized HCC-CRT. Combined with X-ray irradiation, this system activated antitumor immunity by increasing CD8^+ T, M1, and NK1.1 cells while reducing Gr1^+ cells.^[53]

Zhu *et al.* developed a self-amplifying prodrug nanovesicle co-loaded with oxaliplatin and ruxolitinib for CRT in head and neck cancer. Matrix metalloproteinase 2(MMP-2)-mediated PEG shedding facilitates tumor accumulation and deep penetration, inducing ICD and radiosensitisation. By blocking the IFN- γ -JAK-STAT axis, this nanosystem suppresses CRT-upregulated programmed death-ligand 1 (PD-L1) expression and

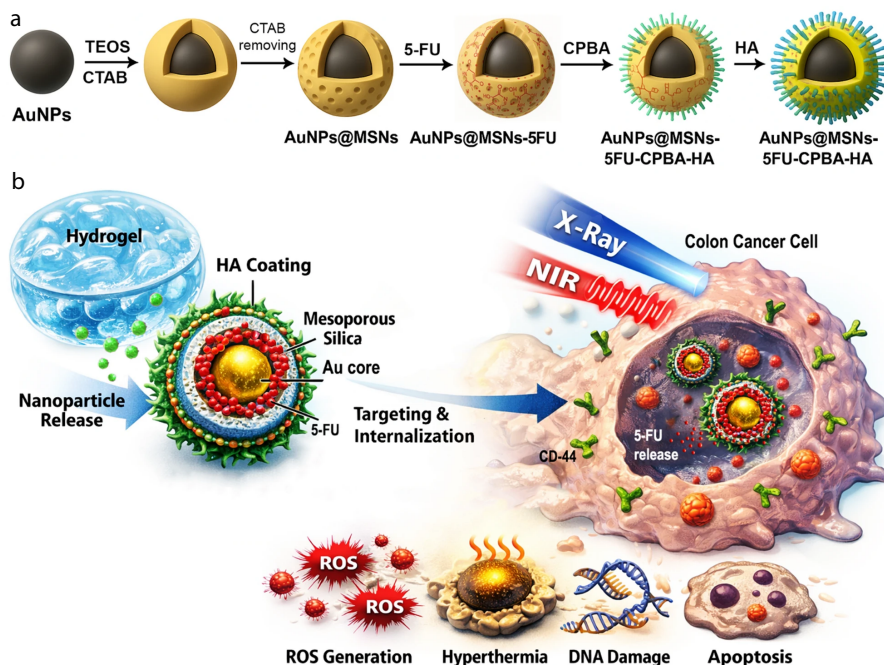


Fig. 6 (a) Schematic structure of nanoparticles; (b) Schematic illustration of the AuNPs@MSNs-5FU-CPBA-HA for targeted combined chemotherapy, photothermal therapy, and radiotherapy. (Reproduced with permission from Ref. [50]; Copyright (2026), The Author(s), Springer Nature.)

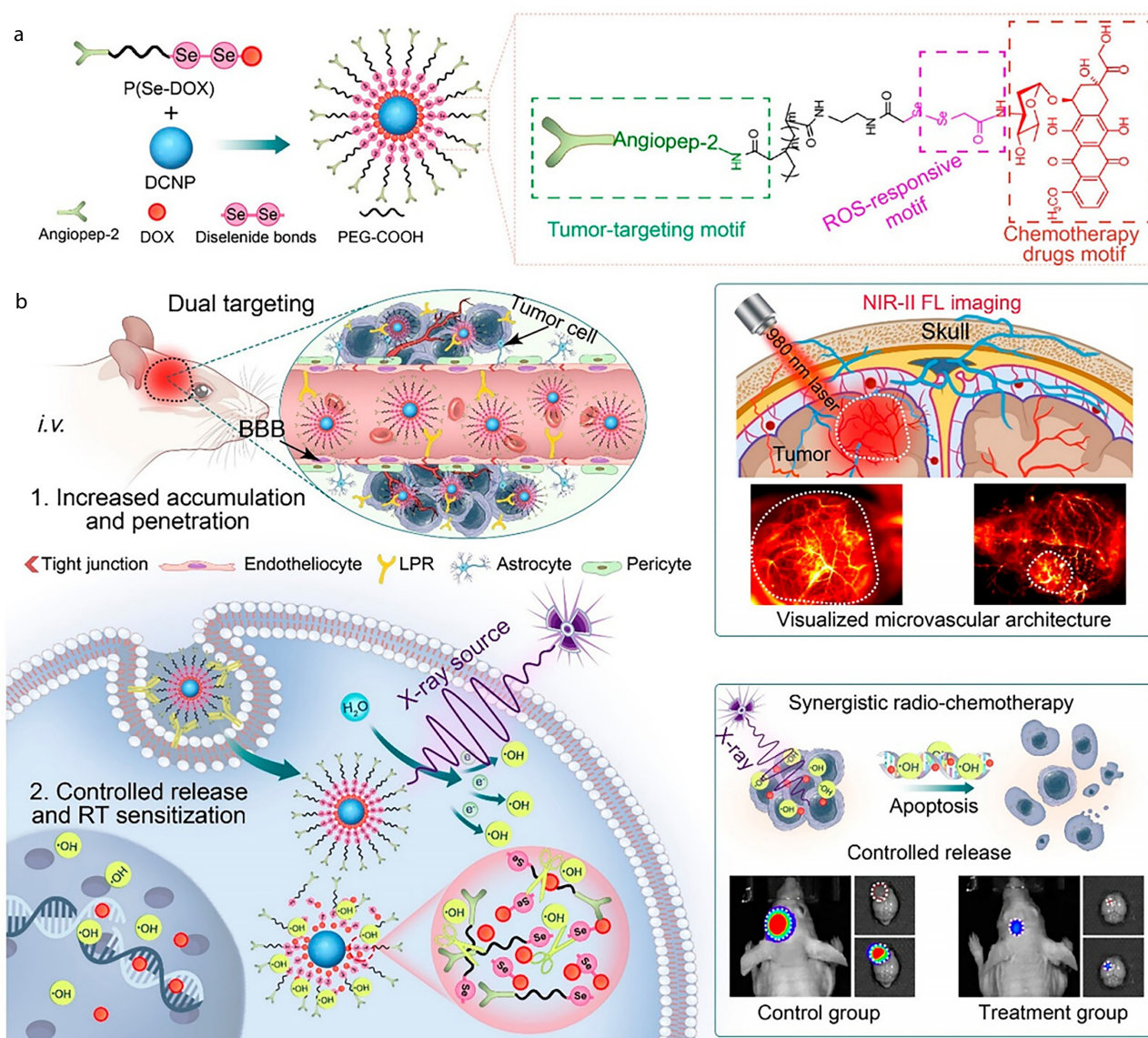


Fig. 7 (a) Schematic structure of nanoparticles; (b) Schematic diagram of the DCNP@P(Se-Dox)@ANG preparation process and targeting strategy. (Reproduced with permission from Ref. [51]; Copyright (2024), American Chemical Society.)

synergizes CRT with immunotherapy.^[54] Chen *et al.* fabricated a dual-functional radiosensitive nanoregulator using gold nanoparticles modified with the AS1411 aptamer and M2pep peptide to remodel tumor-macrophage crosstalk. Low-dose irradiation triggers ROS generation, activates NF- κ B signaling, repolarizes M2 macrophages to M1 macrophages, and activates local antitumor immunity.^[55]

Among various immunotherapies, immune checkpoint inhibitors (ICIs) have been widely used in clinical cancer treatment. However, their clinical application remains limited because most patients lack sensitivity to ICIs and these agents are prone to cause autoimmune adverse effects.^[159] Utilizing nanoparticles to improve the targeting efficiency of ICIs represents a promising strategy for addressing these challenges. For instance, Zheng *et al.* encapsulated α -PD-L1 within MnO₂ nanoparticles. Upon radiotherapy, this system reprograms the TIME and elicits potent antitumor immune responses.^[56]

4 CLINICAL APPLICATIONS OF NS IN CRT

In addition to preclinical studies of NS-enabled CRT, several nanoplateforms have been assessed in clinical trials, including cisplatin, PTX, doxorubicin liposomes, nab-paclitaxel, nanocamptothecin, and metal nanoparticles (Table 2). Although these NS have achieved antitumor efficacy in preclinical studies, successful clinical translation remains challenging. Key obstacles include the biological complexity of the tumor and the host microenvironment. Comprehensive long-term biosafety and biodistribution data are urgently required. Furthermore, precise and customized models for nanoparticle-enhanced radiotherapy must be developed. Given these challenges, the clinical application of such complex nanoplateforms necessitates multidisciplinary collaboration to devise patient-specific nanochemoradiotherapy strategies.^[160]

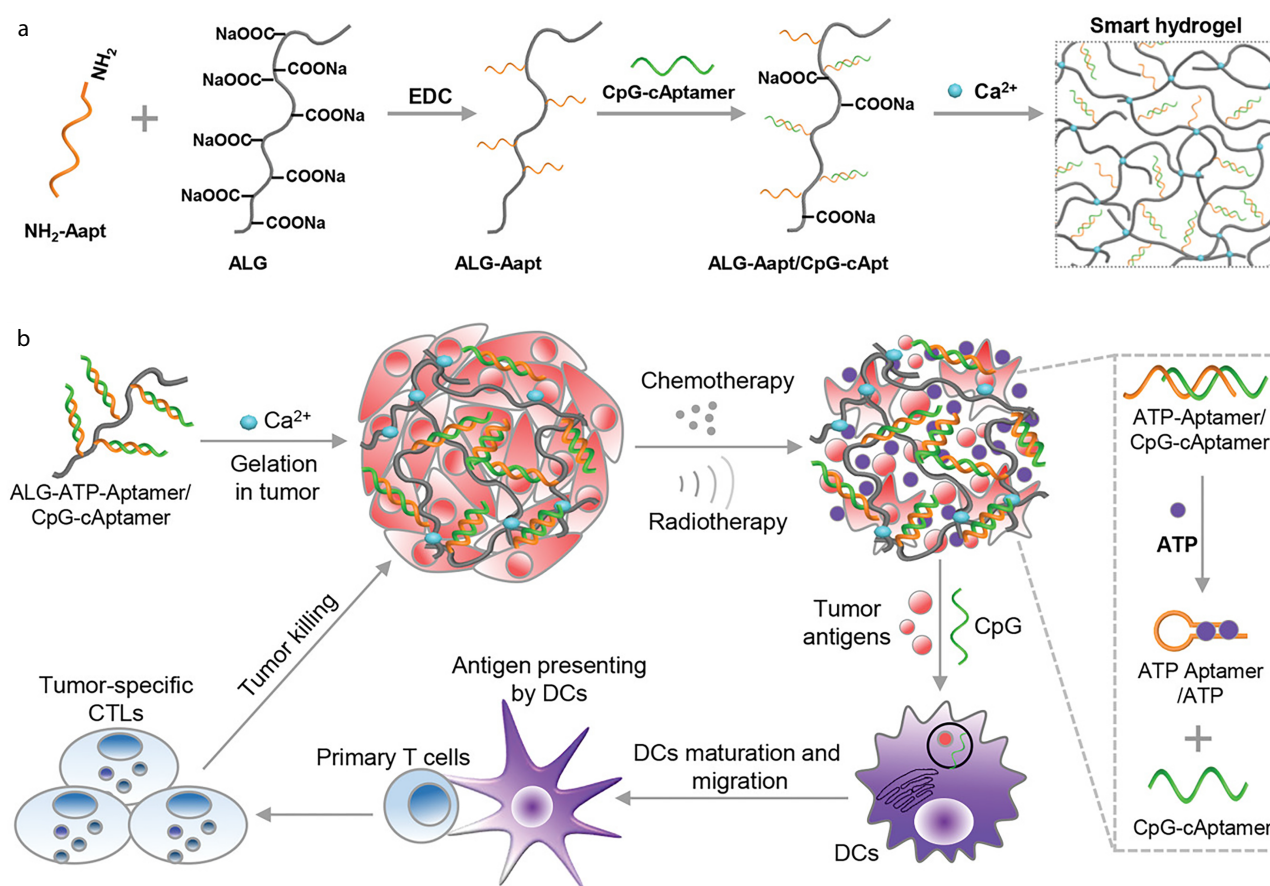


Fig. 8 (a) Schematic construction of adenosine triphosphate (ATP)-responsive ALG-Apt/CpG hydrogels; (b) Schematic diagram of the mechanism of action of smart hydrogel at the tumor site. In the presence of ATP, CpG is released to induce immunogenic cell death. (Reproduced with permission from Ref. [52]; Copyright (2021), Wiley-VCH GmbH.)

4.1 Liposomes

4.1.1 Cisplatin liposomes

In clinical trials of liposomal cisplatin, SPI-077 was evaluated in a phase I study of head and neck squamous cell carcinoma (HNSCC). Among the 20 patients, it demonstrated low systemic toxicity and a 25% disease-free survival rate.^[161] In another cohort of 12 patients receiving liposomal cisplatin, 5-FU, and concurrent radiotherapy, no severe acute or chronic hepatic, renal, or gastrointestinal toxicity was observed. Extending the treatment cycle increased the complete tumor response rate from 33% to 80%, supporting further investigation of this chemoradiotherapy combination.^[162,186]

4.1.2 Paclitaxel liposomes

The effectiveness and viability of CRT with paclitaxel liposomes and cisplatin in locally advanced esophageal squamous cell carcinoma (ESCC) were assessed in a clinical trial. These findings demonstrated that CRT treatment with cisplatin and paclitaxel liposomes is a safe and successful treatment for locally advanced ESCC.^[163,187] In another trial, the same combination showed significant antitumor activity with manageable toxicity against locally advanced lung squamous cell carcinoma (LSCC).^[164]

4.1.3 Doxorubicin liposomes

Liposomal doxorubicin combined with radiotherapy has been

evaluated in multiple clinical trials across various cancers, including glioblastoma, ovarian cancer, recurrent breast cancer, prostate cancer, non-small cell lung cancer, and head and neck cancer.^[165,188–191] In a trial of radiotherapy plus temozolomide and PEGylated liposomal doxorubicin, 35 patients achieved a median survival of 13.4 months with favorable tolerability.^[166]

4.2 Albumin-bound Paclitaxel (Nab-paclitaxel)

Nab-paclitaxel (about 130 nm) is a clinically evaluated nanochemotherapeutic drug that avoids solvent-related toxicity and exhibits radiosensitizing activity.^[192] Leveraging the transendothelial transport of albumin and the tumor EPR effect improves paclitaxel delivery and intratumoral accumulation.^[193,194] In a phase III trial for metastatic breast cancer, the maximum tolerated dose was 49% higher than that of solvent-based paclitaxel, which was attributed to the lack of toxic solvents.^[195] It also synergizes directly with gemcitabine and capecitabine by boosting tumor accumulation.^[194] Mechanistically, nab-paclitaxel downregulates gemcitabine-metabolizing cytidine deaminase (CDA), while paclitaxel-derived ROS further degrade CDA, slowing gemcitabine breakdown and strengthening therapeutic synergy.^[196] Currently, it is indicated for breast, lung, pancreatic, and head and neck cancers.^[197]

Surgical resection remains the optimal treatment for pancreatic cancer; however, most patients present with locally advanced or borderline resectable disease. Nab-paclitaxel

Table 2 Clinical trials of nanomedicine in CRT.

No.	Nanoparticles	Patient populations	Clinical trail	Phase
1	Cisplatin liposomes	HNSCC	/[161]	I
2	Cisplatin liposomes/5-FU	Gastric cancer	/[162]	I/II
3	Paclitaxel liposomes/carboplatin	ESCC	/[163]	/
4		LSCC	/[164]	/
5	Pegylated liposomal doxorubicin/temozolomide	GBM	NCT00944801[165]	I/II
6		GBM	/[166]	II
7	GEM/nab-Paclitaxel	Pancreatic cancer	/[167]	/
8			NCT02301143[168]	II
9	Cisplatin/nab-Paclitaxel	Esophageal squamous cell carcinoma	ChiCTR1900021079[169]	I
10	Cisplatin/nab-Paclitaxel/cetuximab	HNSCC	NCT02573493[170]	II
11			NCT01412229[171]	II
12	Cisplatin/nab-Paclitaxel/5-FU	HNSCC	NCT01566435[172]	II
13	Carboplatin/nab-paclitaxel	Non-small cell lung cancer	Phase I: UMIN000010480, Phase II: UMIN000023802[173]	I/II
14			UMIN 000014764, JRCTs042180077[174]	I
15			UMIN000020359[175]	I
16			UMIN000011681[176]	II
17			UMIN000012719[177]	I/II
18	CRLX101/capecitabine	Rectal cancer	NCT02010567[178]	I/II
19	AGuIX	BrM	NCT02820454[179]	Ib
20			NCT03818386[180]	II
21		Lung tumors and pancreatic cancer	NCT04899908 (ongoing)[181]	II
22			NCT04789486 (ongoing)[181]	I/II
23	AGuIX/TMZ	GBM	NCT04881032[182]	I/II
24	Promitil	Metastatic or inoperable tumors	NCT03823989[183]	Ib
25	NBTXR3	HNSCC	NCT01946867[184]	I
26	NBTXR3/cetuximab	HNSCC	NCT04892173 (ongoing)[185]	III

combined with radiotherapy shows toxicity similar to standard CRT, offering an alternative for patients intolerant to 5-FU or gemcitabine.[198] A clinical trial confirmed the feasibility of gemcitabine/nab-paclitaxel plus radiotherapy, with longer median overall survival and early tumor shrinkage favoring subsequent resections.[167] This regimen has been validated as safe in multiple clinical studies.[168,199]

Another phase I trial evaluated the safety, dose-limiting toxicity, and maximum tolerated dose of nab-paclitaxel/cisplatin combined with radiotherapy for advanced esophageal squamous cell carcinoma, demonstrating mild, manageable toxicity, and favorable antitumor activity.[169] Consistent outcomes have been reported in studies on head and neck cancer.[170–172] The nab-paclitaxel/carboplatin/radiotherapy combination is under investigation for unresectable locally advanced non-small cell lung cancer.[173–177] In elderly inoperable patients, weekly nab-paclitaxel/carboplatin plus thoracic radiation achieved a 76.5% overall response rate.[174] Biweekly administration improved survival and reduced grade ≥ 2 pneumonia, although grade 1 pneumonia remained frequent and warrants further investigation.[173]

4.3 Nano-camptothecin

CRLX101 is a camptothecin-loaded nanoparticle-drug conjugate that enhances efficacy by inhibiting tumor HIF-1 α signaling and DNA repair while also acting as a radiosensitizer.[200] A clinical trial evaluated the pathological complete response (pCR) rate in neoadjuvant chemoradiotherapy for locally advanced rectal cancer, with 33% of patients achieving pCR at a weekly dose of 15 mg/m². [178]

4.4 AGuIX

AGuIX is a novel gadolinium-based nanoparticle radiosensitizer that has been clinically evaluated for the treatment of brain metastases. At just 3 nm, these ultrasmall NPs are rapidly cleared with no long-term toxicity, supporting their safe clinical use.[201] AGuIX preferentially accumulates and is retained in brain metastases for up to one week, enabling personalized radiotherapy; it also visualizes biomarkers and provides sustained MRI contrast.[202] In a Phase Ib trial, 13 of the 14 patients achieved tumor stabilization or shrinkage. Phase I data confirmed the absence of off-target activity outside the radiation field.[179] In subsequent Phase II clinical trials, AGuIX exhibited favorable accumulation in brain metastases (BrM), while exerting minimal effects on healthy brain tissue. Furthermore, it enhances radiotherapy efficacy, striking a balance between therapeutic efficacy and biosafety. [180–182]

4.5 Promitil

Promitil is a liposomal prodrug nanoformulation of mitomycin C (MMC), in which the active agent is conjugated through readily cleavable disulfide linkages.[203] In preclinical animal studies, this prodrug formulation demonstrated approximately three-fold lower systemic toxicity than free MMC, while maintaining equivalent antitumor efficacy.[204] Subsequent preclinical studies further demonstrated that when combined with 5-FU in chemoradiotherapy, Promitil possesses radiosensitizing activity.[205] In clinical trials, Promitil consistently showed a favorable safety profile and improved dose tolerability. Notably, in a Phase Ib study enrolling 19 patients with metastatic or inoperable tumors, the combination of Promitil and radiotherapy achieved

robust tumor progression control and good tolerability, with a median overall survival of 63.3 weeks.^[183,206]

4.6 NBTXR3

NBTXR3 is a radioenhancer composed of hafnium oxide nanoparticles with a size of approximately 50 nm. Owing to its exceptionally high atomic number, NBTXR3 enhances radiation energy deposition within tumor cells and promotes ROS generation. As it is administered *via* intratumoral injection, non-injected normal tissues are completely spared from exposure to the nanoparticles and associated radiation enhancement. In pre-clinical animal studies, NBTXR3 was well distributed within tumors as early as one day post-injection and persisted for one–two weeks.^[207] Previous Phase I clinical trials demonstrated that NBTXR3 exhibits no unexpected toxicity and shows promising preliminary antitumor activity, with a median overall survival of 18.1 months.^[184] Currently, a Phase III clinical trial is underway in elderly patients with locally advanced HNSCC who are ineligible for cisplatin-based therapy. This trial combined NBTXR3 with cetuximab and radiotherapy and is anticipated to improve treatment outcomes in this medically challenging patient population.^[185]

5 CONCLUSIONS AND PERSPECTIVE

CRT spares normal tissues while enhancing tumor killing, making it safer and more effective than chemotherapy or radiotherapy alone. TME, characterized by hypoxia, acidity, oxidative stress, vascular dysfunction, cellular heterogeneity, and dense ECM, severely impairs drug delivery and CRT efficacy, compromising clinical outcomes. Owing to the short circulation half-life and poor performance of small-molecule radiosensitizers, the development of NS to overcome TME-associated delivery barriers and therapeutic resistance has become a central focus in drug research. This review summarizes recent preclinical and clinical advances in this field.

Although nanomaterials can boost radiation absorption, alleviate hypoxia, or sensitize hypoxic cells, dense ECM and complex cellular components in solid tumors limit deep penetration. Tumor physicochemical heterogeneity further undermines single-stimulus-responsive NS, highlighting the need for next-generation NS with robust deep tumor penetration and multimodal sensitization capabilities. While CRT induces ICD in cancer cells, it may also trigger immunosuppression. The complex crosstalk between CRT and the immune system requires innovative strategies to amplify anti-tumor immunity. Clinical trials combining immune checkpoint inhibitors with CRT have significantly improved survival and quality of life, supporting the potential of CRT-immunotherapy combinations. However, heterogeneous patient responses necessitate the identification of predictive biomarkers to select the beneficiaries for immunotherapy.^[208] This challenge underscores the need for TME-based predictive biomarkers for NS-enhanced CRT. Machine-learning models can be developed to integrate TME biomarker profiles. These models may predict the optimal composition and dosing regimen of NS. Such biomarkers can also be used to stratify the patients who are most likely to benefit. Prospective clinical trials with biomarker analysis are thus of greater importance than conventional, one-size-fits-all NS development.

Despite rapid progress in TME-responsive NS for CRT, key challenges remain, particularly in clinical translation. A major obstacle lies in the structural complexity of most TME-responsive NS, which leads to poor batch-to-batch reproducibility and stability. Therefore, simplified and scalable synthetic routes are urgently needed, along with well-defined quality control metrics. Nevertheless, their strong therapeutic potential inspires confidence in the results. Combining CRT with immunotherapy, gene therapy, or other modalities offers new opportunities. The development of theranostic NS that integrates diagnosis and therapy represents a promising clinical direction. With ongoing developments, TME-targeted NS will become a powerful tool for clinical cancer treatment.

BIOGRAPHIES

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Conflict of Interests

The authors declare no interest conflict.

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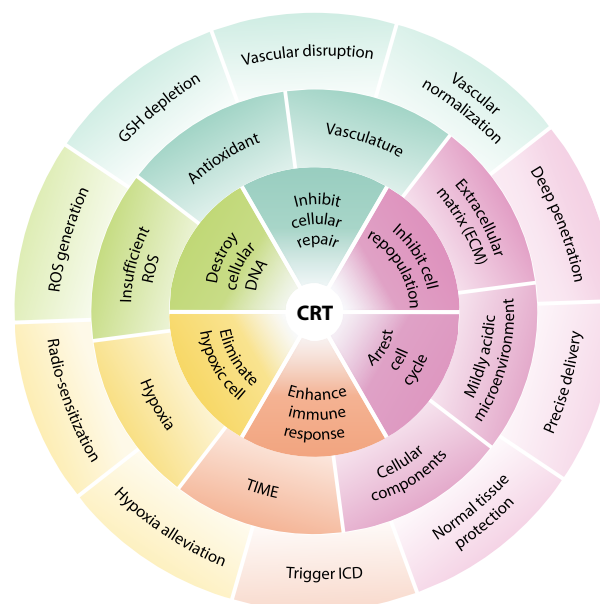
Graphical Abstract

Advances in Engineered Nano-sensitizers for Chemoradiotherapy of Cancer: Overcoming Microenvironmental Barriers

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and Qing-Song Yu

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This review highlights nano-sensitizers that overcome TME barriers, such as hypoxia, acidity, and dense matrix, to enhance chemoradiotherapy (CRT) efficacy, and discusses responsive strategies and clinical translation progress.



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