Materials & Design 267 (2026) 116337

Contents lists available at ScienceDirect

Materials & Design

journal homepage: www.elsevier.com/locate/matdes

Engineering copper-based nanoplatforms in cancer therapy

Ying-Ying Yang [a,b], Xin-Rui Zhang [c], Meng-Qi Fu [a,b,d], Rong Li [a], Bo Chen [e], Xin Li [f,g], Lu Zhang [a,b], Wen-Tao Liu [h], Wen-Ya Zhan [i], Xi-Tong Li [i], Ming-Sheng Zhou [a,b,j,*], Yang Yao [a,b,j,*]

[a] Institute of Life Science (Scientific Experment Center) , Shenyang Medical College, Shenyang 110034, China
[b] Shenyang Key Laboratory of Vascular Biology, Shenyang Medical College, Shenyang 110034, China
[c] Institute of Metal Research, Chinese Academy of Sciences, Shenyang 110016, China
[d] Department of Pathology and Pathophysiology, School of Basic Medical Sciences , Shenyang Medical College, Shenyang 110034, China
[e] Department of Breast Surgery, The First Affiliated Hospital of China Medical University, 155 Nanjing North Street, Heping District, Shenyang 110034, China
[f] School of Stomatology, Shenyang Medical College, Shenyang 110034, China
[g] Key Laboratory of Human Ethnic Specificity and Phenomics of Critical Illness in Liaoning Province, Shenyang 110034, China
[h] School of Rehabilitation, Shenyang Medical College, Shenyang 110034, China
[i] Second Clinical Medical College, Shenyang Medical College, Shenyang 110034, China
[j] Department of Physiology, Shenyang Medical College, Shenyang 110034, China

ARTICLE INFO

Keywords:
Copper-basedmaterials
Multifunctional nanoplatform
Programmed cell death
Cuproptosis

ABSTRACT

Copper-based multifunctional nanoplatforms have emerged as promising tools for multimodal cancer therapy. This is because copper nanoparticles not only induce tumor-killing effects such as “cuproptosis” and oxidative stress, and also possess the precise targeting and efficient drug delivery capabilities inherent to nanomedicines. This review systematically analyzes the synthesis and anticancer mechanisms of copper-based nanomaterials, including reactive oxygen species (ROS)-mediated chemodynamic therapy, photothermal effects, and the novel cell death pathway known as cuproptosis. Special emphasis is placed on the rational design of multifunctional nanoplatforms, which integrate various treatment modalities such as photothermal, sonodynamic, and immunotherapy to enhance tumor killing depth and activate systemic antitumor immunity. These engineered systems enable synergistic activation of multiple programmed cell death pathways and effectively remodel the tumor immune microenvironment. However, several challenges impede clinical translation, including issues related to quality control, synthesis scalability, long-term toxicity, and biocompatibility. Future efforts should focus on developing standardized, scalable synthesis methods, smart nanoplatforms with tumor microenvironment (TME)-responsive properties, and comprehensive safety evaluations to facilitate the clinical adoption of copper-based cancer therapies.

Abbreviations: ATP7B, ATPase copper transporting beta; BSO, buthionine sulfoximine; CA, cinnamaldehyde; CDT, chemodynamic therapy; CT, chemotherapy; Cu-MOFs, copper-based metal–organic frameworks; CuNPs, copper nanoparticles; CuNSs, copper nanosheets; CuNWs, copper nanowires; Cur, curcumin; DCs, dendrite cells; DLAT, dihydrolipoamide S-acetyltransferase; DOX, doxorubicin; EPR, enhanced permeability and retention; ES, elesclomol; FDX1, mitochondrial ferredoxin; GA, glycyrrhizic acid; GOx, glucose oxidase; GPX4, glutathione peroxidase 4; GQD, graphene quantum dot; GSDMD, gasdermin D; GSH, glutathione; HMCIS, hollow mesoporous copper-iron sulfide; HSA, human serum albumin; ICB, immune checkpoint blocking therapy; ICD, immunogenic cell death; IL-18, interleukin-18; IL-1β, interleukin-1 beta; LIAS, lipoyl synthase; MPPa, methyl pyrophaeophorbide a; NIR, near infrared; NLRP3, NLR family pyrin domain containing 3; NMs, nanomaterials; NPs, nanoparticles; OXPHOS, oxidative phosphorylation; PD-L1, programmed cell death ligand 1; PDT, photodynamic therapy; PTT, photothermal therapy; RCD, regulated cell death; ROS, reactive oxygen species; RT, radiation therapy; SDT, sonodynamic therapy; STING, stimulator of interferon genes; TLRs, Toll like receptors; TME, tumor microenvironment; US, ultrasound.

* Corresponding authors at: Institute of Life Science (Scientific Experment Center), Shenyang Medical College, Shenyang 110034, China.
E-mail addresses: yangyingying1230@163.com (Y.-Y. Yang), xrzhang16s@imr.ac.cn (X.-R. Zhang), fumengqi0627@163.com (M.-Q. Fu), lirong0816@symc.edu.cn (R. Li), bochen@cmu.edu.cn (B. Chen), httplixin@163.com (X. Li), zhanglu@symc.edu.cn (L. Zhang), 18842172582@163.com (W.-T. Liu), zhanwenya_a@163.com (W.-Y. Zhan), 13080728602@163.com (X.-T. Li), zhoums@symc.edu.cn (M.-S. Zhou), yaoyang@symc.edu.cn (Y. Yao).

https://doi.org/10.1016/j.matdes.2026.116337
Received 17 March 2026; Received in revised form 1 May 2026; Accepted 1 June 2026
Available online 6 June 2026
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1. Introduction

Cancer remains one of the most significant global health challenges, characterized by high incidence and mortality rates, despite notable advancements in medical research and technology. Conventional cancer treatments face critical limitations, including non-specific targeting, serious side effects, and drug resistance. These challenges highlight the urgent need for more effective, targeted, and less toxic therapeutic strategies [1,2].

Copper-based nanomaterials (NMs) have received considerable attention due to their precise targeting and outstanding therapeutic efficacy. Nanomedicines possess several advantages over conventional drugs, including small particle size, large surface area, high surface reactivity, multiple active centers, and strong adsorption capacity. These properties confer nanomedicines with targeted delivery, sustained release, and good penetration, which are crucial for clinical applications [3–5]. Moreover, the enhanced permeability and retention (EPR) effect of nanomedicines in tumor tissues significantly improves their targeting capabilities, allowing them to overcome or complement the limitations of conventional therapies, such as radiotherapy and chemotherapy, thus positioning them as promising candidates for anticancer therapies [6]. Copper (Cu) is an essential trace element that serves as key catalytic cofactor in various biological activities, including mitochondrial respiration, oxidative stress response, and biocompound synthesis [7,8]. The therapeutic mechanisms of Cu are multifaceted and synergistic. Primarily, they can catalyze a Fenton-like reaction in the acidic TME, converting the abundant hydrogen peroxide (H_2O_2) into highly cytotoxic hydroxyl radicals, an effect known as chemodynamic therapy (CDT) [9]. Recent studies have revealed that Cu^{2+} trigger protein toxicity stress responses, eventually causing cell death through cuproptosis [10]. Furthermore, copper's strong photothermal absorption capability enables effective photothermal therapy (PTT) under near-infrared (NIR) laser irradiation, which not only directly ablates tumors but also synergistically enhances the CDT efficacy [11].

Current research demonstrates that multifunctional nanoplatforms designed with Cu-based NMs have achieved promising tumor-killing effects and can even induce systemic immune responses. These platforms enhance the targeting, biocompatibility, and therapeutic depth of nanomedicines through various strategies, such as loading drugs, antibodies, or nucleic acids onto copper-based nanomaterials to modulate the tumor microenvironment, synergistically trigger multiple forms of regulated cell death (RCD), and amplify oxidative stress cascade reactions [12–18].

Although several excellent reviews have systematically summarized copper-based nanomaterials from specific perspectives, such as activating tumor immunity [19] or material synthesis [20], relatively few have provided an interdisciplinary and comprehensive review that encompasses the synthesis and anticancer mechanisms of copper-based nanomaterials, the immunotherapeutic effects and strategies for improving targeting capability of copper-based nanoplatforms, as well as the clinical translation challenges of copper-based nanodrugs. This review originally proposes a framework oriented to enhancing antitumor efficacy, analyzing the intrinsic relationships among synthesis parameters, material composition, material morphology, and anticancer mechanisms. It also elucidates how to enhance anticancer effects by tuning material synthesis parameters, performing functional modifications, and designing multifunctional nanoplatforms for synergistic therapy, thereby offering valuable guidance for the development of nanomedicine. Finally, the review provides an in-depth analysis of the real-world challenges and technical hurdles impeding their clinical translation, and proposes potential strategies and future research directions aimed at overcoming these barriers and accelerating their transition from bench to bedside.

2. Synthesis of copper-based nanomaterials

Nanoparticles (NPs) of a certain size can gradually accumulate in the vascular region of the tumor and achieve targeted delivery and retention in the tumor tissue, which is called the enhanced permeability and retention (EPR) effect, a passive targeting strategy for delivery. Massive irregular neovascularization in tumors makes them highly permeable for nanoparticles to be extravasated from tumor blood vessels into the tumor tissue. Retention occurs due to the absence of a lymphatic drainage system [21]. For cancer therapy, the size of copper nanoparticles (CuNPs) could have an effect on their accumulation in tumor tissue [22]. But it is not the case that the smaller the size of CuNPs, the better the therapeutic efficacy [23]. The optimal size for achieving the EPR effect in solid tumors is 50–200 nm [24–26]. However, smaller particles or porous structures have greater catalytic surface but may release copper faster (potentially causing off-target effects). Thus, an optimal size is often chosen to balance tumor penetration, catalytic efficiency, and retention [19].

In addition, Cu-based NMs contain Cu^{+} and Cu^{2+}. Furthermore, by varying Cu^{+}/Cu^{2+} ratio, ultra-high peroxidase-like activity was achieved, which may play an important role in anti-tumor activity. Nanoparticles with a large surface area and a high degree of surface reactivity are conducive to the binding of drugs, thereby increasing the therapeutic payload. Therefore, the challenging problems that arises in the synthesis of Cu-based NMs is to control the size, surface shape, and Cu^{+}/Cu^{2+} ratio.

The synthesis approach determines the size and surface functionalization capacity of Cu-based NMs, which directly influences their potential in drug delivery and targeted therapy [27,28]. Therefore, the selection of the most appropriate synthesis method is crucial to optimize the performance of Cu-based NMs in cancer therapy.

2.1. Synthesis methods

The synthesis of Cu-based NMs includes chemical (chemical reduction, sol–gel, solvothermal, chemical vapor deposition, electrochemical, sonochemical method), physical (mechanical milling, microwave-assisted, physical vapor deposition) methods [29].

Chemical reduction is one of the most common and mature methods. In the presence of a reducing agent and a capping agent, copper ions are reduced to Cu atoms from a solution of its salts. Then undergo nucleation and growth processes, ultimately forming Cu nanocrystals with various morphologies dispersed in the solution. The main advantage of this method is that it is easy to control the size and shape of nanoparticles by adjusting thermodynamic and kinetic parameters [30,31]. For example, by adjusting the temperature to control the relative rates of atomic deposition and surface diffusion, the morphology of Cu nanocrystals can be tuned: nanosheets are synthesized at low temperatures, whereas nanocubes are obtained at high temperatures [32] (Fig. 1A). High precursor concentration or the use of a strong, fast-acting reducing agent typically leads to rapid nucleation, resulting in smaller nanoparticles. Capping agents selectively adsorb to specific crystal facets during growth, effectively inhibiting their addition of new atoms [33]. Different capping agents adsorb on different crystal facets of copper, thus yielding crystals with distinct morphologies. For example, using I^{-} as a capping agent produces nanosheets [34] (Fig. 1C), while using Oleylamine produces nanowires [35] (Fig. 1B). This kinetically controlled anisotropic growth is the primary mechanism for obtaining non-spherical shapes. Surprisingly, the strength of the reducing agent not only affects the ratio of Cu^{+} to Cu^{2+} but also influences the stability of the nanocrystals [36].

Sonochemical method using ultrasonic treatment from 20 kHz to 50 MHz, which causes cavitation phenomena, accelerating the synthesis process and allowing to obtain unique nanostructures [37]. Nanosheets (CFT) are produced via sonication-assisted liquid delamination of bulk $CuFeTe_2$ crystals [38] (Fig. 1D). Ultrasound not only assists in synthesis

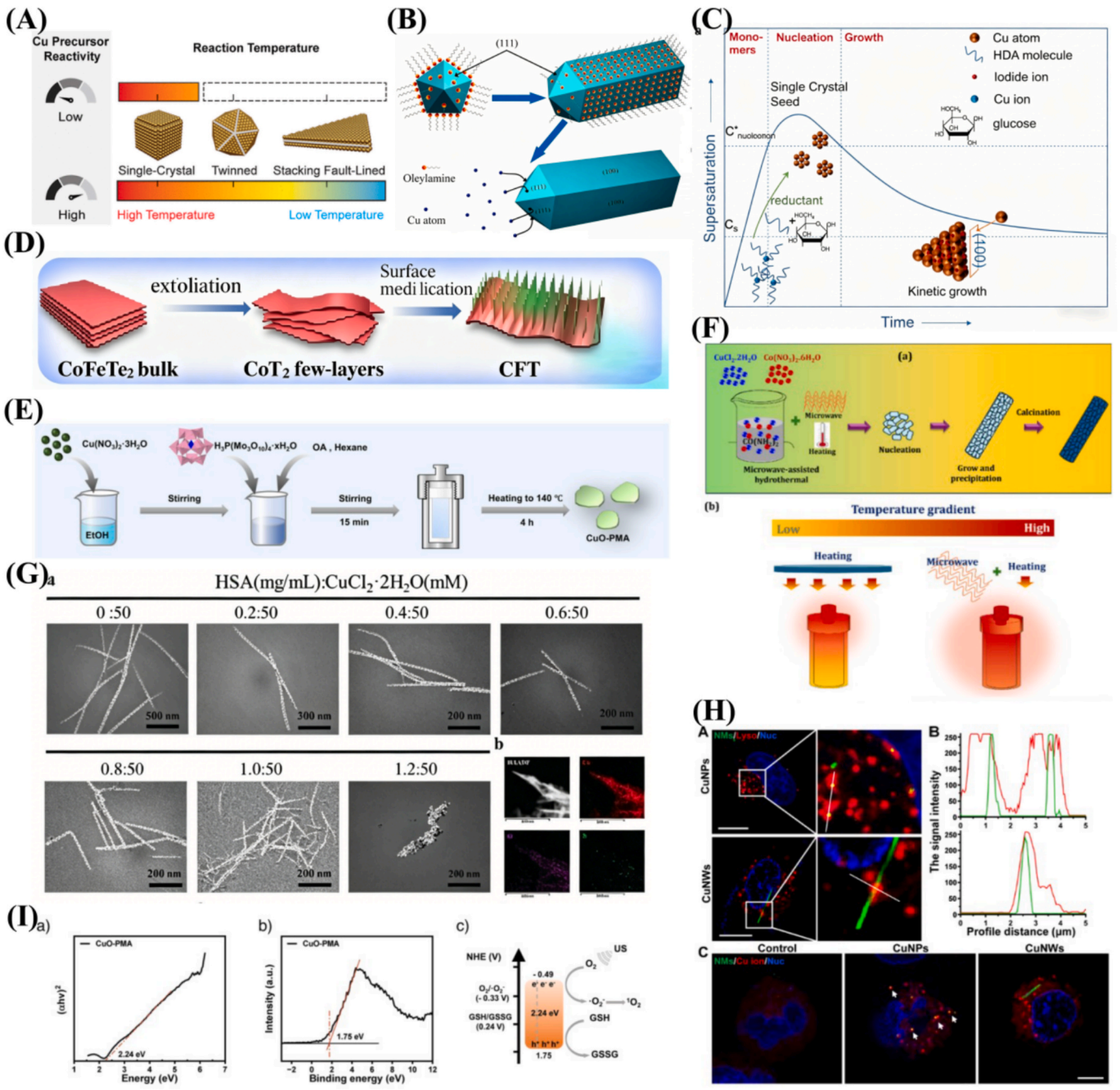


Fig. 1. (A) The Effect of Reaction Temperature and Copper Precursor Reactivity on the Morphology of Copper Nanocrystals [32]. Copyright © 2024, American Chemical Society. (B) Proposed growth mechanism for Cu nanowires grown via a seed-mediated method. [35]. Copyright © 2014, American Chemical Society. (C) Using I^- as a capping agent produces nanosheets [34]. © 2021 IOP Publishing Ltd. (D) Nanosheets (CFT) are produced via sonication-assisted liquid delamination of bulk $CuFeTe_2$ crystals. [38]. (E) One-pot solvothermal method [43]. © 2025 Wiley-VCH GmbH. (F) Due to the absence of thermal gradient effects of microwave heating, nanorods were fabricated in a short time with uniform and controlled morphology [66]. (G) HSA-mediated biomineralisation method [50]. © 2024 Wiley-VCH GmbH. (H) CuNWs are completely internalized by cancer cells and escape from the endolysosomal system [53]. Copyright © 2024, American Chemical Society. (I) Nanosheet CuO-PMA exhibits excellent sonocatalytic properties [43]. © 2025 Wiley-VCH GmbH.

but also impacts the final oxidation state. Copper zero-valent (Cu^0) nanoparticles are synthesized using sonochemical method and continuously release Cu^+ during ultrasound application [39]. In the electrochemical method, CuNPs are produced by means of an electrolytic solution of metal salts at the interface of the electrode and electrolyte. It involves a chemical reaction and electric current. The method produces smaller, more surface-area nanoparticles [40]. In electrochemical deposition, parameters like applied potential and deposition time directly control the dynamic Cu^{2+} reduction process, allowing for precise product design [41]. Thermolysis is a widely used and essential method for preparing inorganic NPs due to its simplicity, environmental friendliness, and minimal invasiveness. The original reactant solution is heated, mixed with organic solvents, and evaporated to obtain uniform NPs. Thermolysis is capable of decomposing polydisperse NPs into monodisperse NPs, and their morphology can be precisely controlled [42]. The core principle of solvothermal method involves carrying out chemical reactions in a closed vessel (autoclave) under self-generated pressure at temperatures typically above the boiling point of the solvent used. The high-temperature and high-pressure environment facilitates the dissolution–recrystallization process, enabling the direct

preparation of nanomaterials with excellent crystallinity. Simple parameters like temperature and pH have profound effects. By precisely adjusting reaction parameters, the Cu^{+}/Cu^{2+} ratios, size, morphology and crystal phase of the products can be effectively controlled. For instance, low temperature (60-90°C) leads to $Cu(OH)_2$ precursors, while 180°C yields CuO. Nanosheets, CuO-PMA can be synthesized via a one-pot solvothermal method [43] (Fig. 1E).

The microwave-assisted method utilizes microwave irradiation of solution mixtures to convert electromagnetic energy into heat, thereby accelerating the synthesis of copper nanoparticles. Compared to traditional methods, microwave-assisted synthesis of nanoparticles offers faster reaction times and improved control over particle size, resulting in more consistent and smaller nanoparticles [44] (Fig. 1F).

2.2. Green synthesis

The synthesis of nanoparticles often requires the use of significant amounts of toxic chemicals, resulting in harmful residues that pollute the environment [45]. Green synthesis, mediated by plants, bacteria, algae or fungi, is environmentally friendly and minimizes the use of harmful and toxic chemicals [46,47]. These biogenic NPs are of growing interest because of their high surface area, biocompatibility and environmentally friendly synthesis [48]. Bio-inspired synthesis (e.g., biotemplating and biomineralization) methods are also used to control the shape of nanocrystal. Copper nanorods and nanowires are synthesized using electroless deposition on rod-like viruses, with a diameter of 24–46 nm [49]. Man et al. have synthesised a Cu nanowire through a human serum albumin HSA-mediated biomineralisation method. This study demonstrates that the morphology and size of HCu nanowires can be regulated by adjusting the feed ratio of HSA and Cu [50] (Fig. 1G).

Although green synthesis methods offer advantages such as good biocompatibility and mild synthesis conditions, they often result in lower product purity and yield. The types and concentrations of biological materials used during synthesis must be carefully controlled, limiting their application for large-scale production [51].

2.3. Application of Cu-based Nanocomposite with different morphologies in cancer therapy

Cu nanoparticles: CuNPs are typically defined as spherical or quasi-spherical structures with diameters below 100 nm, representing the most readily obtainable and common crystalline structure. A significant advantage in their synthesis is their inherent thermodynamic stability, which allows for their direct synthesis via straightforward chemical reduction methods in aqueous or organic solvents, often without the stringent requirement for additional capping agents to control shape. CuNPs serve as the primary functional unit in the design of sophisticated multifunctional copper-based nanoplatforms for cancer treatment. These engineered systems leverage the nanoparticles' innate reactivity for therapies like CDT and cuproptosis induction, while their surface provides an adaptable scaffold for integrating targeting ligands, drug cargos, and imaging probes. This synergy enables targeted, multimodal therapies with immense potential to overcome limitations of conventional treatments [52].

Cu nanowires: Copper nanowires (CuNWs) have emerged as a uniquely advantageous platform for cancer therapy, primarily by enabling efficient intracellular copper ion delivery to trigger cuproptosis. Unlike spherical nanoparticles, CuNWs with high aspect ratios (e.g., 5-μm length) exhibit superior biological performance. They are effectively internalized by cancer cells and uniquely escape the endolysosomal trap, allowing direct cytoplasmic release of copper ions, thereby inducing potent cuproptosis more effectively than their spherical counterparts [53] (Fig. 1H). Additionally, CuNWs can be engineered with abundant oxygen vacancies through biomineralization, granting them an exceptional capacity to deplete intracellular glutathione. This not only disrupts the antioxidant defense of cancer cells but also potentiates cuproptosis and Fenton-like reaction-generated reactive oxygen species, achieving synergistic cell death [50].

Beyond direct cytotoxicity, CuNWs are versatile scaffolds for multifunctional theranostic applications. Their surface can be functionalized to enhance targeting and therapy. For instance, a polydopamine coating provides excellent photothermal conversion efficiency (~13.32%) for photothermal therapy and near-infrared-triggered drug release, while also enabling the nanowires to act as T1-weighted magnetic resonance imaging contrast agents [54].

Cu nanosheets: Copper nanosheets (CuNSs) represent a highly promising two-dimensional platform in cancer theranostics due to their unique ultra-high specific surface area and tunable physicochemical properties [55]. This large surface area provides abundant sites for functional modifications and catalyzing reactions, while their planar geometry facilitates efficient cellular internalization and interaction with biological membranes [56]. They can act as nanocatalysts with enzyme-like activities (e.g., KatG-mimicking $Cu(OH)_2$) to deplete glutathione and amplify oxidative stress [57]. CuO-PMA exhibits excellent sonocatalytic properties. As a sub-1 nm nanosheets, electrons and holes separate and rapidly migrate to the material's surface of the nanosheets under US irradiation. Subsequently, redox reactions occur on the surface, where generating a large amount of $^1O_2$ and $\bullet O_2^-$ [43] (Fig. 1I). Moreover, they are excellent carriers for delivering copper ions to trigger potent cuproptosis. Their surface can be readily modified for stimuli-responsive copper ion release, ensuring precise activation of this cell death pathway within tumors while minimizing off-target toxicity [38].

A core advantage lies in their ability to serve as a versatile foundation for multi-modal synergistic therapy. CuNSs can be engineered as efficient sonosensitizers (e.g., CuTCPP) [58] or integrated into Z-scheme heterojunctions (e.g., with $CoWO_4$) to enhance sonodynamic therapy by generating reactive oxygen species.[59].

Cu-MOFs: Copper-based metal–organic frameworks (Cu-MOFs) MOFs, an organic–inorganic porous hybrid polymeric materials, have received substantial attention in the field of drug delivery due to their large specific surface areas, adjustable pore sizes. Cu-MOFs, which combine drug delivery, catalysis, copper-mediated cell death, and photo/thermo-driven functions, have attracted widespread attention as carriers for multifunctional nanoplatforms in cancer therapy. Their high-porosity structure not only provides abundant active sites for catalytic reactions but also creates well-defined spaces for the efficient loading and controlled release of therapeutic carriers, while their tunable framework structure allows for precise regulation of copper ion release kinetics [60]. For instance, HKUST-1 (Cu-BTC) efficiently loads doxorubicin (DOX) [61], especially a CuS/HKUST-1@PDA composite achieves an impressive DOX loading of 88.7% [62]. Similarly, two-dimensional Cu-TCPP, prepared via a hydrothermal method, attain a DOX loading of 33% through π–π stacking interactions [63]. When combined with graphene oxide, the resulting CuG nanocomposite exhibits a DOX loading of 45.7% [64]. Beyond chemotherapy agents, HKUST-1@CMCS enables sustained release of dimethyl fumarate, reaching 66% release over 326 h, indicating its potential for long-term delivery [65]. Importantly, Cu-MOFs display intelligent pH-responsive release behavior. Under acidic conditions (pH 5.0) mimicking the tumor microenvironment, CuG releases more than 97% of loaded DOX, whereas only about 33.5% is released at physiological pH 7.4. This pH-dependent behavior, which avoids an undesirable burst effect, together with the high loading capacities, positions Cu-MOFs as promising smart nanocarriers for targeted cancer therapy.

In summary, precise control of reaction parameters during the synthesis process can effectively regulate the size and morphology of the products. This is crucial for nanomaterials to achieve various functionalities (e.g., catalysis, photothermal effects, sonosensitivity, and drug delivery) in their applications. A key challenge is the development of universal systems for real-time monitoring of nanoparticle parameters, particularly for solution-based techniques. This could be addressed by

developing specialized devices capable of simultaneous synthesis and parameter control (e.g., size or shape) during the synthesis process. Such technology would not only optimize and accelerate the synthesis process, but also advance synthesis methods, for creating novel and unique nanoparticle systems based on Cu-based NMs.

3. Therapeutic advantages of Copper-Based nanomaterials in cancer treatment

With advancements in nanomaterial functionalization, researchers have developed multifunctional nanodrug platforms tailored to the characteristics of various tumors. Cu-based NMs, due to their unique properties, have become a focal point in synergistic cancer therapy approaches. As a transition metals, Cu takes part in several biological functions such as electron transfer and catalytic activity, exhibit anticancer effects through multiple signaling pathways in cancer therapy nanoplatform. CuNPs are used in photodynamic therapy (PDT) and photothermal therapy (PTT) to locally increase ROS levels in tumors, leading to cell apoptosis. After functional modifications, CuNPs can load chemotherapeutic drugs, siRNA, and immunomodulators to enhance the efficacy of combined chemotherapy and immunotherapy.

3.1. Fenton-like reaction and CDT

3.1.1. Fenton-like reaction

Copper is a crucial component that is important for cellular functions. In physiological environments, it typically exists in the Cu^{2+} and Cu^{+} valence states. As a transition metal, copper induced Fenton-like reaction. Cu^{+} reacts with H_2O_2 to generate many ·OH radicals and Cu^{2+}, while Cu^{2+} interact with H_2O_2 to produce the superoxide and Cu^{+} [71]. These two-step reactions can form a self-sustaining cycle, during which a large amount of ROS is generated, including $\bullet O_2^-$ and •OH. However, the second step is noticeably slower than the first, which limits the speed of the loop. Under normal circumstances, tumor cells contain high concentrations of glutathione (GSH), which serves as a primary antioxidant to scavenge hydroxyl radicals (·OH) and protect cells from oxidative damage, while also reducing Cu^{2+} to Cu^{+}. When a large amount of Cu^{2+} accumulates in tumor cells and reacts with GSH, this, on one hand, weakens the cellular antioxidant defense, making the cells more susceptible to subsequent oxidative attacks. On the other hand, this reaction precisely reduces Cu^{2+} back to Cu^{+}, promoting the regeneration of Cu^{+} and accelerating the catalytic cycle. As a result, Cu^{+}-based nanozymes exhibit a distinct advantage in the GSH-rich TME [72].

3.1.2. Chemodynamic therapy

Chemodynamic therapy (CDT), a newer strategy, generates ROS through Fenton or Fenton-like reactions, inducing cell apoptosis [73]. Unlike traditional chemotherapy, CDT uses the intrinsic properties of the nanomaterials to induce tumor cell death. Cu^{2+}/Cu^{+} can be effective under acidic (pH 2.0–4.5) and neutral conditions (pH 6.5–7.0) [74]. This makes it more promising for CDT than Fe^{2+}, which works efficiently under acidic condition [75,76]. Therefore, current research strategies are focusing on improving the efficiency of CDT by increased intracellular acidification [77,78].

3.1.3. Cascade amplification of ROS to enhance Tumor-Killing depth

Overcoming tumor heterogeneity and treatment resistance is the primary goal for improving efficacy. Designing multifunctional nanoplatforms to trigger irreversible oxidative stress within the tumor can significantly enhance killing depth. Therefore, researchers have developed various cascade strategies to explosively generate ROS within tumors:

Synergy with Chemotherapeutic Drugs: Combining chemotherapeutic drugs that intrinsically increase ROS (e.g., artemisinin, cinnamaldehyde) with CuNPs can initiate a self-amplifying cycle of ROS generation, breach cellular antioxidant defense thresholds and effectively overcoming chemotherapy resistance. For instance, Zhu et al. [79] constructed AHCu nanoprodrugs that co-deliver artemisinin and copper. This system cascades the artemisinin-induced ROS burst with a subsequent Fenton-like reaction catalyzed by Cu^{2+}, resulting in significantly amplified oxidative stress and high tumor inhibition. Similarly, Wu et al. [80] utilized cinnamaldehyde and Cu^{2+} to stimulate excessive ROS production, effectively breaking the redox homeostasis and inducing immunogenic cell death.

Bimetallic Synergistic Catalysis: Constructing bimetallic nanostructures (e.g., Cu-Fe, Cu-Mn) utilizes the synergistic effects of different metal ions in Fenton-like reactions to more efficiently convert H_2O_2 in the TME into highly toxic OH, significantly enhancing CDT efficacy. This approach leverages the catalytic properties of various transition metals (Fe, Co, Mn, etc.) [81]. Examples include a CuSe-Ag (CSA) nanozyme that disturbs cellular redox homeostasis [82], and CMPB-MoS_2-PEG, which uses doped Cu/Mn ions to synergistically catalyze H_2O_2 into ROS [83].

Similarly, sonodynamic therapy (SDT) can synergize with CDT, utilizing ultrasound's deep tissue penetration to activate sonosensitizers for ROS production and even generate alkyl radicals [84]. A prime example is the BP@Cu_2O@L-Arg platform, which integrates SDT, CDT, gas therapy, and immune modulation for a cascade attack on breast cancer [85].

3.2. Cu-based nanomaterials induce cancer programmed cell death

3.2.1. Apoptosis

ROS is produced during aerobic metabolism, and cancer cells generate a lot of them to support their rapid progression. However, excessive levels of ROS cause protein inactivation, lipid peroxidation, DNA damage, mitochondrial damage, eventually cell death [86]. DNA damage, characterized by DNA fragmentation, is often induced by elevated intracellular ROS [87]. The pro-apoptotic effects of biogenic and synthetic copper nanoparticles are well-documented. Green-synthesized CuO nanoparticles from *A. indica leaf and S. latifolium extract* induce cancer cell death through oxidative stress/DNA fragmentation [88] and S phase cycle [89], respectively. CuNPs prepared via a chemical reduction method accumulate in ovarian cells, reducing proliferation markers and promoting apoptosis and hormone release [90]. The CuO-900 NPs induce apoptosis by increasing the expression levels of p53 and Bax genes in MCF-7 and HCT-116 cell lines [91].

3.2.2. Cuproptosis

Cuproptosis, a form of regulated cell death triggered by intracellular copper accumulation, was first identified in 2022 by Tsvetkov et al. through their investigation of the anticancer effects of the copper ionophore elesclomol (ES). Cuproptosis is characterized by aggregation of dihydrolipoamide S-acetyltransferase (DLAT) and loss of Fe-S proteins. Cu can bind directly to DLAT, a lipoylated mitochondrial enzyme in the TCA cycle, and promote disulfide bond-dependent aggregation of lipoylated DLAT. Key regulators of protein lipoylation have been identified as mitochondrial ferredoxin (FDX1) and lipoyl synthase (LIAS) [10]. Fe-S proteins are essential cofactors for enzymes in the electron transport chain. Cu has been shown to block the formation of Fe-S clusters through inhibition of the activity of the relevant mitochondrial assembly proteins, which can ultimately lead to cell death [92]. Cuproptosis is distinct from other cell death types because it's independent from ROS, meaning it's resistant to antioxidant-mediated inhibition. The revelation of cuproptosis has spurred research efforts to explore the underlying mechanisms by which copper contributes to cancer progression and its potential as a therapeutic target.

Co-delivering copper ionophores (e.g., in NP@ESCu and Cu/TI platform [93]), depleting glutathione (GSH), or interfering with mitochondrial metabolism can significantly enhance copper-specific cell death. For instance, PCD@Cu downregulates the copper exporter ATP7B, causing intracellular copper accumulation [94]. To counter high

GSH levels, the PCB nanosystem suppresses glutaminase to reduce GSH [95], while Cel-Cu NPs use celastrol as both an ionophore and a GSH scavenger [96]. Strategies also target metabolic adaptations, such as a "dual metabolic interference" approach against Fe-S clusters and OXPHOS [97], and H_2S-responsive nanoparticles that consume H_2S to promote cuproptosis in colon cancer [98].

3.2.3. Ferroptosis and pyroptosis

Copper-based nanomedicines have been demonstrated to induce both ferroptosis and pyroptosis. They efficiently trigger ferroptosis through a core pathway: Cu^{+}-catalyzed ROS generation initiates lipid peroxidation, while copper simultaneously depletes GSH and directly inhibits GPX4 activity. The explosive burst of ROS produced by copper nanomedicines not only drives ferroptosis but also acts as a key danger signal for activating the NLRP3 inflammasome. The activated NLRP3 inflammasome recruits and activates Caspase-1, which cleaves the GSDMD protein. This cleavage releases its N-terminal domain, which forms pores in the cell membrane, leading to cell swelling, rupture, and the massive release of pro-inflammatory cytokines such as IL-1β and IL-18. (See Table 1).

3.2.4. Synergistic triggering of multiple regulated cell death pathways

Simultaneously activating multiple cell death pathways effectively prevents tumor cells from escaping through a single route and is a key strategy to overcome treatment resistance. The cellular stress from these pathways is often highly immunogenic, creating a bridge to systemic immunity.

Linking Cuproptosis and Ferroptosis: Designing copper-iron composite nanomaterials induces cuproptosis while simultaneously triggering ferroptosis via iron-dependent lipid peroxidation. These two pathways form a self-accelerating cycle, leading to more severe cell membrane damage and oxidative stress. This synergy can be achieved by doping CuNPs with iron or loading ferroptosis inducers (e.g., erastin, RSL3) that disrupt the cystine/GSH/GPX4 axis [99–102]. Hollow mesoporous copper-iron sulfide (HMCIS) nanoparticles are a notable example that initiates this self-accelerating cycle, and the resulting ferroptosis acts as a potent ICD inducer [103].

Linking Cuproptosis and Pyroptosis: Engineering copper-based nanoplatform to activate inflammasomes (e.g., NLRP3) and Gasdermin proteins can induce pyroptosis. This lytic form of death results in the massive release of pro-inflammatory factors, dramatically altering the TME. The platform FA-PZ@MOF NPs, which integrates the saponin PPVI, successfully activates the NLRP3/Caspase-1 pathway, leading to the concurrent induction of cuproptosis and pyroptosis and a robust ICD effect [104].

Synergizing with Traditional Apoptosis: ROS generated by CuNPs can activate the mitochondrial apoptosis pathway. When combined with chemotherapeutic drugs, they can cooperatively induce strong apoptotic signals and, under specific conditions, convert it into an immunogenic form. For example, CuNPs co-loaded with Doxorubicin and Camptothecin induce both apoptosis and cuproptosis in TNBC cells, activating the immune system via ICD [94].

Therefore, leveraging the unique chemical properties of copper ions, engineered copper-based nanoplatforms precisely regulate copper delivery and release, simultaneously triggering multiple RCD through mechanisms such as oxidative stress induction, glutathione depletion, and DLAT protein oligomerization due to copper accumulation. This multi-pathway cooperative network exerts a far more potent cytotoxic effect on cancer cells than any single form of cell death, highlighting the platform's potential to overcome drug resistance and achieve synergistic anti-tumor efficacy (Fig. 2).

Table 1
Application Of Copper Nanowires And Nanosheets In Cancer Therapy.

Morphology	Methods	Size (nm)	Applications	Ref.
Nanowires	Biomineralization method	Nano size	Antitumor efficiency	[50]
Nanowires	Thermo-oxidative growth method	–	Rapid cancer screening and diagnosis	[67]
Nanowires	Hydrothermal approach	–	Cancer therapy	[54]
Nanorods Nanowires	Biotemplating	24–46 nm	Nanoelectronics, sensing, and cancer therapy	[49]
nanosheets	Biotemplating/ Hydrothermal	10 nm	Photothermal therapy of lung tumor cells	[68]
nanosheets	Co-precipitation technique	1–2 nm	Cancer treatment, drug delivery, MRI, and other biological applications	[55]
nanosheets	Sonication-assisted liquid delamination	222.6 nm	Cancer therapy	[38]
nanosheets	Alkali-assisted hydrolysis	2.82 nm	Cancer therapy	[57]
nanoclusters	DNA-templating	2 nm	ROS production and cytotoxicity applications	[69]
nanoclusters	Chemical reduction and DNA-templating	5 nm	A dual-target optical biosensor	[70]

3.3. Ideal photothermal therapeutic agents and photosensitizers

Photothermal therapy (PTT) uses nanomaterials such as CuNPs to generate heat upon irradiation, resulting in tumor destruction. The temperature is a critical factor affecting the therapeutic efficacy. As the dominant plasma metal, Cu exhibits strong surface plasma properties throughout the visible region, but is cheaper than Au and Ag [106]. Therefore, CuNPs are ideal photothermal therapeutic agents [107]. Leveraging copper's excellent photothermal conversion properties, PTT is combined with CDT. Local photothermal effects not only directly kill cells but also accelerate the kinetics of Fenton-like reactions, achieving a synergistic killing effect greater than the sum of its parts [108]. The photothermal properties of CuNPs can be enhanced through structural engineering; for example, hollow Copper sulfide nanospheres can rapidly increase temperature with a photothermal conversion efficiency of 30% [109], Ultrathin Cu_9S_5 nanosheets have demonstrated a remarkable photothermal conversion efficiency of 58.96% and also exhibit enzyme-like properties [110]. The performance of copper-based nanocomposites with different morphologies is shown in (Table 2).

Photodynamic therapy (PDT) uses photosensitizers to selectively accumulate in tumor cells and increase their sensitivity to light, inducing the release of ROS to kill the tumor cell [111]. CuNPs combined with irradiation, release significant amounts of ROS, demonstrating their potential as photosensitizers in both infrared and X-ray regions [112–114]. Many CuNPs, such as Cu oxides (CuO and Cu_2O) and Cu sulfides (CuS and Cu_2S), exhibit outstanding therapeutic effects due to enhanced photothermal therapy [115]. Chemically modifying CuNPs increases their photothermal properties. The addition of other metal substances to CuNPs can improve their catalytic properties. Fan et al. [116] prepared HA@Cy-Cu NPs through a hydrothermal method, display exceptional photothermal properties.

4. Engineering of copper-based nanoplatform in tumor immune therapy

The success of modern cancer therapy lies not only in local tumor eradication but also in establishing lasting systemic immune memory. Engineered CuNPs are ideal "mobilizers" of the immune system [133,134].

4.1. Inducing immunogenic cell death (ICD)

Less immunogenic damage-associated molecular patterns (DAMPs) are released because apoptotic cancer cells retain membrane integrity.

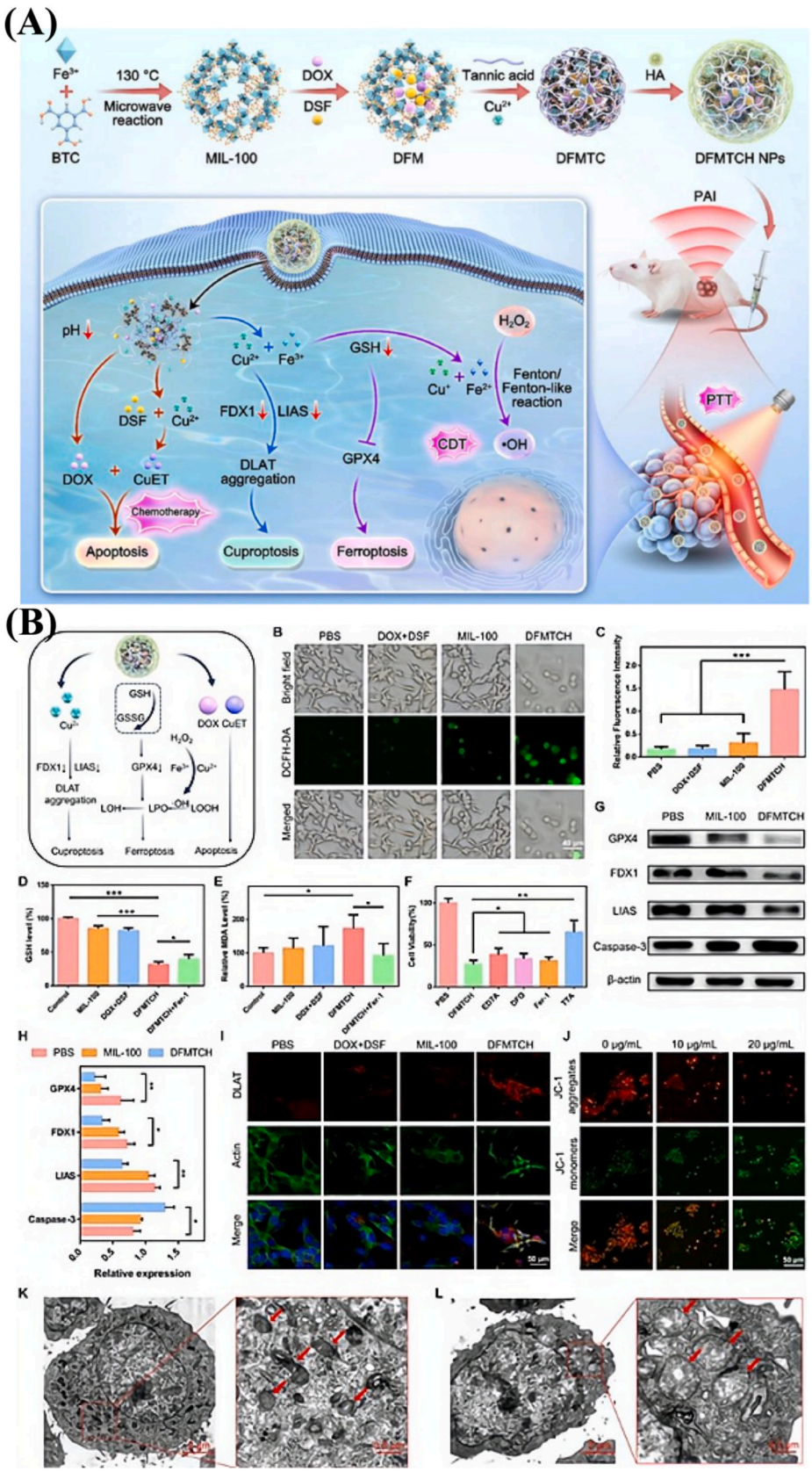


Fig. 2. Copper-based nanoplatforms induce multiple RCDs for synergistic cancer therapy. (A) Schematic representation of DFMTCH NPs synthesis and DFMTCH NPs-based cancer therapy in mice. (B) Mechanism of DFMTCH NPs induced cell death [105].

Table 2
Performance of Copper-based Nanocomposite with different Morphology.

Copper-based Nanocomposite	Morphology	Drug release	Photothermal conversion Efficiency	Therapeutic effect	Ref.
Cu_9S_8@PCM@Cur	hollow nanoparticles	54.1%, (44 ℃)	51.1%, (980 nm)	PTT/CT/ICB/ICD	[117]
DSF@CuMSN-PDA	nanoparticles	79.17%, (pH = 5.0, 48 h)	23.63%, (808 nm)	PTT	[118]
DSF@PEG-HCuS NPs	nanoparticles	50.90%, (acidic milieu); 18.97%, (pH = 7.4) 96 h	23.8%, NIR-II	PTT/CDT killing 89.3% of 4 T1 cells apoptosis rate reached 60.9%.	[119]
HACOCLC	nanoparticles	8.7%, (pH = 7.4); 76%, (pH = 6.4); 100%, (pH = 5.5)	40.3%, 808 nm	CDT/PTT/ Calcium overload	[120]
G5-PEG-LyP-1-CuS-DMXAA NPs (GLCD NPs)	nanoparticles	32.7%, (pH = 7.4); 41.7%, (pH = 6.5) 72 h	59.3%, 1064 nm (0.6 W/cm^2)	Tumor cell survival rate: 6.8% Mature DCs: 57.5%	[121]
FA-CuS PENs@Fe-EGCG	nanoparticles	39.5%, (pH = 7.4); 52.8%, (pH = 6.5); 63.4%,(pH = 6.5) 48 h	51.1%, 1064 nm (1.0 W/cm^2)	MR imaging and chemo/PTT/CDT apoptosis rate reached 48.0%	[122]
CS/Cu2–xSe-TPZ NPs	nanoparticles	40% (pH = 5.0, 24 h)	67.3%, 1064 nm (0.5 W/cm^2)	CDT/PDT/CT Tumor inhibition rate of 96%	[123]
E. coli@Cu_2O	nanoparticles	–	49.76%, (1064 nm) 29.86%, (808 nm)	DCs 30%, CD8 + T cells 50%	[124]
m@NPs-HG	nanoparticles	71.34%, (pH = 5.0); 59.55%, (pH = 6.8); 57.61%, (pH = 7.4) 72 h	808 nm (1.5 W/cm^2)	Tumor inhibition rate of 77.6%	[125]
IONF@CuS NPs	hair-like nanostructures	–	(42 ± 6)%, 1064 nm (0.3 W/cm^2)	40% mortality rate (0.5 pg Cu / cell) 70% mortality rate (0.8 pg Cu / cell)	[126]
$Cu_{2-x}Se$ HNSs	urchin-like hollow nanosphere	–	67.0%, 1064 nm (1.0 W/cm^2)	PTT/HECT/TECT/Cuproptosis/ apoptosis Complete removal of the tumor	[127]
EsCu@TCM	nanosheets	57.3%, (NIR-dependent, 4 h)	808 nm (1.0 W/cm^2)	volume reduction to 21.0%	[128]
β-$Cu_2V_2O_7$/Cs NCs	nanosheets	–	59.5%, 808 nm (1 W/cm^2)	PTT/CDT killing 80% of HepG-2 cells Tumor inhibition rate 95%,	[129]
Cu_3SnS_4 NFs	nanoflakes	–	55.7%, 808 nm (2.0 W/cm^2)	wound healing rate reached 93.5%	[130]
UCNP@Cu-TCPP MOF	MOF	66%, (pH = 6.5, 12 h); 76.6%, (pH = 6.5, 24 h)	980 nm, generation of ($^1O_2$)	CT/CDT/PDT The rate of apoptosis was 5.61%.	[131]
CuS NRs	nanorods	–	38.6%, (808 nm)	PTT/ CDT	[132]

Current cancer therapies suffer from a lack of immunogenicity due to the predominant mode of cell death induced by chemotherapeutic agents and radiation is apoptosis. Recent studies indicate that cuproptosis is usually accompanied by mitochondrial damage, this disruption includes a reduction in the number of mitochondria, rupture and distortion of mitochondrial cristae, immunogenic cell death (ICD) by mitochondrial damage, leading to the release of DAMPs. Mitochondrial-targeted copper delivery identifies the potential of enhancing cuproptosis as a novel approach to improve ICD in cancer treatment. CuNPs significantly improve tumor accumulation of copper to activate cuproptosis-mediated anti-tumor immunity [135]. Moreover, enhanced ROS levels induce immunogenic cell death, which in turn promotes robust systemic immune responses that can eradicate tumors. PTT, PDT or SDT, which can greatly increase ROS level, combine with Cu^{2+}-mediated CDT and cuproptosis achieved promising antitumor therapy [136,137]. Dying tumor cells release DAMPs, acting as an “in situ tumor vaccine” that attracts and activates dendritic cells (DCs), thereby initiating a T cell-mediated adaptive immune response.

4.2. Activating innate immunity: the cGAS-STING pathway

The cGAS-STING pathway is a crucial innate immune signaling cascade that functions as a universal cytosolic DNA sensor. It plays a pivotal role in defending against infections and in antitumor immunity. The enzyme cyclic GMP-AMP synthase (cGAS) binds to cytosolic double-stranded DNA (dsDNA), which originate from the damaged nuclear or mitochondrial DNA from cancer cells. Upon binding DNA, cGAS catalyzes the synthesis of a second messenger molecule called 2′3′-cGAMP. cGAMP binds to and activates the adaptor protein STING (Stimulator of Interferon Genes), located on the endoplasmic reticulum membrane. Activated STING traffics to the Golgi apparatus, initiating a signaling cascade that ultimately leads to the production of type I interferons (IFNs) and other pro-inflammatory cytokines. These molecules alert the immune system to mount a response.

Copper-based nanoplatforms are potent agonists of the cGAS-STING pathway. They activate this pathway through multiple mechanisms (Fig. 3A):

Causing Genomic and Mitochondrial DNA Damage: Combining chemotherapy or radiation with CuNPs can cause nuclear and mitochondrial DNA (mtDNA) breaks and their release into the cytoplasm, where they are directly recognized by cGAS. The CZP NPs release Cu^{2+} and $Zn2^{+}$ to disrupt mitochondria, leading to mtDNA leakage and cGAS-STING activation [138]. Similarly, LGG-PDA@Cu-CPT leverages camptothecin-induced DNA damage to activate the pathway [139].

Direct Delivery of STING Agonists: Encapsulating small molecule STING agonists within CuNPs enables their efficient delivery to tumor or immune cells. The Gel@M/CuO_2/DOX/STING platform co-delivers the STING agonist c-GAMP alongside other therapeutics, directly upregulating type I interferons [140]. Activation of the STING pathway leads to robust production of type I interferons, a crucial step for initiating an anti-tumor immune response.

It is evident that increasing endogenous damaged dsDNA is an

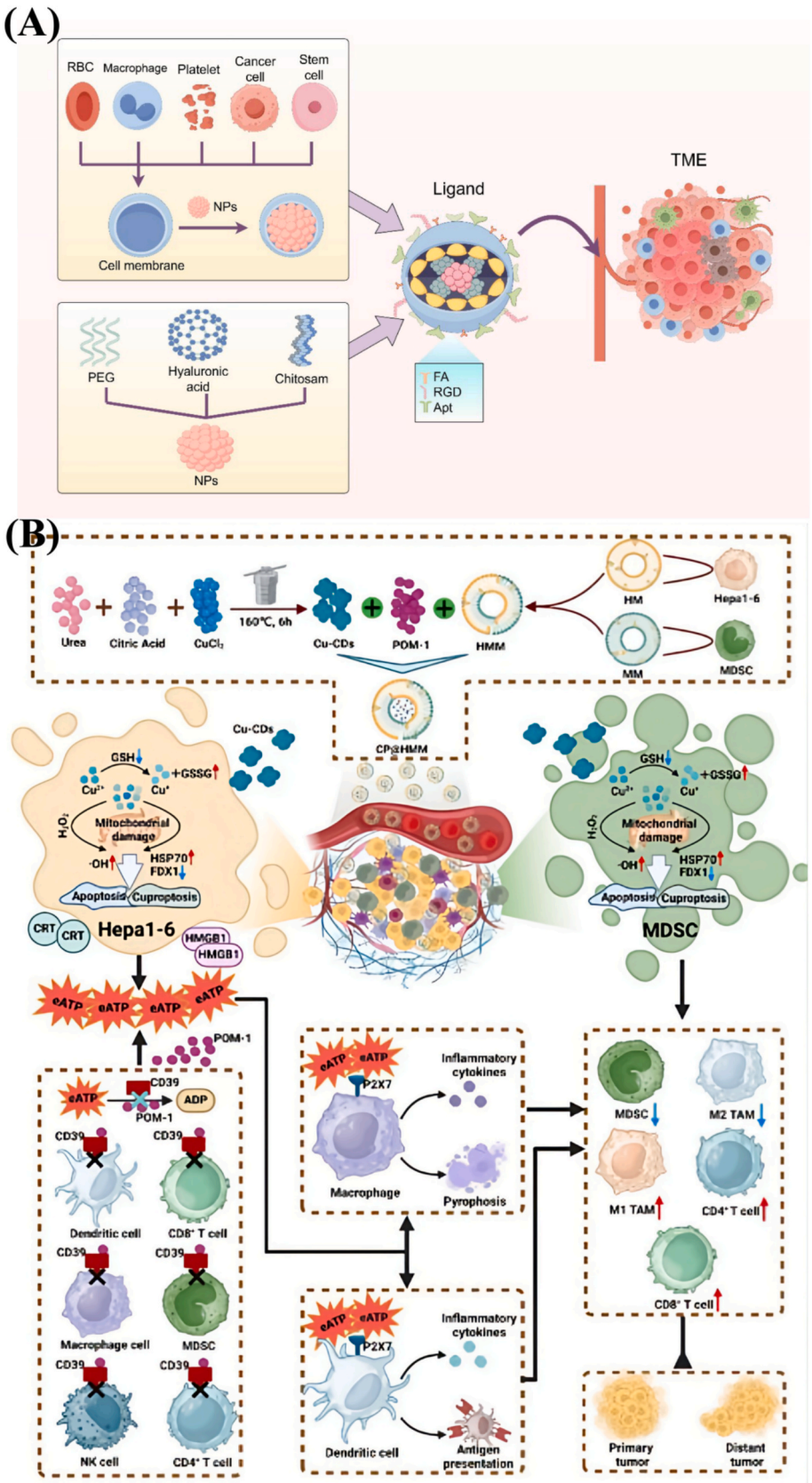


Fig. 3. Copper-based nanoplatforms designed to activate cGAS-STING pathway. (A) Multiple targeting mechanisms of copper-based nanoplatforms on cGAS-STING pathway. (B) In vivo anti-tumor immune microenvironment remodeling by the HCuSPtA NPs [105]. © 2025 Elsevier B.V.

effective strategy for activating the cGAS/STING signaling pathway. The aforementioned research demonstrates that copper nanoparticles cause genomic and mitochondrial DNA damage, thereby activating the STING pathway. However, DNA repair mechanisms contribute to tumor drug resistance. To block these repair pathways, HCuS@Pt@ATMi carries an ataxia telangiectasia mutated inhibitor (ATMi), aiming to induce a dysfunctional DNA repair system and achieve irreversible dsDNA damage. This study reveals that HCuSPtA, under near-infrared light irradiation, possesses a strong capacity to activate the immune system [141] (Fig. 3B).

4.3. Reversing immunosuppression and combining with immunotherapy

Numerous studies have shown that metal ions play a crucial role in immunoregulation [2,142,143]. Specifically, Cu^{2+} promotes the release of inflammatory cytokines, promotes T-cell activation and promotes macrophage M1 polarization in cancer immunotherapy [144]. CuNPs released Cu ions not only realized the amplification of ROS generation, but also triggered cuproptosis. More importantly, the immunosuppressive TME can be reversed by the greatly increased ROS levels and highly efficient cuproptosis.

Overcoming Checkpoint Inhibitor Resistance: Studies show that combining CuNPs with anti-PD-1/PD-L1 antibodies can effectively reverse the immunosuppressive TME, converting “cold” tumors into “hot” ones, significantly improving the efficacy of immune checkpoint inhibitors (ICIs). While copper can upregulate PD-L1, this very mechanism is exploited when combined with αPD-L1 antibodies, as demonstrated by NP@ESCu [145]. Interestingly, significant enhancement of antitumor efficacy in metastatic breast cancer was achieved with copper nanoplatform-loaded PD-L1 siRNA [146]. To combine cuproptosis with immune checkpoint inhibition, Li et al. designed Cu/TI to downregulate PD-L1 using 5-carboxy-8-ydroxyquinoline (TI) [147]. The PD-L1 inhibitor BMS-1 was used to form the nanodrug CMS/PEG-B-P. Numerous studies show that copper-based nanoparticle-loaded immune checkpoint inhibitor therapies can enhance the immune response as a new immunotherapeutic approach [148].

Copper-based nanoplatform can also be used to downregulate emerging immune checkpoints like ecto-5-nucleotidase (CD73) and CD47, enhancing anti-tumor immunity by reducing adenosine production and boosting macrophage phagocytosis, respectively. Metabolic immune checkpoint CD73 is overexpressed in tumor cell, contributes to its immune evasion by producing extracellular adenosine (ADO). Au and Cu can decrease the expression of CD73 by alleviating the tumor hypoxia through their Fenton-like reaction. Accordingly, Au@Cu_{2-x}Se nanoparticles attenuate the ADO-driven immunosuppression to enhance T cell infiltration. This work demonstrates that CuNPs modulation of CD73-mediated tumor immunosuppression is a novel strategy to improve cancer immunotherapy [149] (Fig. 4). CD47, a “don't eat me” molecule, binds to the SIRPα receptor on the macrophage surface, inhibiting its behavior. HA@Cu_2O@DNA carrying the CRISPR/Cas9 system can reprogram tumor cells by down-regulating CD47, enhancing macrophage activity [150].

Serving as a Cancer Vaccine Platform: Copper-based nanoplatforms demonstrate immense potential as sophisticated cancer nanovaccines, designed to initiate and amplify a robust, systemic antitumor immune response. Their application extends beyond direct tumor killing to encompass intelligent antigen capture and presentation, a key principle for vaccination. Cu-based nanovaccines, by producing and presenting tumor antigens and adjuvant signals, efficiently promote DC maturation and antigen presentation, stimulating potent, antigen-specific cytotoxic T lymphocyte (CTL) responses.

Current research strategies include targeting immunomodulators or specific antigen delivery, as well as enhancing the cytotoxic effects of nanovaccines to directly transform tumors into antigen sources. For example, ECNM delivers immunomodulators like IDO1 inhibitors to reverse immunosuppression and elicit a potent abscopal effect. Further enhancing specificity, ECNM employs homotypic targeting by coating the nanoparticle with a cancer cell membrane, enabling precise delivery [151]. For defined antigen delivery, systems such as Cu–N-CDs@OVA successfully co-deliver a model antigen (OVA) with the immunostimulatory copper nanomaterial, activating systematic immunity upon external stimulation [152]. The innovative Cu-THBQ/AX framework induces in situ cuproptosis and pyroptosis, effectively transforming the tumor itself into an antigen source while simultaneously reversing the “cold” tumor microenvironment [153]. Interestingly, a prominent strategy involves creating “in situ” or “personalized” vaccines derived from treated tumors. LC-TCV platform utilizes near-infrared-irradiated Cu_{2-x}Se to induce ICD in tumor cells, causing them to release a suite of DAMPs and tumor-associated antigens. These inactivated, antigen-laden cells are then formulated into a vaccine that effectively promotes DCs maturation and cytotoxic T lymphocyte recruitment [154] (Fig. 5).

Collectively, these strategies position copper-based nanovaccines as powerful tools for initiating antigen-specific immune cascades and achieving long-term immunological memory. The clinical translation of tumor vaccines faces significant hurdles. These include antigen selection and delivery, the highly immunosuppressive tumor microenvironment, tumor heterogeneity and immune evasion. Therefore, current research focuses not on vaccines as monotherapies, but on rationally combining them with agents that modulate the TME (such as immune checkpoint blockers, metabolic modulators, or chemotherapy) to unleash their full therapeutic potential. These engineered copper-based nanoplatforms simultaneously function as in situ vaccine generators and intelligent drug delivery systems. By integrating “killing, antigen release, and microenvironment remodeling” into a single, targeted intervention, copper-based nanoplatforms represent a next-generation, broadly applicable strategy to overcome the key limitations of conventional cancer vaccines.

Enhancing the Efficacy of CAR T-cell Therapy: The clinical success of CAR T-cell therapy in hematological malignancies has not fully translated to solid tumors, which present formidable barriers including an immunosuppressive TME, poor T-cell trafficking, antigen heterogeneity, and T-cell exhaustion. Copper-based nanoplatforms are emerging as versatile engineering tools designed to systematically dismantle these barriers, thereby potentiating CAR T-cell therapy through multifunctional synergy. ACSP@TCM encapsulates Au/Cu_{2-x}Se and 3-bromopyruvate with a CAR-T cell membrane, which has an attractive synergistic CDT/PTT effect that can induce ICD of NALM 6 cells. In addition, 3-bromopyruvate regulates the acidity of the TME to provide a more favorable environment for the survival of CAR T cells by inhibiting the efflux of lactic acid.. The nanodrug tFNAs@ESCu/aPD-L1 employs a similar strategy, inducing cuproptosis and blocking PD-L1 to reshape the immunosuppressive TME, thereby enhancing GD2-CAR-T cell infiltration and antitumor activity against OS (Fig. 6). Furthermore, researchers reprogram CAR T-cells using disulfiram and copper plus ionising irradiation (IR). The reprogrammed cells have memory-like characteristics, high toxicity, and can spread and persist in the body. They also trigger strong, lasting anti-tumor responses in mice, showing that this therapy can be used to treat solid tumors [156].

Integrating multiple therapeutic strategies into a single platform to induce ICD and modulate the tumor microenvironment represents the ultimate manifestation of precise and highly effective synergistic therapy. The following case demonstrates the immense potential of this integrated design approach (Table 3).

In conclusion, the rational design of copper-based nanoplatform has progressed to a stage where complex, multi-mechanistic actions can be engineered into a single platform. These advanced nanoplatforms simultaneously enhance tumor killing depth through cascaded ROS and synergistic RCD, and ignite a robust, systemic immune response, paving the way for the next generation of cancer therapeutics. (See Fig. 7)

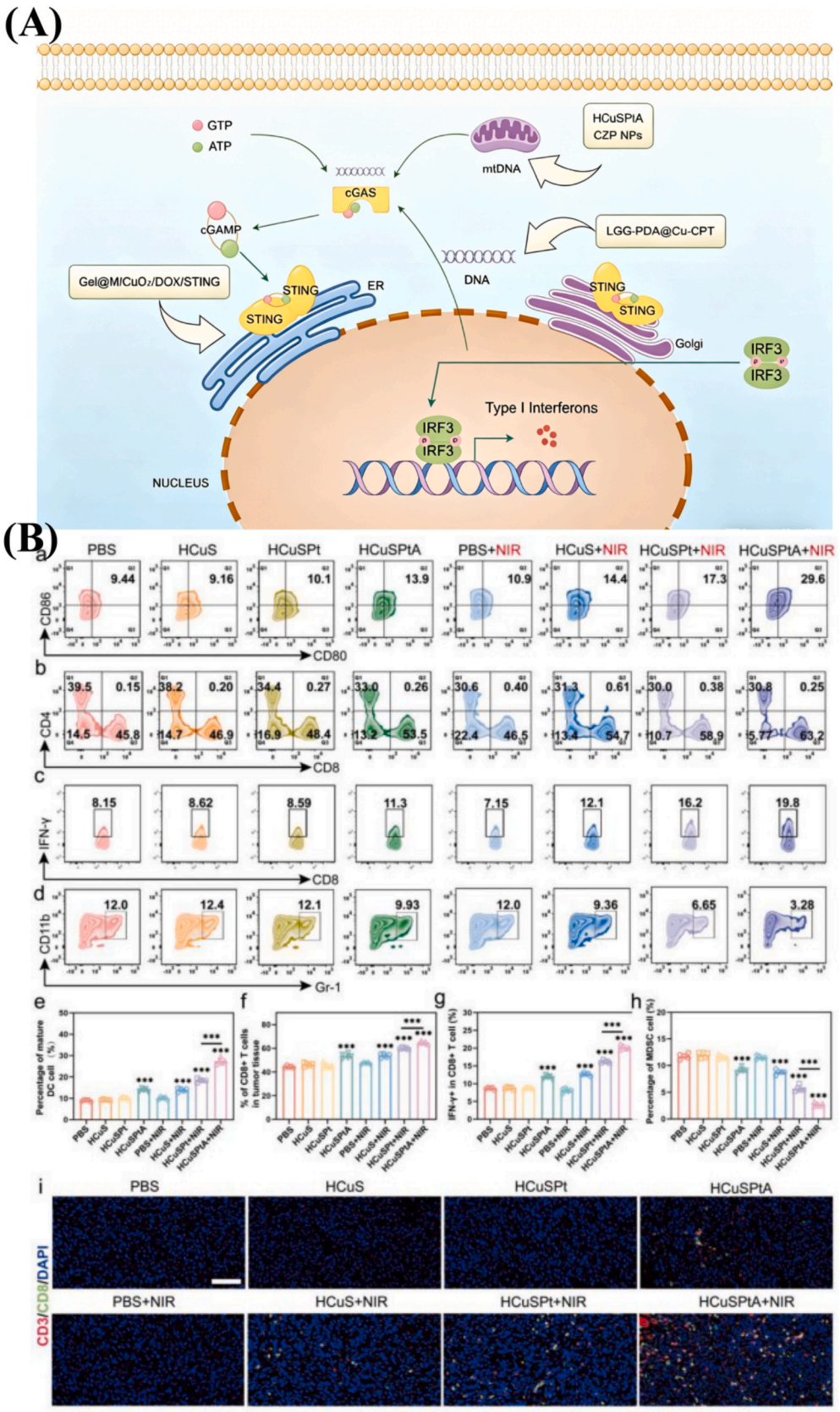


Fig. 4. Au@Cu_{2-x}Se reverses immunosuppression by decreasing CD73 expression. (A) Schematic illustration of targeting metabolic immune checkpoint CD73 to boost glioblastoma immunotherapy by joint use of ACS NPs, DSF, and radiotherapy. (B) Au@Cu_{2-x}Se treatment effectively activates immune cell infiltration [149]. Copyright © 2024, American Chemical Society.

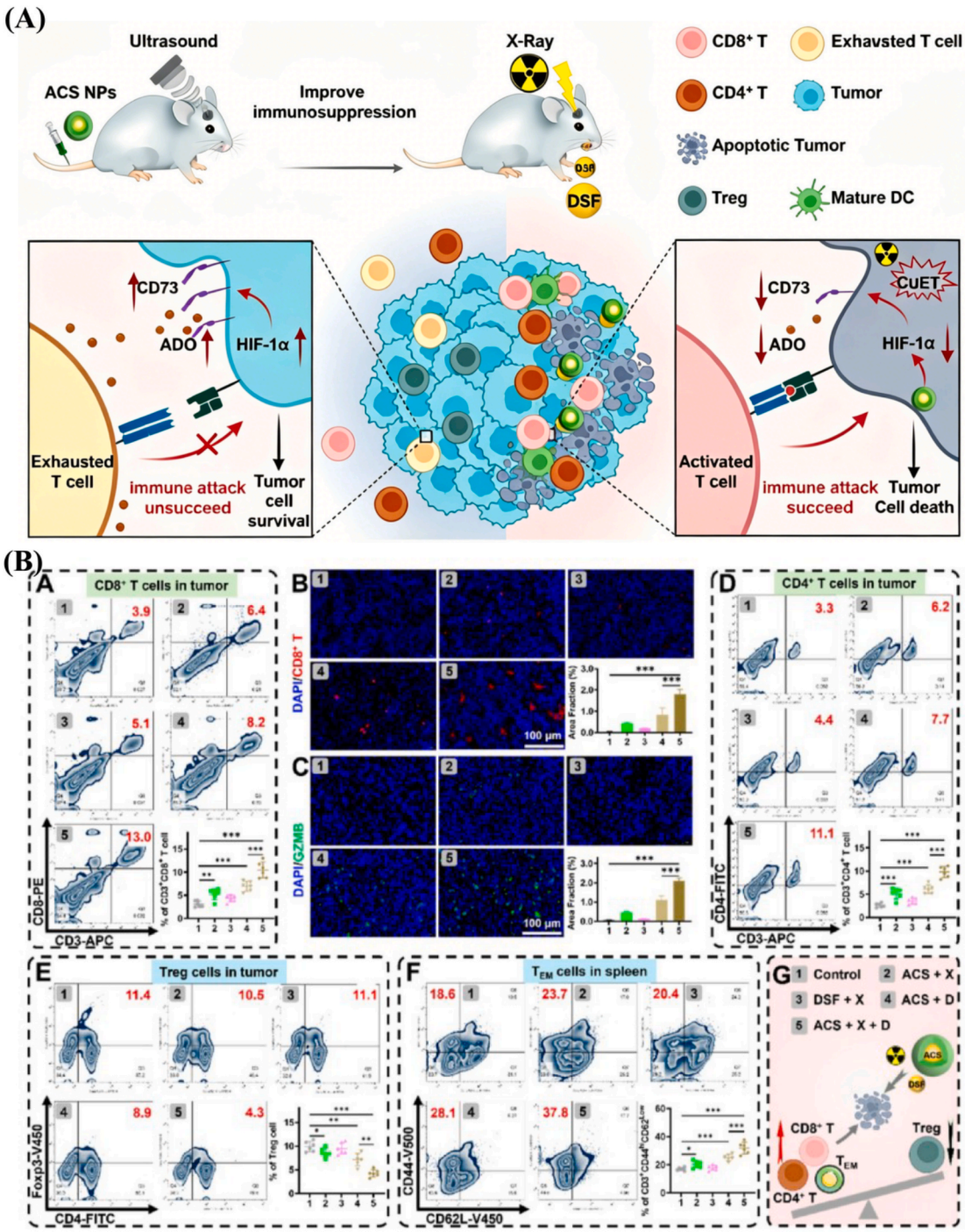


Fig. 5. LC-TCVs induce cellular immune response as an in situ vaccine. (A) Schematic diagram of the synthesis method and antitumor mechanism of LC-TCV. (B) LC-TCV-induced cellular immune responses in vivo [155].© 2025 Elsevier Inc.

5. Design engineering copper-based nanoplatform to enhance specific targeting

5.1. Active targeting

Drug delivery by nanoparticles can occur through two mechanisms: passive and active targeting. Passive targeting relies on a generic tumor physiology phenomenon, whereas active targeting involves molecular recognition to achieve precise drug delivery.

Active targeting is typically achieved by functionalizing NPs with various targeting ligands that can selectively bind to specific receptors on the cell surface to enhance the internalization of the NPs by the tumor cells and improve their retention in the tumor tissue [167].

Aptamers are short, single-stranded DNA or RNA molecules that can bind selectively to target molecules with high affinity. They offer several advantages, including smaller size, lack of immunogenicity, ease of modification and stability [168]. AS1411 aptamer effectively attaches to nucleolin for targeting breast cancer cells [169]. Polyvalent aptamer (PApt), comprising polyvalent epithelial cell adhesion molecule aptamers for tumor targeting and repetitive PolyT sequences for copper chelation, facilitates efficient loading and targeted delivery of CuPEs [170].

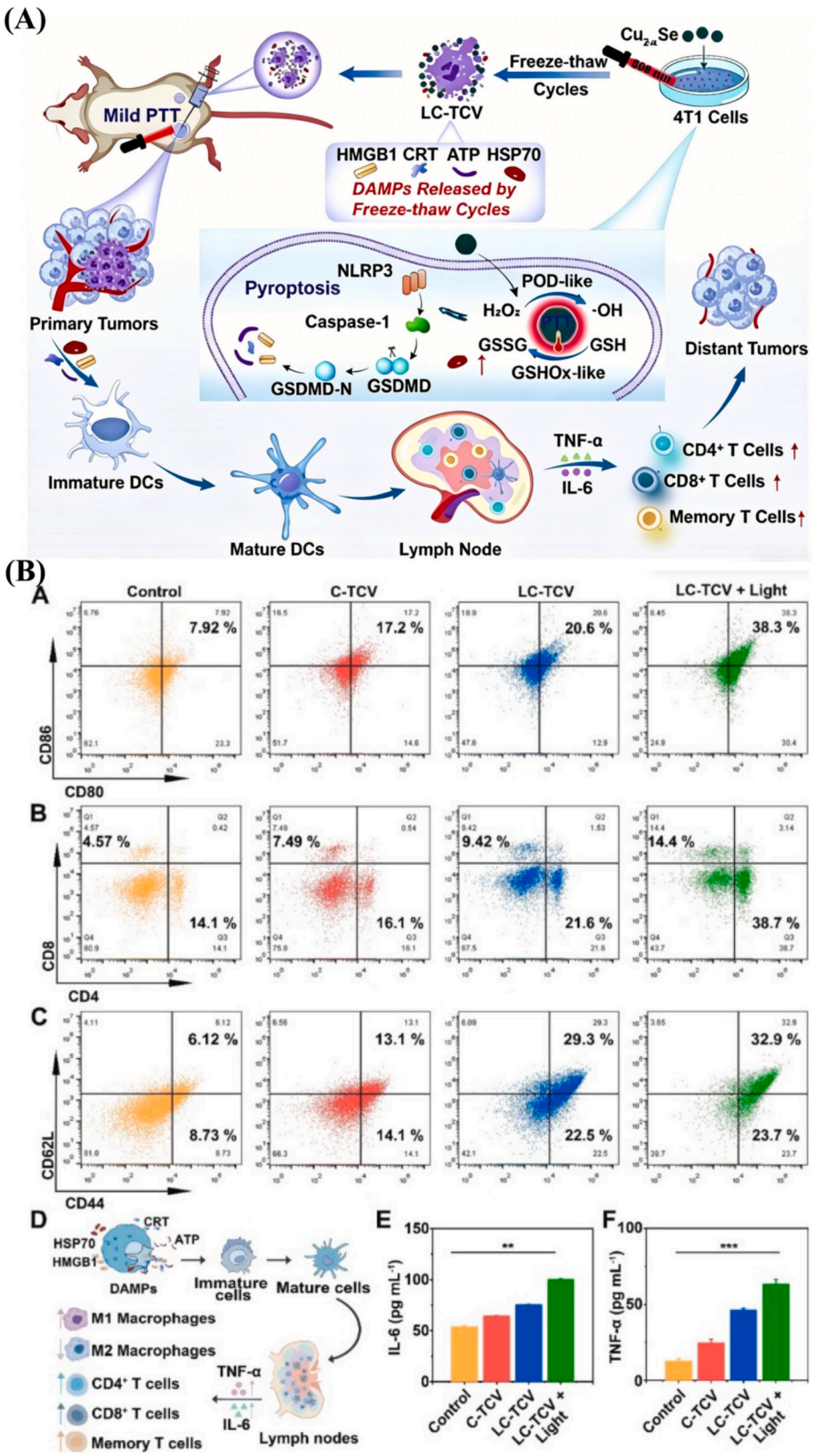


Fig. 6. Nanodrug improves the antitumor activity and reduces the exhaustion of CAR-T cells in vitro [157].© 2025 The Author(s). Published by Elsevier Inc.

RGD peptides (arginine-glycine-aspartic acid) target integrin receptors that are highly expressed on cancer cells for enhanced specificity [171]. mCu&Ce@ICG/RGD is designed to accurately recognise osteosarcoma, achieving efficient suppression and dual-mode bio-imaging [172].

Due to its specific binding to CA IX, which is overexpressed on tumor cells, BS can be used to functionalize nanoparticles for specific targeting [173]. The folate receptor (FR) is overexpressed on the surface of many

Table 3
Summary of Multifunctional nanoplatform for synergistic cancer therapy.

Copper-based nanoplatform	Therapy modality	Performance	Advantages	Ref.
ZCPO@HA	Ferroptosis/Cuproptosis/ICD	Zu^{2+} and ·OH cause mitochondrial damage, activates cGAS-STING pathway	Activating the adaptive immune response and innate immune response.	[158]
CACuPDA	Ferroptosis/Cuproptosis/ICB/ICD	CA stimulates ROS production; Redox imbalance amplifies ferroptosis and cuproptosis, triggers cellular lysis	GSH/GPX4-depleted sensitizes lung tumor to ICB.	[159]
E. coli@Cu_2O	PTT/ferroptosis/cuproptosis/ICB	Microbial nanohybrid photothermal-enhanced ferroptosis/cuproptosis and immunosuppression reversion	Precise tumor therapy	[124]
MARS	CDT/RT/ICD/starvation therapy	GOx catalyzes glucose to produce H_2O_2. Cu + mediated Fenton-like reaction and RT sensitization	Inducing radical storms and activating cascade-amplified systemic immunity.	[160]
Cu_9S_8@PCM@Cur	PTT/CT/ICB/ICD	PTT (980 nm NIR); lauric acid controls Cur release via hyperthermia; Cur enhances photothermal ablation, induces ICD; Cur downregulates PD-L1 via inhibiting EGFR-STAT3	A multimodal approach that synchronizes PTT, CT, and immune reprogramming.	[117]
$Cu_{2-x}Se$(R837)-iRGD	ICB/Cuproptosis/ICD/RT	$Cu_{2-x}Se$ induces cuproptosis, promotes ICD; R837 induces DCs maturation by activating; Combines with RT to enhance ROS production	Nanoformulations combined with radiotherapy.	[161]
C&P-DOX	CT-PTT-ICD	$Cu_{2-x}Se$ generates localized hyperthermia; GSH depletion; DOX induce apoptosis; induce immunogenic cell death.	effectively penetrates deep tumors, integrating active synergistic chemo-photothermal-immune therapy.	[162]
$CuWO_4$, CWO	ICD/ferroptosis/cuproptosis/SDT	CWO as piezoelectric sonosensitizers with narrow bandgap increase ROS; CWO deplete GSH and NADPH	Combines piezoelectric catalysis for cascade activation of immune regulation.	[163]
GQD/$Cu_{2-x}Se$	Cuproptosis/ICD/chemotherapy/SDT	Cu produce ROS and induce cuproptosis; GQD/$Cu_{2-x}Se$ possessed enhanced US-activated ROS generation	Utilization of TME-responsive cuproptosis inducers for immunotherapy.	[164]
CNMCF	ICB/ICD/PDT/CDT	Cu consume GSH to amplify ROS levels; NIR/pH dual-responsive; MPPa serves as the PDT agent	Elicited strong anti-tumor immune response.	[165]
DSF/$Cu_{2-x}Se$@PCM (DCP)	NIR-II (1064 nm) light-triggered in situ precise chemotherapy	Highly effective in vitro and in vivo antitumor effects, photoacoustic imaging, photoacoustic response properties	Solves the long-standing asynchronous release problem of DSF and copper sources, significantly improving cytotoxic complex generation efficiency in tumor lesions	[166]

types of cancer. Coupling CuNPs with folic acid, which specifically binds to the FR, promotes the internalisation of CuNPs into the cytoplasm [174]. The FA-nanosystem, which has imaging functions was observed to selectively aggregate in tumor cells overexpressing folate receptors, resulting a more significant tumor inhibitory effect [175,176].

5.2. Surface modification for stability and biocompatibility

Particles with negative or neutral surface charges can achieve better accumulation results within tumors [177]. Modifying the surface of metallic nanoparticles can markedly enhance their stability and biocompatibility. For example, encapsulating the nanoparticles in polymers or other biocompatible materials can prevent them from being cleared by the immune system, thereby extending their circulation time in the body. In particular, nanoplatforms camouflaged by cell membrane can effectively reduce uptake, thereby achieving homologous tumor targeting [178].

PEGylation or chitosan coating, is a common approach used to improve the stability of nanoparticles. CuO nanoparticles are capped by polyethylene-glycol (PEG) and polyvinyl-pyrrolidone (PVP) on the surface. Biological assays show higher activity of CuO-PEG and CuO-PVP compared to uncapped CuO nanoparticles, with CuO-PEG showing better antitumor activity [179]. After surface modification by polyethylene glycol, the formed pCu3P NPs show negligible influence on the viability of 4 T1 cells, presenting remarkable biocompatibility [180]. Hyaluronic acid is a natural, harmless mucopolysaccharide that is quickly degraded by hyaluronidase enzymes, making it ideal for targeted drug delivery [181]. Furthermore, HA binds to the CD44 receptor which is highly expressed on the surface of tumor cells [123], enhancing the targeting of cancer therapies [182]. Chitosan (CS) is a biodegradable, hydrophilic polymer that exhibits exceptional biocompatibility and stability, as well as low immunogenicity. It is therefore an ideal candidate for drug delivery systems [183]. A bimetallic chitosan/hyaluronic acid nanoparticle (5FCN) has been developed for the treatment of TNBC. Studies in vitro and in vivo demonstrated that 5FCN exhibits superior efficacy in killing TNBC cells with few side effects [184].

Biomimetic cell membrane coatings have also been devised to decorate the surface of the CuNPs. Tumor cell proteins and receptors allow the cells to evade the immune system. By coating the cancer cell membrane, the targeting ability of nanoparticles can be greatly enhanced. However, the CCM-coated nanoparticles trigger anti-tumor immune responses when they taken up by tumor cells. The DU145 cell (PCa cell) membrane was coated onto the surface of CuNPs to create a biomimetic nanoplatform (DCM@GDY-CuMOF@DOX), which providing an effective and safe treatment for PCa [185]. Coating CuNPs with platelet membrane [186], neutrophil [187] or red blood cell membrane [188] enables them to escape immune system clearance. This results in efficient accumulation of Cu within the tumor, enhancing the targeting and biocompatibility of nanomedicines [189]. Moreover, some receptors on platelet membranes can target tumor cells directly by interacting with specific components [190].

5.3. Stimuli-responsive targeting

Stimuli-responsive targeting involves releasing the drug in response to specific internal or external stimuli, such as heat, light, ultrasound, pH levels, enzymes or redox conditions. This approach controls the release of the drug, enhancing its effectiveness and reducing side effects.

Scientists have explored numerous methods to modify metal nanoparticles. By adjusting nanoparticle size, charge, and ligand exposure in response to changes in pH, redox gradients, or ATP concentrations, tumor cell targeting effects can be incorporated into a single CuNP. Liang et al. designed pH/glutathione dual-responsive drug-releasing nanoparticles [192]. Yin et al. developed triple-responsive nanoparticles (pH, laser, and GSH), ensuring highly controllable drug release at tumor sites [72]. CDDP@$Cu_2Cl(OH)_3$-CDs is designed specifically for colon cancer, using the overproduction H_2S in tumors to promote tumor energy remodeling for cancer treatment [193].

6. Current Challenges and limitations

Copper nanomaterials represent a transformative frontier in cancer therapy, boasting a versatile agent that includes direct tumor ablation, remodeling of the TME, and integrated diagnostics and treatment. A

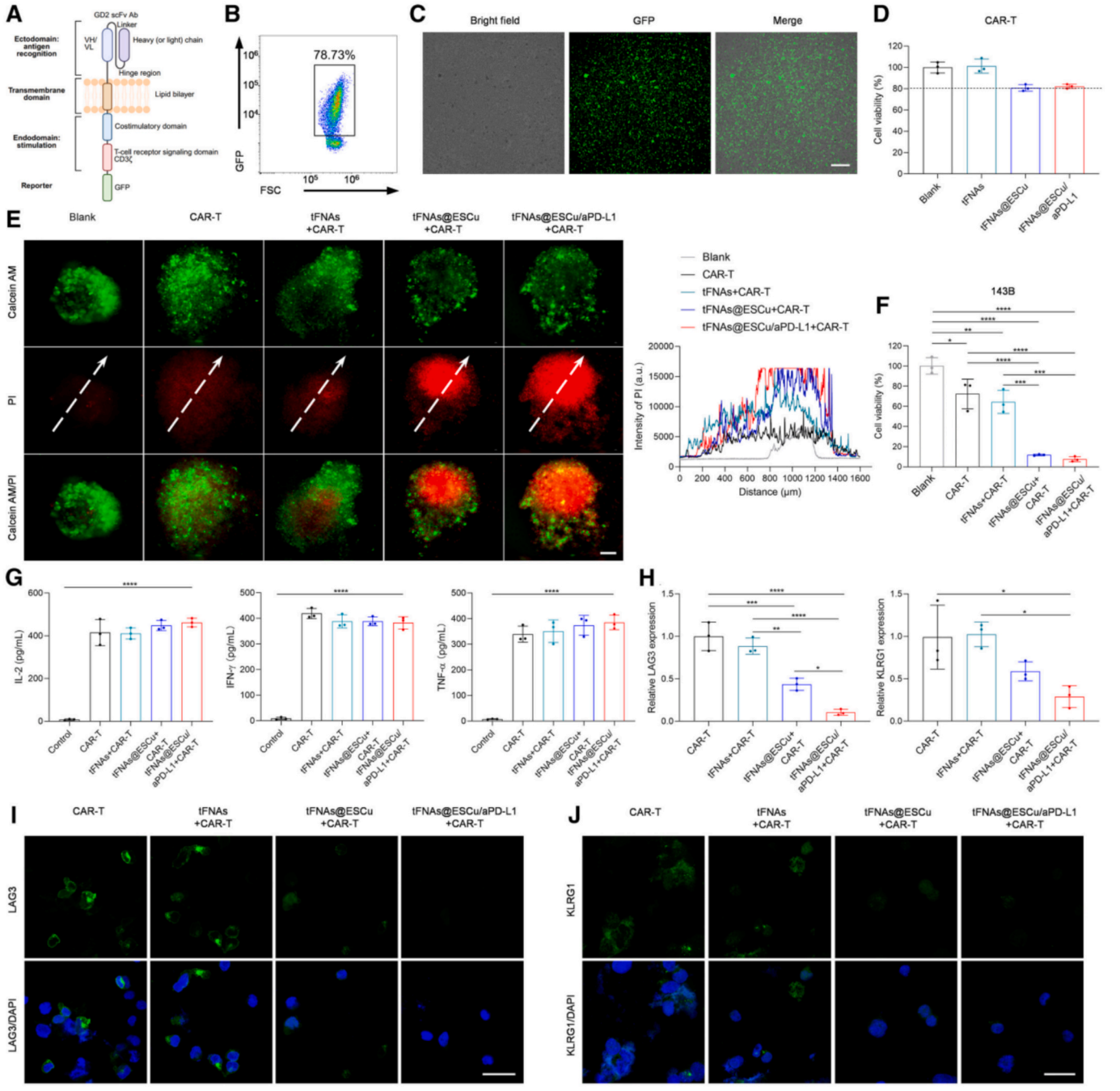


Fig. 7. Design engineering Copper-based nanoplatform to enhance specific targeting. (A) Nanoparticles encapsulated by polymers or cell membrane and functionalized with various ligands. (B) CP@HMM, which is encapsulated by a hybrid membrane composed of Hepa1-6 and MDSCs membrane, targets cancer cells and MDSCs and facilitates the targeted delivery of copper-doped carbon dots to these cells [191]. Copyright © 2025, American Chemical Society.

particularly exciting prospect is their ability to activate anti-tumor immunity. Preclinical studies have validated the potential of copper-based nanoplatforms in treating various aggressive cancers. Copper-based nanoplatforms thus offer a new frontier in the battle against cancer, combining the strengths of diverse therapies to create powerful, synergistic treatment modalities. However, no purely therapeutic copper nanoparticle drugs for cancer are currently in clinical trials. The most advanced clinical applications are in the field of cancer diagnostics and imaging, primarily using the radioactive isotope Copper-64 (^{64}Cu). More recently, the theranostic agent ^{64}Cu/^{67}Cu-SAR-bisPSMA (NCT04868604) has entered Phase I/II clinical trials, where ^{64}Cu enables precise imaging and ^{67}Cu provides targeted radiotherapy within the same molecular platform. While purely therapeutic copper nanoparticle platforms (e.g., copper oxide nanoparticles, copper-based drug delivery systems) remain predominantly at the preclinical stage owing to challenges in toxicity control, scalable manufacturing, and regulatory approval, the successful clinical translation of copper-based diagnostic and theranostic agents establishes a solid foundation. This existing clinical experience not only validates the biocompatibility and targeting potential of copper-based platforms but also provides critical insights for designing next-generation therapeutic copper nanomaterials.

The transition from widespread preclinical success to clinical application remains a significant hurdle, hampered by challenges in quality control and standardization, long-term toxicity concerns.

6.1. Quality control and standardization

As the field of copper-based therapy advances, there is a growing need for rigorous quality control and standardization in both nanoparticle formulation and biological evaluation.

One aspect of quality control lies in the production of the nanomaterials themselves. Slight variations in synthesis (particle size, surface coating, copper oxidation state) can lead to significant differences in ROS-generating ability and toxicity. Due to the varying EPR effect of different-sized nanoparticles, a batch of 30-nm copper oxide nanoparticles may exhibit much higher reactivity than 50-nm particles, even if even if nominally the same formulation. Reporting of copper ion release kinetics in simulated TME conditions is also important, as it correlates with both efficacy and safety. To ensure safety, nanoparticles should be surface-functionalized for specific targeting of cancer cells and achieve precise release via various TME-responsive mechanisms. The targeting ability and responsiveness of the material directly influence copper release at the tumor site, thereby impacting the nanodrug's therapeutic efficacy and safety profile.

Therefore, establishing a standardized quality control system is essential. This can be achieved through the following approaches: 1. Establish and adhere to strict, reproducible synthesis procedures with real-time monitoring to minimize batch-to-bariability in critical quality attributes like size, coating thickness, and copper oxidation state. 2. Ensuring batch-to-batch consistency in copper content and reactivity will likely involve good manufacturing practice (GMP) controls, including controlling the material synthesis, surface modification, stringent checks on copper leaching during storage and on nanoparticle aggregation. 3. Exploring machine learning to predict and optimize these parameters, which could eventually lead to “tuning” of nanomaterial properties for consistency.

6.2. Balancing efficacy and safety

The clinical translation of copper nanomaterials hinges on resolving the fundamental dichotomy between their potent therapeutic efficacy and potential systemic toxicity. This balance is paramount and must be addressed through rational nanomaterial design.

The primary challenge lies in confining the potent cytotoxic activity of copper—including ROS generation via CDT and the induction of cuproptosis/ferroptosis—strictly to tumor tissues. While strategies like leveraging the EPR effect and active targeting (discussed in Section 5) enhance tumor accumulation, they are often insufficient to completely prevent off-target accumulation. A more sophisticated approach involves engineering “smart” nanoplatforms that release copper ions only in response to specific TME triggers, such as mild acidity, elevated H_2O_2, or overexpressed enzymes. This TME-responsive release, combined with surface functionalization (e.g., PEGylation, biomimetic coatings) to improve biocompatibility and prolong circulation, forms the first line of defense against systemic toxicity. Comprehensive safety assessments, investigating long-term biodistribution and clearance pathways, are indispensable complements to these design strategies.

Beyond spatial control, a more nuanced challenge is orchestrating the dual immunomodulatory role of ROS. While elevated ROS can trigger ICD and stimulate anti-tumor immunity, excessive oxidative stress can paradoxically foster an immunosuppressive microenvironment and damage healthy cells. This suggests the existence of a therapeutic window for intratumoral ROS that maximizes immune activation. Future research must focus on defining this window across different tumor types, which exhibit heterogeneous redox states.

To achieve this precise control, the next generation of CuNPs must evolve from being mere “reactors” to becoming self-regulating “thermostats” of oxidative stress. Pioneering concepts include:

Feedback-Controlled Nanosystems: Designing particles that incorporate intrinsic feedback mechanisms. For instance, a nanosystem could co-deliver a pro-oxidant (e.g., Cu^{2+}) and an antioxidant (e.g., a ROS-scavenging molecule) that is activated only when ROS levels exceed a specific threshold, thereby preventing “overshooting” and maintaining ROS within the immunogenic zone.

Real-Time Monitoring and Adjustment: Developing non-invasive imaging techniques to sense intratumoral ROS levels in real-time could allow for external adjustment of treatments (e.g., modulating laser intensity for PTT).

Ultimately, leveraging machine learning to analyze vast datasets linking synthesis parameters, material properties, and biological outcomes can guide the reverse design of CuNPs with an optimal efficacy-safety profile, paving the way for their successful clinical integration.

6.3. Clinical trial design

The clinical translation of copper-based nanomedicines must overcome a series of practical challenges bridging the gap from the laboratory to the clinic. In clinical trials, the development and validation of a robust set of biomarkers is indispensable for assessing treatment response and guiding patient stratification. This system should encompass:

Pharmacokinetic and Targeting Biomarkers: If radiolabeled with ^{64}Cu, positron emission tomography (PET) can be used to track the nanoparticle's tumor accumulation and whole-body distribution in real-time, quantitatively confirming targeting efficiency.

Pharmacodynamic and Efficacy Biomarkers: Therapy-induced immunogenic cell death can be indirectly assessed by measuring the release of DAMPs into the peripheral blood, such as dynamic changes in HMGB1 and extracellular ATP levels. Concurrently, changes in the levels of copper and key cell death-related proteins (e.g., aggregated lipoylated DLAT) in pre- and post-treatment tumor biopsies can directly corroborate the mechanism of action.

Safety Biomarkers: Regular monitoring of 24-hour urinary copper excretion serves as a simple and effective safety indicator. A transient post-dose increase followed by a return to baseline suggests effective clearance of excess copper and a low risk of systemic toxicity.

In conclusion, the outlook for copper-based nano-immunotherapy is promising. The coming years will be decisive in transforming this exciting concept into a clinical reality. Achieving this goal will require close multidisciplinary collaboration among materials scientists, oncologists, and regulatory experts to collectively refine the nanoplatforms, design intelligent clinical trials, and ensure patient safety. It is reasonable to anticipate that by precisely igniting this “oxidative fire” within the tumor, we can successfully rally the immune system to achieve a lasting victory over cancer.

CRediT authorship contribution statement

Ying-Ying Yang: Writing – original draft. **Xin-Rui Zhang:** Writing – original draft. **Meng-Qi Fu:** Conceptualization. **Rong Li:** Data curation. **Bo Chen:** Investigation. **Xin Li:** Data curation. **Lu Zhang:** Investigation. **Wen-Tao Liu:** Data curation. **Wen-Ya Zhan:** Investigation. **Xi-Tong Li:** Methodology. **Ming-Sheng Zhou:** Writing – review & editing. **Yang Yao:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the grants from the Scientific Research Foundation of Liaoning Province (LJ212510164013) to YY.

Data availability

Data will be made available on request.

References:

[1] C. Kumawat, T. Takahashi, I. Date, Y. Tomita, M. Tanaka, S. Arataki, T. Komatsubara, A.O.P. Flores, D. Yu, M. Jain, State-of-the-art and new treatment approaches for spinal cord tumors, Cancers 16 (13) (2024), https://doi.org/10.3390/cancers16132360.

[2] Y.S. Li, L.Y. Ye, Y.X. Luo, W.J. Zheng, J.X. Si, X. Yang, Y.N. Zhang, S.B. Wang, H. Zou, K.T. Jin, T. Ge, Y. Cai, X.Z. Mou, Tumor-targeted delivery of copper-manganese biomineralized oncolytic adenovirus for colorectal cancer immunotherapy, Acta Biomater. 179 (2024) 243–255, https://doi.org/10.1016/j.actbio.2024.02.044.

[3] L. Vigderman, E.R. Zubarev, Starfruit-shaped gold nanorods and nanowires: synthesis and SERS characterization, Langmuir : the ACS Journal of Surfaces and Colloids 28 (24) (2012) 9034–9040, https://doi.org/10.1021/la300218z.

[4] K.L. Aillon, Y. Xie, N. El-Gendy, C.J. Berkland, M.L. Forrest, Effects of nanomaterial physicochemical properties on in vivo toxicity, Adv. Drug Deliv. Rev. 61 (6) (2009) 457–466, https://doi.org/10.1016/j.addr.2009.03.010.

[5] S. Bhattacharyya, R.A. Kudgus, R. Bhattacharya, P. Mukherjee, Inorganic nanoparticles in cancer therapy, Pharm. Res. 28 (2) (2011) 237–259, https://doi.org/10.1007/s11095-010-0318-0.

[6] E.Y. Makhani, A. Zhang, J.B. Haun, Quantifying and controlling bond multivalency for advanced nanoparticle targeting to cells, Nano Convergence 8 (1) (2021) 38, https://doi.org/10.1186/s40580-021-00288-1.

[7] K. Jiang X. Feng X. Gao Y. Wang C. Cai Z. Li H. Lin Preparation of Multicolor Photoluminescent Carbon Dots by Tuning Surface States 9 2019 Nanomaterials (Basel, Switzerland) 10.3390/nano9040529.

[8] J. Liu, S. Lu, Q. Tang, K. Zhang, W. Yu, H. Sun, B. Yang, One-step hydrothermal synthesis of photoluminescent carbon nanodots with selective antibacterial activity against Porphyromonas gingivalis, Nanoscale 9 (21) (2017) 7135–7142, https://doi.org/10.1039/c7nr02128c.

[9] B. Cheng, D. Li, C. Li, Z. Zhuang, P. Wang, G. Liu, The Application of Biomedicine in Chemodynamic Therapy: From Material Design to Improved Strategies, Bioengineering (Basel, Switzerland) 10(8) (2023). https://doi.org/10.3390/bioengineering10080925.

[10] P. Tsvetkov, S. Coy, B. Petrova, M. Dreishpoon, A. Verma, M. Abdusamad, J. Rossen, L. Joesch-Cohen, R. Humeidi, R.D. Spangler, J.K. Eaton, E. Frenkel, M. Kocak, S.M. Corsello, S. Lutsenko, N. Kanarek, S. Santagata, T.R. Golub, Copper induces cell death by targeting lipoylated TCA cycle proteins, Science (New York, N.Y.) 375(6586) (2022) 1254-1261. https://doi.org/10.1126/science.abf0529.

[11] L.K. Karunanidhi Gowsalya, R. Vivek, Inorganic nanoparticle-based nanomedicines for cancer immunotherapy, Nanomedicine in Cance Immunotherapy (2024) 243–269.

[12] S. Singh, K. Pal, Folic-acid adorned alginate-polydopamine modified paclitaxel/Zn-CuO nanocomplex for pH triggered drug release and synergistic antitumor efficacy, Int. J. Biol. Macromol. 234 (2023) 123602, https://doi.org/10.1016/j.ijbiomac.2023.123602.

[13] X. Li, Y. Pan, J. Zhou, G. Yi, C. He, Z. Zhao, Y. Zhang, Hyaluronic acid-modified manganese dioxide-enveloped hollow copper sulfide nanoparticles as a multifunctional system for the co-delivery of chemotherapeutic drugs and photosensitizers for efficient synergistic antitumor treatments, J. Colloid Interface Sci. 605 (2022) 296–310, https://doi.org/10.1016/j.jcis.2021.07.092.

[14] S. Lu, H. Tian, B. Li, L. Li, H. Jiang, Y. Gao, L. Zheng, C. Huang, Y. Zhou, Z. Du, J. Xu, An ellagic acid coordinated copper-based nanoplatform for efficiently overcoming cancer chemoresistance by cuproptosis and synergistic inhibition of cancer cell stemness, Small (Weinheim an der Bergstrasse Germany) 20 (17) (2024) e2309215, https://doi.org/10.1002/smll.202309215.

[15] G. Tan, G. Hou, J. Qian, Y. Wang, W. Xu, W. Luo, X. Chen, A. Suo, Hyaluronan-decorated copper-doxorubicin-anlotinib nanoconjugate for targeted synergistic chemo/chemodynamic/antiangiogenic tritherapy against hepatocellular carcinoma, J. Colloid Interface Sci. 662 (2024) 857–869, https://doi.org/10.1016/j.jcis.2024.02.085.

[16] R. Rai, S. Alwani, I. Badea, Polymeric nanoparticles in gene therapy: new avenues of design and optimization for delivery applications, Polymers 11 (4) (2019), https://doi.org/10.3390/polym11040745.

[17] S. Kim, J.H. Kim, W.Y. Kwon, S.H. Hwang, B.S. Cha, J.M. Kim, S.S. Oh, K.S. Park, Synthesis of DNA-templated copper nanoparticles with enhanced fluorescence stability for cellular imaging, Mikrochim. Acta 186 (7) (2019) 479, https://doi.org/10.1007/s00604-019-3620-5.

[18] T. Nourollahian, S. Taghavi, K. Abnous, S.M. Taghdisi, S. Nekooei, M. Ramezani, M. Alibolandi, Targeted doxorubicin-loaded core–shell copper peroxide-mesoporous silica nanoparticles for combination of ferroptosis and chemotherapy of metastatic breast cancer, Int. J. Pharm. 662 (2024) 124487, https://doi.org/10.1016/j.ijpharm.2024.124487.

[19] C. Xia, Z. Luo, Z. Feng, Q. Zhang, C. Xia, Mechanism and application of copper-based nanomedicines in activating tumor immunity through oxidative stress modulation, Volume 16 - 2025 (2025). https://doi.org/10.3389/fphar.2025.1646890.

[20] S. Vijayaram, H. Razafindralambo, Y.-Z. Sun, S. Vasantharaj, H. Ghafarifarsani, S. H. Hoseinifar, M. Raeeszadeh, Applications of green synthesized metal nanoparticles - a review, Biol. Trace Elem. Res. 202 (1) (2024) 360–386, https://doi.org/10.1007/s12011-023-03645-9.

[21] J. Wu, The enhanced permeability and retention (EPR) effect: the significance of the concept and methods to enhance its application, Journal of Personalized Medicine 11 (8) (2021), https://doi.org/10.3390/jpm11080771.

[22] A. Banerjee, J. Qi, R. Gogoi, J. Wong, S. Mitragotri, Role of nanoparticle size, shape and surface chemistry in oral drug delivery, J. Control. Release 238 (2016) 176–185, https://doi.org/10.1016/j.jconrel.2016.07.051.

[23] J. Wang, W. Mao, L.L. Lock, J. Tang, M. Sui, W. Sun, H. Cui, D. Xu, Y. Shen, The role of micelle size in tumor accumulation, Penetration, and Treatment, ACS Nano 9 (7) (2015) 7195–7206, https://doi.org/10.1021/acsnano.5b02017.

[24] M.S. Abdelhamid, A.S. Wadan, H.A. Saad, W.A. El-Dakroury, A.W. Hageen, D. H. Mohammed, S. Mourad, O.A. Mohammed, M.A. Abdel-Reheim, A.S. Doghish, Nanoparticle innovations in targeted cancer therapy: advancements in antibody-drug conjugates, Naunyn Schmiedebergs Arch. Pharmacol. (2025), https://doi.org/10.1007/s00210-024-03764-7.

[25] S. Chen, H. Huang, Q. Li, J. Cai, Z. Miao, P. Xie, S. Tang, D. He, Carrier-free nanoparticles based on self-assembly of 5-FU and copper-genistein complexes for the combined treatment of hepatocellular carcinoma, Drug Deliv. Transl. Res. 15 (4) (2025) 1299–1316, https://doi.org/10.1007/s13346-024-01676-w.

[26] H. Sun, L. Zhang, N. Zhao, H. Xin, Cu(2+)-citrate-chitosan complex nanoparticles for the chemodynamic therapy of lung cancer, ACS Omega 9 (7) (2024) 8425–8433, https://doi.org/10.1021/acsomega.3c09619.

[27] F. LewisOscar, D. MubarakAli, C. Nithya, R. Priyanka, V. Gopinath, N.S. Alharbi, N. Thajuddin, One pot synthesis and anti-biofilm potential of copper nanoparticles (CuNPs) against clinical strains of *Pseudomonas aeruginosa*, Biofouling 31 (4) (2015) 379–391, https://doi.org/10.1080/08927014.2015.1048686.

[28] A.K. Arun, K. Sharma, U.N. GauravTaneja, A. Deepd, S.K. Rajput, Synthesis and preliminary therapeutic evaluation of copper nanoparticles against diabetes mellitus and-induced micro-(renal) and macro-vascular (vascular endothelial and cardiovascular) abnormalities in rats, RSC Adv. 6 (2016) 36870–36880.

[29] D. Letchumanan, S.P.M. Sok, S. Ibrahim, N.H. Nagoor, N.M. Arshad, Plant-based biosynthesis of copper/copper oxide nanoparticles: an update on their applications in biomedicine, mechanisms, and toxicity, Biomolecules 11 (4) (2021), https://doi.org/10.3390/biom11040564.

[30] C. Li, S. Liu, Y. Xu, T. Ren, Y. Guo, Z. Wang, X. Li, L. Wang, H. Wang, Controllable reconstruction of copper nanowires into nanotubes for efficient electrocatalytic nitrate conversion into ammonia, Nanoscale 14 (34) (2022) 12332–12338, https://doi.org/10.1039/d2nr03767j.

[31] P. Iyengar, J. Huang, G.L. De Gregorio, C. Gadiyar, R. Buonsanti, Size dependent selectivity of Cu nano-octahedra catalysts for the electrochemical reduction of CO (2) to CH(4), Chem. Commun. (Camb) 55 (60) (2019) 8796–8799, https://doi.org/10.1039/c9cc02522g.

[32] L. Zaza, D.C. Stoian, N. Bussell, P.P. Albertini, C. Boulanger, J. Leemans, K. Kumar, A. Loiudice, R. Buonsanti, Increasing precursor reactivity enables continuous tunability of copper nanocrystals from single-crystalline to twinned and stacking fault-lined, J. Am. Chem. Soc. 146 (47) (2024) 32766–32776, https://doi.org/10.1021/jacs.4c12905.

[33] S. Ye, A.R. Rathmell, Y.-C. Ha, A.R. Wilson, B.J. Wiley, The Role of Cuprous Oxide Seeds in the One-Pot and Seeded Syntheses of Copper Nanowires, 10(9) (2014) 1771-1778. https://doi.org/https://doi.org/10.1002/smll.201303005.

[34] C. Li, S. Khuje, D. Petit, Y. Huang, A. Sheng, L. An, M. Di Luigi, A. Jalouli, M. Navarro, A. Islam, S. Ren, Printed copper-nanoplate conductor for electromagnetic interference, Nanotechnology 33 (11) (2021), https://doi.org/10.1088/1361-6528/ac40bc.

[35] H.-J. Yang, S.-Y. He, H.-Y. Tuan, Self-seeded growth of five-fold twinned copper nanowires: mechanistic study, characterization, and SERS applications, LangmuirThe ACS Journal of Surfaces and Colloids 30 (2) (2014) 602–610, https://doi.org/10.1021/la4036198.

[36] G. Granata, T. Yamaoka, F. Pagnanelli, A. Fuwa, Study of the synthesis of copper nanoparticles: the role of capping and kinetic towards control of particle size and stability, J. Nanopart. Res. 18 (5) (2016) 133, https://doi.org/10.1007/s11051-016-3438-6.

[37] A.A. Vodyashkin, P. Kezimana, F.Y. Prokonov, I.A. Vasilenko, Y.M. Stanishevskiy, Current methods for synthesis and potential applications of cobalt nanoparticles: a review, Crystals (2022).

[38] M. Liu, J. Zheng, M. Yu, Q. Wang, Y. Yuan, N. Shao, X. Yang, T. Shen, L. Wang, A. Li, R. Liu, J. Cao, X. Liu, F. Cao, Y. Feng, Stimuli-Responsive CuFeTe(2) Nanosheets for Amplified Cuproptosis/Ferroptosis in Triple-Negative Breast Cancer Therapy, Advanced science (Weinheim, Baden-Wurttemberg, Germany) (2025) e05739. https://doi.org/10.1002/advs.202505739.

[39] G.K. Dinesh, M. Pramod, S. Chakma, Sonochemical synthesis of amphoteric Cu (0)-Nanoparticles using Hibiscus rosa-sinensis extract and their applications for degradation of 5-fluorouracil and lovastatin drugs, J. Hazard. Mater. 399 (2020) 123035, https://doi.org/10.1016/j.jhazmat.2020.123035.

[40] F.R. Rasoul Khayyam Nekouei, Arsalan Ravanbakhsh, Copper nanopowder synthesis by electrolysis method in nitrate and sulfate solutions, Powder Technology 250 91-96. https://doi.org/doi.org/10.1016/j.powtec.2013.10.012.

[41] C. Wei, Q. Liu, Shape-, size-, and density-tunable synthesis and optical properties of copper nanoparticles, CrstEngComm 19 (24) (2017) 3254–3262, https://doi.org/10.1039/C7CE00750G.

[42] S. Shao, W. Wu, F. Meng, M. Duan, M. Zhang, Copper-Based Nanomaterials: A Rising Star in Cancer Therapy, 6(10) (2023) 2300049. https://doi.org/https://doi.org/10.1002/adtp.202300049.

[43] J. Shao, B. Ding, H. Chen, Z. Liu, S. Liu, X. Ma, J. Wang, Z. Wang, J. Zhang, K. He, Y. Hu, P. Ma, J. Lin, Sub-1 nm CuO-Phosphomolybdic Acid Nanosheets for Ultrasound-Controlled Pyroptosis Activation and Tumor Immunotherapy, Angewandte Chemie (International ed. in English) 64(36) (2025) e202508544. https://doi.org/10.1002/anie.202508544.
[44] M. Devaraji, P.V. Thanikachalam, R. As, R. S, B. J, Microwave-assisted synthesis of copper oxide nanoparticles using an Andrographis paniculata leaf extract: Characterization and multifunctional biological activities, Nano-Structures & Nano-Objects 40 (2024) 101376. https://doi.org/https://doi.org/10.1016/j.nanoso.2024.101376.
[45] N. Shen, T. Wang, Q. Gan, S. Liu, L. Wang, B. Jin, Plant flavonoids: classification, distribution, biosynthesis, and antioxidant activity, Food Chem. 383 (2022) 132531, https://doi.org/10.1016/j.foodchem.2022.132531.
[46] T. Pinto, A. Aires, F. Cosme, E. Bacelar, M.C. Morais, I. Oliveira, J. Ferreira-Cardoso, R. Anjos, A. Vilela, B. Gonçalves, Bioactive (Poly)phenols, Volatile Compounds from Vegetables, Medicinal and Aromatic Plants, Foods (Basel, Switzerland) 10(1) (2021). https://doi.org/10.3390/foods10010106.
[47] V.R. Priya, S. Lakhawat, V.K. Yadav, A. Gacem, M. Abbas, K.K. Yadav, H. Park, B. Jeon, S. Mishra, Millets: sustainable treasure house of bioactive components, Int. J. Food Prop. 26 (2023) 1822–1840.
[48] P. Singh Jassal, D. Kaur, R. Prasad, J. Singh, Green synthesis of titanium dioxide nanoparticles: development and applications, Journal of Agriculture and Food Research 10 (2022) 100361, https://doi.org/10.1016/j.jafr.2022.100361.
[49] J.C. Zhou, C.M. Soto, M.S. Chen, M.A. Bruckman, M.H. Moore, E. Barry, B. R. Ratna, P.E. Pehrsson, B.R. Spies, T.S. Confer, Biotemplating rod-like viruses for the synthesis of copper nanorods and nanowires, J. Nanobiotechnol. 10 (2012) 18, https://doi.org/10.1186/1477-3155-10-18.
[50] R. Man, M. Xia, H. Li, F. Tian, J. Zhang, Z. Yu, B. Tang, Human serum albumin mediated controllable synthesis of defect-rich copper hydroxide nanowire for cuproptosis-based anti-tumor therapy, Adv. Healthc. Mater. 13 (23) (2024) e2401078, https://doi.org/10.1002/adhm.202401078.
[51] Y. Huang, P. Li, R. Zhao, L. Zhao, J. Liu, S. Peng, X. Fu, X. Wang, R. Luo, R. Wang, Z. Zhang, Silica nanoparticles: Biomedical applications and toxicity, Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 151 (2022) 113053. https://doi.org/10.1016/j.biopha.2022.113053.
[52] D. Tank, A. Bishnoi, S. Goswami, N.J. Ambegaonkar, P. Patel, M. Chahar, S. Khaturia, V.K. Yadav, Recent advances in phyto- and microorganisms-mediated synthesis of copper nanoparticles and their emerging applications in healthcare, environment, agriculture and food industry, Bioprocess Biosyst. Eng. 48 (12) (2025) 1949–1982, https://doi.org/10.1007/s00449-025-03196-4.
[53] Z. Chen, Y. Li, Y. Yin, M. Song, F. Wang, G. Jiang, Cu Nanowires trigger efficient cuproptosis via special intracellular distribution and excessive Cu Ion release, Nano Lett. 24 (37) (2024) 11446–11453, https://doi.org/10.1021/acs.nanolett.4c02503.
[54] S. Thirumurugan, K. Samuvel Muthiah, R. Sakthivel, M.Y. Liao, H. Kasai, R. J. Chung, Polydopamine-coated Cu-BTC nanowires for effective magnetic resonance imaging and photothermal therapy, Pharmaceutics 15 (3) (2023), https://doi.org/10.3390/pharmaceutics15030822.
[55] S. Murugan, M. Ashokkumar, K.J.S. Kumar, M. Nandhagopal, Exploring the multifunctionality of Cu/Mn-doped ZnS nanosheets: a promising material for cancer therapy and advanced antimicrobial applications, J. Biomed. Mater. Res. B Appl. Biomater. 113 (11) (2025) e35684, https://doi.org/10.1002/jbm.b.35684.
[56] D. Jiang, B. Yang, J. Shi, Bifunctional KatG-mimic activity of nanosheet for coupled catalytic therapy of hypoxic tumor, Adv. Healthc. Mater. 14 (30) (2025) e02490, https://doi.org/10.1002/adhm.202502490.
[57] Y. Yao, B. Yang, J. Shi, Crystalline copper hydroxide nanosheets with katg-like dual activities for synergized nanocatalytic tumor therapy, Nano Lett. 25 (20) (2025) 8369–8378, https://doi.org/10.1021/acs.nanolett.5c01657.
[58] J. Bing, B. Zhou, M. Chen, Y. Shen, M. Zhou, H. Lin, W. Wu, J. Shi, Nanomedicine-enabled concurrent regulations of ROS generation and copper metabolism for sonodynamic-amplified tumor therapy, Biomaterials 318 (2025) 123137, https://doi.org/10.1016/j.biomaterials.2025.123137.
[59] Z. Yang, Z. Li, C. Yang, L. Meng, W. Guo, L. Jing, Synthesis of closely-contacted Cu2O-CoWO4 nanosheet composites for cuproptosis therapy to tumors with sonodynamic and photothermal assistance, Adv. Sci. 12 (2) (2025) 2410621, https://doi.org/10.1002/advs.202410621.
[60] L. Yang, K. Wang, L. Guo, X. Hu, M. Zhou, Unveiling the potential of HKUST-1: synthesis, activation, advantages and biomedical applications, J. Mater. Chem. B 12 (11) (2024) 2670–2690, https://doi.org/10.1039/d3tb02929h.
[61] C.J. Wijaya, F.E. Soetaredjo, S. Ismadji, S. Gunawan, Synthesis of cellulose nanocrystals/HKUST-1 composites and their applications: crystal violet removal and doxorubicin loading, Polymers 14 (22) (2022), https://doi.org/10.3390/polym14224991.
[62] P. Zou, Y. Pan, W. Luo, R. Huang, X. Lin, Y. Xie, Construction of CuS/HKUST-1@PDA drug carrier for enhanced chemo-photothermal synergistic therapy triggered by near-infrared light in tumor treatment, Colloids Surf. B Biointerfaces 254 (2025) 114784, https://doi.org/10.1016/j.colsurfb.2025.114784.
[63] R. Zeng, T. He, L. Lu, K. Li, Z. Luo, K. Cai, Ultra-thin metal-organic framework nanosheets for chemo-photodynamic synergistic therapy, J. Mater. Chem. B 9 (20) (2021) 4143–4153, https://doi.org/10.1039/d1tb00528f.
[64] Z. Gharehdaghi, R. Rahimi, S.M. Naghib, F. Molaabasi, Cu (II)-porphyrin metal-organic framework/graphene oxide: synthesis, characterization, and application as a pH-responsive drug carrier for breast cancer treatment, Journal of Biological Inorganic Chemistry : JBIC : a Publication of the Society of Biological Inorganic Chemistry 26 (6) (2021) 689–704, https://doi.org/10.1007/s00775-021-01887-3.
[65] G. Huang, J. Chen, X. Tang, D. Xiong, Z. Liu, J. Wu, W.Y. Sun, B. Lin, Facile method to prepare a novel biological HKUST-1@CMCS with macroscopic shape control for the long-acting and sustained release, ACS Appl. Mater. Interfaces 11 (10) (2019) 10389–10398, https://doi.org/10.1021/acsami.8b21424.
[66] N.N. Huyen, X.D. Ngo, V.T. Huong Mai, P.T. Lan Huong, P.D. Thang, L.A. Tuan, Green light-responsive photoelectrochemical sensing nanoplatform based on copper cobaltite nanorods for ultrasensitive detection of furazolidone antibiotic residue in food samples, RSC Adv 15(5) (2025) 3122-3138. https://doi.org/10.1039/d4ra08497g.
[67] J. Ma, J. Zhao, X. Liu, C. Gu, S. Zeng, M.D. Birowosuto, J. Jiang, T. Jiang, K. Wu, Ultrasensitive SERS-based detection of prostate cancer exosome using Cu2O–CuO@Ag composite nanowires, Biosens. Bioelectron. 243 (2024) 115775, https://doi.org/10.1016/j.bios.2023.115775.
[68] M. Xu, Y. Xu, C. Du, G. Gu, G. Wei, Biomimetic CuCoO2 nanosheets reinforced with self-assembling peptide nanofibers for tumor photothermal therapy, RSC Adv. 14 (53) (2024) 39163–39172, https://doi.org/10.1039/d4ra07435a.
[69] C. Wei, H. Lin, H. Bai, G-/C-rich ssDNA-based Fe and Cu/Fe nanoclusters with peroxidase-like activity for intracellular ROS production and cytotoxicity applications, Mikrochim. Acta 190 (5) (2023) 201, https://doi.org/10.1007/s00604-023-05788-x.
[70] S. Zoughi, F. Faridbod, S. Mohebbi, S. Moradi, Simultaneous recognition of two MicroRNAs associated with early stages of lung cancer by DNA hairpin-templated fluorescent nanoclusters, Mikrochim. Acta 192 (11) (2025) 763, https://doi.org/10.1007/s00604-025-07610-2.
[71] A. Li, S. Chu, M. Yuan, J. Zhang, H. Liu, Y. Zhu, J. Xu, X. Jiang, W. Xue, Near-infrared-II photocharging nanozyme for enhanced tumor immunotherapy, J. Colloid Interface Sci. 676 (2024) 783–794, https://doi.org/10.1016/j.jcis.2024.07.172.
[72] J. Yin, C. Liu, J. Guo, M. Li, B. Chen, X. Zhang, B. Wang, X. Zhu, D. Chen, A copper-loaded self-assembled nanoparticle for disturbing the tumor redox balance and triple anti-tumor therapy, J. Mater. Chem. B 12 (14) (2024) 3509–3520, https://doi.org/10.1039/d3tb02576d.
[73] Z. Tang, Y. Liu, M. He, W. Bu, Chemodynamic Therapy: Tumour Microenvironment-Mediated Fenton and Fenton-like Reactions, Angewandte Chemie (International ed. in English) 58(4) (2019) 946-956. https://doi.org/10.1002/anie.201805664.
[74] T. Gu, H. Dong, T. Lu, L. Han, Y. Zhan, Fluoride ion accelerating degradation of organic pollutants by Cu(II)-catalyzed Fenton-like reaction at wide pH range, J. Hazard. Mater. 377 (2019) 365–370, https://doi.org/10.1016/j.jhazmat.2019.05.073.
[75] S. Kim, J.H. Seo, D.I. Jeong, M. Yang, S.Y. Lee, J. Lee, H.J. Cho, Fenton-like reaction, glutathione reduction, and photothermal ablation-built-in hydrogels crosslinked by cupric sulfate for loco-regional cancer therapy, Biomater. Sci. 9 (3) (2021) 847–860, https://doi.org/10.1039/d0bm01470b.
[76] Y. Wang, F. Gao, X. Li, G. Niu, Y. Yang, H. Li, Y. Jiang, Tumor microenvironment-responsive fenton nanocatalysts for intensified anticancer treatment, J. Nanobiotechnol. 20 (1) (2022) 69, https://doi.org/10.1186/s12951-022-01278-z.
[77] G. He, Y. Pan, F. Zeng, S. Qin, X. Luan, Q. Lu, C. Xie, P. Hu, Y. Gao, J. Yang, B. He, Y. Song, Microfluidic synthesis of CuH nanoparticles for antitumor therapy through hydrogen-enhanced apoptosis and cuproptosis, ACS Nano 18 (12) (2024) 9031–9042, https://doi.org/10.1021/acsnano.3c12796.
[78] L. Zhang, J.M. Fu, L.B. Song, K. Cheng, F. Zhang, W.H. Tan, J.X. Fan, Y.D. Zhao, Ultrasmall Bi/Cu coordination polymer combined with glucose oxidase for tumor enhanced chemodynamic therapy by starvation and photothermal treatment, Adv. Healthc. Mater. 13 (2) (2024) e2302264, https://doi.org/10.1002/adhm.202302264.
[79] X. Zhu, C. Bi, W. Cao, S. Li, C. Yuan, P. Xu, D. Wang, Q. Chen, L. Zhang, A self-assembled copper-artemisinin nanoprodrug as an efficient reactive oxygen species amplified cascade system for cancer treatment, J. Mater. Chem. B 12 (36) (2024) 8902–8910, https://doi.org/10.1039/d4tb01237b.
[80] H. Wu, Z. Zhang, Y. Cao, Y. Hu, Y. Li, L. Zhang, X. Cao, H. Wen, Y. Zhang, H. Lv, X. Jin, A Self-Amplifying ROS-Responsive Nanoplatform for Simultaneous Cuproptosis and Cancer Immunotherapy, Advanced science (Weinheim, Baden-Wurttemberg, Germany) 11(23) (2024) e2401047. https://doi.org/10.1002/advs.202401047.
[81] Y. Liu, J. Wang, Multivalent metal catalysts in Fenton/Fenton-like oxidation system: a critical review, Chem. Eng. J. 466 (2023) 143147, https://doi.org/10.1016/j.cej.2023.143147.
[82] P. Ling, D. Song, P. Yang, C. Tang, W. Xu, F. Wang, NIR-II-responsive versatile nanozyme based on H(2)O(2) cycling and disrupting cellular redox homeostasis for enhanced synergistic cancer therapy, ACS Biomater Sci. Eng. 10 (8) (2024) 5290–5299, https://doi.org/10.1021/acsbiomaterials.4c00929.
[83] S. Guan, X. Liu, Y. Fu, C. Li, J. Wang, Q. Mei, G. Deng, W. Zheng, Z. Wan, J. Lu, A biodegradable "Nano-donut" for magnetic resonance imaging and enhanced chemo/photothermal/chemodynamic therapy through responsive catalysis in tumor microenvironment, J. Colloid Interface Sci. 608 (Pt 1) (2022) 344–354, https://doi.org/10.1016/j.jcis.2021.09.186.
[84] J. Song, C. Tang, Y. Wang, J. Ba, K. Liu, J. Gao, J. Chang, J. Kang, L. Yin, Multifunctional nanoparticles for enhanced sonodynamic-chemodynamic immunotherapy with glutathione depletion, Nanomedicine (Lond.) 19 (2) (2024) 145–161, https://doi.org/10.2217/nnm-2023-0218.
[85] J. Wang, Y. Sang, W. Chen, L. Cheng, W. Du, H. Zhang, B. Zheng, L. Song, Y. Hu, X. Ma, Glutathione depletion-induced ROS/NO generation for cascade breast cancer therapy and enhanced anti-tumor immune response, Int. J. Nanomed. 19 (2024) 2301–2315, https://doi.org/10.2147/ijn.S440709.

[86] P.M.P.C. Nagajyothi, T.V.M. Sreekanth, Doo Hwan Kim, Jaesool Shim, Green synthesis: in-vitro anticancer activity of copper oxide nanoparticles against human cervical carcinoma cells, Arab. J. Chem. 10 (2017) 215–225.
[87] B. Perillo, M. Di Donato, A. Pezone, E. Di Zazzo, P. Giovannelli, G. Galasso, G. Castoria, A. Migliaccio, ROS in cancer therapy: the bright side of the moon, Exp. Mol. Med. 52 (2) (2020) 192–203, https://doi.org/10.1038/s12276-020-0384-2.
[88] G.M. Sulaiman, A.T. Tawfeeq, M.D. Jaaffer, Biogenic synthesis of copper oxide nanoparticles using olea europaea leaf extract and evaluation of their toxicity activities: an in vivo and in vitro study, Biotechnol. Prog. 34 (1) (2018) 218–230, https://doi.org/10.1002/btpr.2568.
[89] Z. Hosseini, A. Ahmadi, A. Shadi, S.J. Hosseini, H. Nikmanesh, Green-synthesized copper oxide nanoparticles induce apoptosis and up-regulate HOTAIR and HOTTIP in pancreatic cancer cells, Nanomedicine (Lond.) 19 (18–20) (2024) 1629–1641, https://doi.org/10.1080/17435889.2024.2367958.
[90] A.V. Sirotkin, P. Romero-Navarro, B. Loncová, Z. Fabová, M. Bartušová, A.H. Harrath, F. Alonso, Counteractive Effects of Copper Nanoparticles and Betacellulin on Ovarian Cells, Nanomaterials (Basel, Switzerland) 14(23) (2024). https://doi.org/10.3390/nano14231965.
[91] H. Abdollahzadeh, Y. Pazhang, A. Zamani, Y. Sharafi, Green synthesis of copper oxide nanoparticles using walnut shell and their size dependent anticancer effects on breast and colorectal cancer cell lines, Sci. Rep. 14 (1) (2024) 20323, https://doi.org/10.1038/s41598-024-71234-4.
[92] D. Brancaccio, A. Gallo, M. Piccioli, E. Novellino, S. Ciofi-Baffoni, L. Banci, [4Fe-4S] cluster assembly in mitochondria and its impairment by copper, J. Am. Chem. Soc. 139 (2) (2017) 719–730, https://doi.org/10.1021/jacs.6b09567.
[93] Y. Zhao, L. Yu, L. Zhang, H. Liu, Y. Zhou, J.S. Kim, Activated aggregation-induced emission therapeutics agents for triggering regulated cell death, Aggregate 5 (3) (2024) e503.
[94] N. Wang, Y. Liu, D. Peng, Q. Zhang, Z. Zhang, L. Xu, L. Yin, X. Zhao, Z. Lu, J. Peng, Copper-Based Composites Nanoparticles Improve Triple-Negative Breast Cancer Treatment with Induction of Apoptosis-Cuproptosis and Immune Activation, Advanced healthcare materials (2024) e2401646. https://doi.org/10.1002/adhm.202401646.
[95] N. Zhang, W. Ping, K. Rao, Z. Zhang, R. Huang, D. Zhu, G. Li, S. Ning, Biomimetic copper-doped polypyrrole nanoparticles induce glutamine metabolism inhibition to enhance breast cancer cuproptosis and immunotherapy, J. Control. Release 371 (2024) 204–215, https://doi.org/10.1016/j.jconrel.2024.05.045.
[96] S. Lu, Y. Li, Y. Yu, Glutathione-scavenging celastrol-cu nanoparticles induce self-amplified cuproptosis for augmented cancer immunotherapy, Advanced Materials (deerfield Beach Fla.) 36 (35) (2024) e2404971, https://doi.org/10.1002/adma.202404971.
[97] Y. Qin, H. Lu, Y. Shu, J.H. Wang, Atovaquone-coordinated copper-polyphenol nanoplatform orchestrates dual metabolic interference for synergistic cuproptosis and apoptosis, ACS Appl. Mater. Interfaces 17 (14) (2025) 21001–21012, https://doi.org/10.1021/acsami.5c05104.
[98] L. Qiao, Y. Ou, L. Li, S. Wu, Y. Guo, M. Liu, D. Yu, Q. Chen, J. Yuan, C. Wei, C. Ou, H. Li, D. Cheng, Z. Yu, Z. Li, H(2)S-driven chemotherapy and mild photothermal therapy induced mitochondrial reprogramming to promote cuproptosis, J. Nanobiotechnol. 22 (1) (2024) 205, https://doi.org/10.1186/s12951-024-02480-x.
[99] J. Xie, Y. Yang, Y. Gao, J. He, Cuproptosis: mechanisms and links with cancers, Mol. Cancer 22 (1) (2023) 46, https://doi.org/10.1186/s12943-023-01732-y.
[100] X. Lu, X. Chen, C. Lin, Y. Yi, S. Zhao, B. Zhu, W. Deng, X. Wang, Z. Xie, S. Rao, Z. Ni, T. You, L. Li, Y. Huang, X. Xue, Y. Yu, W. Sun, X. Shen, Elesclomol Loaded Copper Oxide Nanoplatform Triggers Cuproptosis to Enhance Antitumor Immunotherapy, Advanced science (Weinheim, Baden-Wurttemberg, Germany) 11(18) (2024) e2309984. https://doi.org/10.1002/advs.202309984.
[101] J. Wang, W. Zhang, Z. Xie, X. Wang, J. Sun, F. Ran, W. Jiang, Y. Liu, Z. Wang, H. Ran, D. Guo, NIR-responsive copper nanoliposome composites for cascaded ferrotherapy via ferroptosis actived ICD and IFN-γ released, Biomaterials 308 (2024) 122570, https://doi.org/10.1016/j.biomaterials.2024.122570.
[102] Y. Zhang, N. Zhang, J. Xing, Y. Sun, X. Jin, C. Shen, L. Cheng, Y. Wang, X. Wang, In situ hydrogel based on Cu–Fe3O4 nanoclusters exploits oxidative stress and the ferroptosis/cuproptosis pathway for chemodynamic therapy, Biomaterials 311 (2024) 122675, https://doi.org/10.1016/j.biomaterials.2024.122675.
[103] L. Huang, J. Zhu, G. Wu, W. Xiong, J. Feng, C. Yan, J. Yang, Z. Li, Q. Fan, B. Ren, Y. Li, C. Chen, X. Yu, Z. Shen, A strategy of “adding fuel to the flames” enables a self-accelerating cycle of ferroptosis-cuproptosis for potent antitumor therapy, Biomaterials 311 (2024) 122701, https://doi.org/10.1016/j.biomaterials.2024.122701.
[104] X. Yi, H. Xie, K. Huang, J. Luo, W. Li, Q. Zeng, F. He, W. Shi, D. Wang, L. Wang, Tumor-targeting nanomaterials based on metal-organic frameworks mediate tumor immunotherapy by promoting cuproptosis and pyroptosis in hepatocellular carcinoma cells, Mater. Today Bio 32 (2025) 101745, https://doi.org/10.1016/j.mtbio.2025.101745.
[105] X. Yan, H. Liu, L. Guo, C. Liu, S. Zhang, X. Wang, Y. Tang, R. Zhou, X. Jiang, E. Wang, S. Gao, C. Xu, Multifunctional drug delivery nanoparticles for combined chemotherapy/chemodynamic/photothermal therapy against colorectal cancer through synergistic cuproptosis/ferroptosis/apoptosis, Mater. Today Bio 30 (2025) 101427, https://doi.org/10.1016/j.mtbio.2024.101427.
[106] Y. Xin, K. Yu, L. Zhang, Y. Yang, H. Yuan, H. Li, L. Wang, J. Zeng, Copper-based plasmonic catalysis: recent advances and future perspectives, Advanced Materials (deerfield Beach Fla.) 33 (32) (2021) e2008145, https://doi.org/10.1002/adma.202008145.
[107] X. Li, J.F. Lovell, J. Yoon, X. Chen, Clinical development and potential of photothermal and photodynamic therapies for cancer, Nat. Rev. Clin. Oncol. 17 (11) (2020) 657–674, https://doi.org/10.1038/s41571-020-0410-2.
[108] Z. Liu, J. Ling, N. Wang, X.K. Ouyang, Redox homeostasis disruptors enhanced cuproptosis effect for synergistic photothermal/chemodynamic therapy, J. Colloid Interface Sci. 678 (Pt A) (2025) 1060–1074, https://doi.org/10.1016/j.jcis.2024.08.234.
[109] B. Ji, H. Cai, Y. Yang, F. Peng, M. Song, K. Sun, F. Yan, Y. Liu, Hybrid membrane camouflaged copper sulfide nanoparticles for photothermal-chemotherapy of hepatocellular carcinoma, Acta Biomater. 111 (2020) 363–372, https://doi.org/10.1016/j.actbio.2020.04.046.
[110] T. Xu, S. Liu, Z. Wei, W. Zhang, G.Y. Zhang, T. Liu, L. Dai, P. Yin, Y. Song, Ultrathin Cu(9)S(5) nanosheets with sulfur vacancy for multimodal tumor therapy, ACS Appl. Mater. Interfaces 16 (12) (2024) 14489–14502, https://doi.org/10.1021/acsami.3c17902.
[111] M. Overchuk, R.A. Weersink, B.C. Wilson, G. Zheng, Photodynamic and photothermal therapies: synergy opportunities for nanomedicine, ACS Nano 17 (9) (2023) 7979–8003, https://doi.org/10.1021/acsnano.3c00891.
[112] L. Ma, X. Zou, W. Chen, A new X-ray activated nanoparticle photosensitizer for cancer treatment, J. Biomed. Nanotechnol. 10 (8) (2014) 1501–1508, https://doi.org/10.1166/jbn.2014.1954.
[113] B. Sah, J. Wu, A. Vanasse, N.K. Pandey, L. Chudal, Z. Huang, W. Song, H. Yu, L. Ma, W. Chen, M.P. Antosh, Effects of nanoparticle size and radiation energy on copper-cysteamine nanoparticles for X-ray induced photodynamic therapy, Nanomaterials (basel Switzerland) 10 (6) (2020), https://doi.org/10.3390/nano10061087.
[114] Q. Zhang, X. Guo, Y. Cheng, L. Chudal, N.K. Pandey, J. Zhang, L. Ma, Q. Xi, G. Yang, Y. Chen, X. Ran, C. Wang, J. Zhao, Y. Li, L. Liu, Z. Yao, W. Chen, Y. Ran, R. Zhang, Use of copper-cysteamine nanoparticles to simultaneously enable radiotherapy, oxidative therapy and immunotherapy for melanoma treatment, Signal Transduct. Target. Ther. 5 (1) (2020) 58, https://doi.org/10.1038/s41392-020-0156-4.
[115] N. Verma, N. Kumar, Synthesis and biomedical applications of copper oxide nanoparticles: an expanding horizon, ACS Biomater Sci. Eng. 5 (3) (2019) 1170–1188, https://doi.org/10.1021/acsbiomaterials.8b01092.
[116] X. Li, D. Xi, M. Yang, W. Sun, X. Peng, J. Fan, An organic nanotherapeutic agent self-assembled from cyanine and Cu (II) for combined photothermal and chemodynamic therapy, Adv. Healthc. Mater. 10 (20) (2021) e2101008, https://doi.org/10.1002/adhm.202101008.
[117] A. Ji, P. Yang, B. Ma, J. Li, Y. Yu, X. Zhang, P. Chen, H. Yao, L. Shi, H. Hu, S. Gao, H. Cheng, Photothermal-responsive curcumin-loaded copper-based nanocomposites for targeted drug release and combined immunotherapy, J. Colloid Interface Sci. 698 (2025) 138042, https://doi.org/10.1016/j.jcis.2025.138042.
[118] J. Ling, Y. Cai, H. Feng, Z. Liu, X.K. Ouyang, Polydopamine-modified copper coordination mesoporous silica nanoparticles loaded with disulfiram for synergistic chemo-photothermal therapy, Pharmaceutics 16 (4) (2024), https://doi.org/10.3390/pharmaceutics16040512.
[119] W. Liu, H. Xiang, M. Tan, Q. Chen, Q. Jiang, L. Yang, Y. Cao, Z. Wang, H. Ran, Y. Chen, Nanomedicine enables drug-potency activation with tumor sensitivity and hyperthermia synergy in the second near-infrared biowindow, ACS Nano 15 (4) (2021) 6457–6470, https://doi.org/10.1021/acsnano.0c08848.
[120] X. Zhu, Y. Lu, M. Sun, X. Wu, H. Zhang, Z. Wang, Y. Jin, G. Tan, A hyaluronic acid Schiff base @ hollow calcium peroxide @ copper carbon dots nanoconjugate enhances chemodynamic tumor therapy based on multiple approaches strategy, Int. J. Biol. Macromol. 311 (Pt 4) (2025) 144039, https://doi.org/10.1016/j.ijbiomac.2025.144039.
[121] Y. Zhang, Z. Ouyang, M. Zhan, R. Yang, Y. Gao, L. Li, R. Guo, X. Shi, X. Cao, An intelligent vascular disrupting dendritic nanodevice incorporating copper sulfide nanoparticles for immune modulation-mediated combination tumor therapy, Small 19 (39) (2023) e2301914, https://doi.org/10.1002/smll.202301914.
[122] N. Liu, R. Pan, S. Su, T. Yao, Y. Fan, J. Zhu, Copper sulfide nanoparticles coated with Fe-EGCG networks for targeted MR imaging and chemo/photothermal/chemodynamic synergetic therapy of tumors, Biomater. Sci. (2026), https://doi.org/10.1039/d6bm00006a.
[123] C. Li, W. Jia, Z. Guo, Y. Kang, C. Zhou, R. Zhao, X. Cheng, N. Jia, A copper-platinum nanoplatform for synergistic photothermal and chemodynamic tumor therapy via ROS outburst and GSH exhaustion, J. Mater. Chem. B 12 (3) (2024) 800–813, https://doi.org/10.1039/d3tb02288a.
[124] Y. Ruan, H. Zhuang, X. Zeng, L. Lin, X. Wang, P. Xue, S. Xu, Q. Chen, S. Yan, W. Huang, Engineered microbial nanohybrids for tumor-mediated NIR II photothermal enhanced ferroptosis/cuproptosis and immunotherapy, Adv. Healthc. Mater. 13 (4) (2024) e2302537, https://doi.org/10.1002/adhm.202302537.
[125] Y. Wang, Y. Yang, J. Ma, J. Wang, L. Chu, Q. Wang, S. Sun, X. Wang, C. Zhang, Injectable biomimetic nano-hydrogel composite based on copper selenide nanoparticles and carboxymethyl chitosan for synergistic chemo-photothermal cancer therapy, Colloids Surf. B Biointerfaces 256 (Pt 2) (2025) 115092, https://doi.org/10.1016/j.colsurfb.2025.115092.
[126] A. Curcio, A.V. de Walle, E. Benassai, A. Serrano, N. Luciani, N. Menguy, B. B. Manshian, A. Sargsian, S. Soenen, A. Espinosa, A. Abou-Hassan, C. Wilhelm, Massive intracellular remodeling of CuS nanomaterials produces nontoxic bioengineered structures with preserved photothermal potential, ACS Nano 15 (6) (2021) 9782–9795, https://doi.org/10.1021/acsnano.1c00567.
[127] L. Yang, Z. Zhao, B. Tian, M. Yang, Y. Dong, B. Zhou, S. Gai, Y. Xie, J. Lin, A singular plasmonic-thermoelectric hollow nanostructure inducing apoptosis

and cuproptosis for catalytic cancer therapy, Nat. Commun. 15 (1) (2024) 7499, https://doi.org/10.1038/s41467-024-51772-1.
[128] S. Xu, Z. Chen, Y. Huang, Y. Zhong, W. Chen, Triphenylphosphine-chitosan functionalized MoS(2) nanosheets delivering elesclomol-Cu(II) complex for enhanced cuproptosis-mediated cancer therapy, Biomacromolecules 26 (8) (2025) 5438–5449, https://doi.org/10.1021/acs.biomac.5c01024.
[129] K.S. Muthiah, S.R. Natarajan, S. Jayaraman, Y.C. Lin, U. Dhawan, R.J. Chung, β -Cu(2)V(2)O(7)/Cs NIR (II) responsive nanocomposite for synergistic chemodynamic/photothermal therapy with multi-modal imaging in hepatocellular carcinoma, Biomater Adv 180 (2026) 214602, https://doi.org/10.1016/j.bioadv.2025.214602.
[130] Y. Yang, C. Wang, N. Wang, J. Li, Y. Zhu, J. Zai, J. Fu, Y. Hao, Photogenerated reactive oxygen species and hyperthermia by Cu(3)SnS(4) nanoflakes for advanced photocatalytic and photothermal antibacterial therapy, J. Nanobiotechnol. 20 (1) (2022) 195, https://doi.org/10.1186/s12951-022-01403-y.
[131] A. Ghosh, A. Singh, S. Guha, B. Saha, G. Das, S.K. Sahu, A multifunctional NIR responsive upconversion porphyrin nanoprobe for Fenton/FRET induced ROS amplification and targeted drug delivery, J. Colloid Interface Sci. 700 (Pt 1) (2025) 138311, https://doi.org/10.1016/j.jcis.2025.138311.
[132] S. Ramamoorthy, S. Bajhal, A. Sundaramurthy, The role of surface modification in improving the effectiveness of CuS nanorods for cancer ablation therapy and antibacterial applications, Surf. Interfaces 39 (2023) 103001, https://doi.org/10.1016/j.surfin.2023.103001.
[133] P. Farhangnia, H. Khorramdelazad, H. Nickho, A.A. Delbandi, Current and future immunotherapeutic approaches in pancreatic cancer treatment, J. Hematol. Oncol. 17 (1) (2024) 40, https://doi.org/10.1186/s13045-024-01561-6.
[134] A. Jang, J.N. Lichterman, J.Y. Zhong, J.E. Shoag, J.A. Garcia, T. Zhang, P. C. Barata, Immune approaches beyond traditional immune checkpoint inhibitors for advanced renal cell carcinoma, Hum. Vaccin. Immunother. 19 (3) (2023) 2276629, https://doi.org/10.1080/21645515.2023.2276629.
[135] Y. Li, J. Liu, Y. Chen, R.R. Weichselbaum, W. Lin, Nanoparticles Synergize Ferroptosis and Cuproptosis to Potentiate Cancer Immunotherapy, Advanced science (Weinheim, Baden-Wurttemberg, Germany) 11(23) (2024) e2310309. https://doi.org/10.1002/advs.202310309.
[136] J. Hu, L. Yan, Z. Cao, B. Geng, X. Cao, B. Liu, J. Guo, J. Zhu, Tumor Microenvironment Activated Cu Crosslinked Near-Infrared Sonosensitizers for Visualized Cuproptosis-Enhanced Sonodynamic Cancer Immunotherapy, Advanced science (Weinheim, Baden-Wurttemberg, Germany) 11(43) (2024) e2407196. https://doi.org/10.1002/advs.202407196.
[137] Y. Dai, L. Zhu, X. Li, F. Zhang, K. Chen, G. Jiao, Y. Liu, Z. Yang, Z. Guo, B. Zhang, Q. Shen, Q. Zhao, A biomimetic cuproptosis amplifier for targeted NIR-II fluorescence/photoacoustic imaging-guided synergistic NIR-II photothermal immunotherapy, Biomaterials 305 (2024) 122455, https://doi.org/10.1016/j.biomaterials.2023.122455.
[138] B. Zhou, M. Chen, Z. Hao, L. Li, Y. Zhang, B. Fang, M. Shao, G. Ren, K. Wang, H. Liu, J. Zhu, X. Zhang, S. Yuan, I. Sitou, J. Zhao, J. Huang, Z. Yu, F. Qiu, Zinc-copper bimetallic nanoplatforms trigger photothermal-amplified cuproptosis and cGAS-STING activation for enhancing triple-negative breast cancer immunotherapy, J. Nanobiotechnol. 23 (1) (2025) 137, https://doi.org/10.1186/s12951-025-03186-4.
[139] X. Zhou, X. Pan, Z. Shen, R. Kang, Y. Pang, L. Luo, F. Liu, S. Yu, J. Zhang, Q. Shen, Eliminating intratumoral bacteria with cGAS-STING-activating nanodrug-bacteria biohybrids potentiates cancer immunotherapy, Biomaterials 325 (2026) 123629, https://doi.org/10.1016/j.biomaterials.2025.123629.
[140] Y. Fang, S. Huang, Q. Hu, J. Zhang, J.A. King, Y. Wang, Z. Wei, J. Lu, Z. He, X. Kong, X. Yang, J. Ji, J. Li, G. Zhai, L. Ye, Injectable zwitterionic physical hydrogel with enhanced chemodynamic therapy and tumor microenvironment remodeling properties for synergistic anticancer therapy, ACS Nano 17 (24) (2023) 24883–24900, https://doi.org/10.1021/acsnano.3c05898.
[141] Z. Li, H. Chen, C. Wang, T. Deng, J. Huang, H. Ye, J. Chen, C. Huang, Z. Chen, Augmenting cGAS/STING-mediated innate immunity by copper-based nanoplatform for synergistic cancer immunotherapy via inducing irreversible DNA damage, J. Control. Release 386 (2025) 114075, https://doi.org/10.1016/j.jconrel.2025.114075.
[142] L. Chen, D. Wang, J. Qiu, X. Zhang, X. Liu, Y. Qiao, X. Liu, Synergistic effects of immunoregulation and osteoinduction of ds-block elements on titanium surface, Bioact. Mater. 6 (1) (2021) 191–207, https://doi.org/10.1016/j.bioactmat.2020.08.001.
[143] T. Wang, Y. Liu, Q. Li, Y. Luo, D. Liu, B. Li, Cuproptosis-related gene FDX1 expression correlates with the prognosis and tumor immune microenvironment in clear cell renal cell carcinoma, Front. Immunol. 13 (2022) 999823, https://doi.org/10.3389/fimmu.2022.999823.
[144] L. Zhao, Y. Gui, J. Cai, X. Deng, Biometallic ions and derivatives: a new direction for cancer immunotherapy, Mol. Cancer 24 (1) (2025) 17, https://doi.org/10.1186/s12943-025-02225-w.
[145] B. Guo, F. Yang, L. Zhang, Q. Zhao, W. Wang, L. Yin, D. Chen, M. Wang, S. Han, H. Xiao, N. Xing, Cuproptosis induced by ROS responsive nanoparticles with elesclomol and copper combined with αPD-L1 for enhanced cancer immunotherapy, Advanced Materials (deerfield Beach Fla.) 35 (22) (2023) e2212267, https://doi.org/10.1002/adma.202212267.
[146] Z. Li, L. Cheng, X. Xu, R. Jia, S. Zhu, Q. Zhang, G. Cheng, B. Wu, Z. Liu, X. Tong, B. Xiao, F. Dai, Cuproptosis-based layer-by-layer silk fibroin nanoplatform-loaded PD-L1 siRNA combining photothermal and chemodynamic therapy against metastatic breast cancer, Mater. Today Bio 29 (2024) 101298, https://doi.org/10.1016/j.mtbio.2024.101298.
[147] Y. Li, J. Liu, R.R. Weichselbaum, W. Lin, Mitochondria-Targeted Multifunctional Nanoparticles Combine Cuproptosis and Programmed Cell Death-1 Downregulation for Cancer Immunotherapy, Advanced science (Weinheim, Baden-Wurttemberg, Germany) 11(35) (2024) e2403520. https://doi.org/10.1002/advs.202403520.
[148] Z. Yao, C. Qi, F. Zhang, H. Yao, C. Wang, X. Cao, C. Zhao, Z. Wang, M. Qi, C. Yao, X. Wang, H. Xia, Hollow Cu2MoS4 nanoparticles loaded with immune checkpoint inhibitors reshape the tumor microenvironment to enhance immunotherapy for pancreatic cancer, Acta Biomater. 173 (2024) 365–377, https://doi.org/10.1016/j.actbio.2023.10.024.
[149] H. Zhang, L. Yang, M. Han, Y. Han, Z. Jiang, Q. Zheng, J. Dong, T. Wang, Z. Li, Boost infiltration and activity of T cells via inhibiting Ecto-5'-nucleotidase (CD73) immune checkpoint to enhance glioblastoma immunotherapy, ACS Nano 18 (34) (2024) 23001–23013, https://doi.org/10.1021/acsnano.4c04553.
[150] H. Hu, S. Li, Y. Zhou, H. Lv, Z. Dong, Y. Wang, J. Sheng, X. Wang, W. Fan, W. Xu, A 'two-missile' nanoplatform for targeting triple-negative breast cancer: prodrug activation and immune enhancement, Mater. Today Bio 32 (2025) 101891, https://doi.org/10.1016/j.mtbio.2025.101891.
[151] H. Wu, X. Lu, Y. Hu, J. Baatarbolat, Z. Zhang, Y. Liang, Y. Zhang, Y. Liu, H. Lv, X. Jin, Biomimic Nanodrugs Overcome Tumor Immunosuppressive Microenvironment to Enhance Cuproptosis/Chemodynamic-Induced Cancer Immunotherapy, Advanced science (Weinheim, Baden-Wurttemberg, Germany) 12(5) (2025) e2411122. https://doi.org/10.1002/advs.202411122.
[152] A. Yang, L. Chen, S. Tang, X. Guo, H. Su, B.P. Jiang, X.C. Shen, Light/ultrasound dual responsive carbon dots-based nanovaccines for multimodal activation tumor immunotherapy of melanoma, Adv. Healthc. Mater. 14 (13) (2025) e2405194, https://doi.org/10.1002/adhm.202405194.
[153] Y. Liu, R. Niu, X. Zhang, B. Zhang, X. Chen, J. Guo, S. Song, Y. Wang, H. Zhang, Y. Zhao, Metal-organic framework-based nanovaccine for relieving immunosuppressive tumors via hindering efferocytosis of macrophages and promoting pyroptosis and cuproptosis of cancer cells, ACS Nano 18 (19) (2024) 12386–12400, https://doi.org/10.1021/acsnano.4c01518.
[154] J. Chang, M. Wang, J. Wang, G. Zhu, Y. Xie, Y. Qian, Q. Sun, C. Li, Generation of personalized whole tumor cells vaccine for pyroptosis-enhanced anticancer immunity via Cu(2)(-)(x)Se photothermal activation under NIR irradiation, J. Colloid Interface Sci. 700 (Pt 2) (2025) 138488, https://doi.org/10.1016/j.jcis.2025.138488.
[155] J. Chang, M. Wang, J. Wang, G. Zhu, Y. Xie, Y. Qian, Q. Sun, C. Li, Generation of personalized whole tumor cells vaccine for pyroptosis-enhanced anticancer immunity via Cu2-xSe photothermal activation under NIR irradiation, J. Colloid Interface Sci. 700 (2025) 138488, https://doi.org/10.1016/j.jcis.2025.138488.
[156] W. Wu, H. Li, W. Chen, Y. Hu, Z. Wang, W. She, L. Huang, Y. Liu, P. Jiang, CAR T cell membrane camouflaged nanocatalyst augments CAR T cell therapy efficacy against solid tumor, Small 20 (37) (2024) 2401299, https://doi.org/10.1002/smll.202401299.
[157] Z. Huang, N. Li, Z. Gao, J. Chen, Z. Xue, C. Wu, J. Chen, L. Li, Y. Lu, Cuproptosis improves CAR-T cell therapy in osteosarcoma, Cell Biomaterials 1 (10) (2025) 100148, https://doi.org/10.1016/j.celbio.2025.100148.
[158] B. Liu, X. Chen, Y. Zhu, H. Chen, J. Tan, Z. Yang, J. Li, P. Zheng, L. Feng, Q. Wang, S. Gai, L. Zhong, P. Yang, Z. Cheng, J. Lin, One-step symbiosis of bimetallic peroxides nanoparticles to induce ferroptosis/cuproptosis and activate cGAS-STING pathway for enhanced tumor immunotherapy, Advanced Materials (deerfield Beach Fla.) 37 (21) (2025) e2500337, https://doi.org/10.1002/adma.202500337.
[159] C. Jiang, X. Li, S. Wan, S. Ji, Q. Wang, S. Hu, P. Chen, B. Wang, T. Ge, J. Zhang, Y. Cao, Y. Yang, D. Zhang, Y. Li, P. Zhang, Copper-doped polydopamine nanoparticles-mediated GSH/GPX4-depleted ferroptosis and cuproptosis sensitizes lung tumor to checkpoint blockade immunotherapy, Small 21 (23) (2025) e2503208, https://doi.org/10.1002/smll.202503208.
[160] L. Bai, J. Yang, S. Yu, Z. Xiang, Y. Zeng, M. Shen, X. Kou, Q. Wu, C. Gong, Self-sufficient nanoparticles with dual-enzyme activity trigger radical storms and activate cascade-amplified antitumor immunologic responses, Acta Pharm. Sin. B 14 (2) (2024) 821–835, https://doi.org/10.1016/j.apsb.2023.10.003.
[161] J. Yao, P. Chen, D. Xie, J. Chen, X. Lin, Y. Xu, Copper-induced cuproptosis and immunogenic cell death synergize with radiotherapy and PD-1 blockade in osteosarcoma, ACS Appl. Mater. Interfaces 17 (33) (2025) 46635–46650, https://doi.org/10.1021/acsami.5c08888.
[162] B.-Q. Chen, Y.-H. Shi, Y. Zhang, D.-G. Zhang, X.-C. Lu, Q.-X. Xu, Y.-J. Pan, R. K. Kankala, S.-B. Wang, A.-Z. Chen, Four-pronged nanomotor strategy achieves efficient TNBC treatment via synergistic chemo-photothermal-immune therapy, Adv. Funct. Mater. 35 (48) (2025) 2504621, https://doi.org/10.1002/adfm.202504621.
[163] L. Zhu, Z. Guo, Y. Luo, H. Huang, K. Zhang, B. Duan, R. Peng, H. Yao, C. Liang, K. Wang, High-Efficiency Carriers' Separation Strategy Based Ultrasmall-Bandgap CuWO(4) Sono-Enhances GSH Antagonism for Cuproptosis Cascade Immunotherapy, Advanced science (Weinheim, Baden-Wurttemberg, Germany) 12(29) (2025) e00576. https://doi.org/10.1002/advs.202500576.
[164] Y. Wang, T. Yan, J. Cai, H. Dou, Y. Zhu, B. Geng, D. Pan, L. Shen, A heterojunction-engineering nanodrug with tumor microenvironment responsiveness for tumor-specific cuproptosis and chemotherapy amplified sono-immunotherapy, Biomaterials 321 (2025) 123319, https://doi.org/10.1016/j.biomaterials.2025.123319.
[165] C. Qu, H. Zhang, M. Sun, S. Jin, X. Wu, Z. Lan, G. Tan, Z. Wang, Y. Bao, Y. Jin, Graphitic carbon nitride/methyl pyrophaeophorbide a-copper/folate nanoconjugate for enhanced immunogenic death combined with PD-L1 immune

checkpoint blockades, Int. Immunopharmacol. 160 (2025) 114982, https://doi.org/10.1016/j.intimp.2025.114982.
[166] Y.J. Pan, Y. Zhang, B.Q. Chen, Y. Zhao, J.Y. Wang, C.Y. Li, D.G. Zhang, R. K. Kankala, S.B. Wang, G. Liu, A.Z. Chen, NIR-II light triggered burst-release cascade nanoreactor for precise cancer chemotherapy, Bioact. Mater. 33 (2024) 311–323, https://doi.org/10.1016/j.bioactmat.2023.10.033.
[167] D. Fan, Y. Cao, M. Cao, Y. Wang, Y. Cao, T. Gong, Nanomedicine in cancer therapy, Signal Transduct. Target. Ther. 8 (1) (2023) 293, https://doi.org/10.1038/s41392-023-01536-y.
[168] Z. Fu, J. Xiang, Aptamer-Functionalized Nanoparticles in Targeted Delivery and Cancer Therapy, International journal of molecular sciences 21(23) (2020). https://doi.org/10.3390/ijms21239123.
[169] M. Imanimoghadam, E. Yaghoobi, F. Alizadeh, M. Ramezani, M. Alibolandi, K. Abnous, S.M. Taghdisi, Improving chemotherapy effectiveness: utilizing CuS nanoparticles coated with AS1411 aptamer and chitosan for targeted delivery of doxorubicin to cancerous cells, J. Pharm. Sci. 113 (7) (2024) 1865–1873, https://doi.org/10.1016/j.xphs.2024.02.005.
[170] S. Wang, X. Liu, D. Wei, H. Zhou, J. Zhu, Q. Yu, L. Luo, X. Dai, Y. Jiang, L. Yu, Y. Yang, W. Tan, Polyvalent aptamer nanodrug conjugates enable efficient tumor cuproptosis therapy through copper overload and glutathione depletion, J. Am. Chem. Soc. 146 (44) (2024) 30033–30045, https://doi.org/10.1021/jacs.4c06338.
[171] S. Gao, H. Ge, L. Gao, Y. Gao, S. Tang, Y. Li, Z. Yuan, W. Chen, Silk Fibroin Nanoparticles for Enhanced Cuproptosis and Immunotherapy in Pancreatic Cancer Treatment, Advanced science (Weinheim, Baden-Wurttemberg, Germany) 12(18) (2025) e2417676. https://doi.org/10.1002/advs.202417676.
[172] M. Cheng, Q. Kong, Q. Tian, W. Cai, C. Wang, M. Yuan, W. Wang, P. Wang, W. Yan, Osteosarcoma-targeted Cu and Ce based oxide nanoplatform for NIR II fluorescence/magnetic resonance dual-mode imaging and ros cascade amplification along with immunotherapy, J. Nanobiotechnol. 22 (1) (2024) 151, https://doi.org/10.1186/s12951-024-02400-z.
[173] H. Huang, H. Guo, J. Liu, C. Ni, L. Xia, X. Cao, J. Xia, X. Shi, R. Guo, Dendrimer/metal-phenolic nanocomplexes encapsulating CuO(2) for targeted magnetic resonance imaging and enhanced ferroptosis/cuproptosis/chemodynamic therapy by regulating the tumor microenvironment, Acta Biomater. 183 (2024) 252–263, https://doi.org/10.1016/j.actbio.2024.05.035.
[174] A. Gupta, C.D. Kaur, S. Saraf, S. Saraf, Targeting of herbal bioactives through folate receptors: a novel concept to enhance intracellular drug delivery in cancer therapy, J. Recept. Signal Transduct. Res. 37 (3) (2017) 314–323, https://doi.org/10.3109/10799893.2016.1147581.
[175] S. Cui, D. Yin, Y. Chen, Y. Di, H. Chen, Y. Ma, S. Achilefu, Y. Gu, In vivo targeted deep-tissue photodynamic therapy based on near-infrared light triggered upconversion nanoconstruct, ACS Nano 7 (1) (2013) 676–688, https://doi.org/10.1021/nn304872n.
[176] Q. Xia, Y. Zhang, H. Zhang, X. Zhang, X. Wu, Z. Wang, R. Yan, Y. Jin, Copper nanocrystalline-doped folic acid-based super carbon dots for an enhanced antitumor effect in response to tumor microenvironment stimuli, J. Mater. Chem. B 10 (39) (2022) 8046–8057, https://doi.org/10.1039/d2tb01363k.
[177] E. Blanco, H. Shen, M. Ferrari, Principles of nanoparticle design for overcoming biological barriers to drug delivery, Nat. Biotechnol. 33 (9) (2015) 941–951, https://doi.org/10.1038/nbt.3330.
[178] M. Zhan, Y. Xu, L. Jia, H. Yu, H. Wang, M. Shen, X. Shi, Biomimetic copper-containing nanogels for imaging-guided tumor chemo-chemodynamic-immunotherapy, Acta Biomater. 189 (2024) 491–504, https://doi.org/10.1016/j.actbio.2024.09.030.
[179] R. Javed, M. Ahmed, I.U. Haq, S. Nisa, M. Zia, PVP and PEG doped CuO nanoparticles are more biologically active: Antibacterial, antioxidant, antidiabetic and cytotoxic perspective,, Korean J. Couns. Psychother. 79 (2017) 108–115, https://doi.org/10.1016/j.msec.2017.05.006.
[180] F. Qi, Y. Chang, R. Zheng, X. Wu, Y. Wu, B. Li, T. Sun, P. Wang, H. Zhang, H. Zhang, Copper phosphide nanoparticles used for combined photothermal and photodynamic tumor therapy, ACS Biomater Sci. Eng. 7 (6) (2021) 2745–2754, https://doi.org/10.1021/acsbiomaterials.1c00189.
[181] M. Mohammed, N. Devnarain, E. Elhassan, T. Govender, Exploring the applications of hyaluronic acid-based nanoparticles for diagnosis and treatment of bacterial infections, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 14 (4) (2022) e1799.
[182] W. Gao, J. Zhang, L. Ding, Y. Chang, F. Gao, P. Yang, X. Ma, Y. Guo, Tumor targeted cuprous-based nanocomposite as responsive cascade nanocatalyst for efficient tumor synergistic therapy, Chemistry (weinheim an Der Bergstrasse, Germany) 30 (10) (2024) e202302961, https://doi.org/10.1002/chem.202302961.
[183] S. Maghsoudian, M.P. Yektakasmaei, A. Shaabani, S. Perseh, Y. Fatahi, Z. Nouri, M. Gholami, N. Sayyari, H.A. Hoseinzadeh, H. Motasadizadeh, R. Dinarvand, Synergistic effects of doxorubicin loaded silk fibroin nanoparticles and Cu-TiO(2) nanoparticles for local chemo-sonodynamic therapy against breast cancer, Int. J. Biol. Macromol. 289 (2025) 138910, https://doi.org/10.1016/j.ijbiomac.2024.138910.
[184] J. Wang, J. Wang, J. Zhang, H. Ye, D. Wang, L. Tao, Y. Yao, Y. Chen, X. Shen, Bimetallic chitosan/hyaluronic acid nanoparticles self-amplify ferroptosis/cuproptosis in triple-negative breast cancer, Int. J. Biol. Macromol. 308 (2025) 142535, https://doi.org/10.1016/j.ijbiomac.2025.142535.
[185] W. Xie, Y. Zhang, Q. Xu, G. Zhong, J. Lin, H. He, Q. Du, H. Tan, M. Chen, Z. Wu, Y. Deng, Z. Han, J. Lu, J. Ye, F. Zou, Y. Zhuo, W. Zhong, A unique approach: biomimetic graphdiyne-based nanoplatform to treat prostate cancer by combining cuproptosis and enhanced chemodynamic therapy, Int. J. Nanomed. 19 (2024) 3957–3972, https://doi.org/10.2147/ijn.S455355.
[186] D. Wu, X. Chen, S. Yao, Y. He, G. Chen, X. Hu, Y. Chen, Z. Lv, J. Yu, K. Jin, Y. Cai, X. Mou, Platelet membrane coated Cu9S8-SNAP for targeting NIR-II mild photothermal enhanced chemodynamic/gas therapy of triple-negative breast cancer, Small 20 (35) (2024) 2400919, https://doi.org/10.1002/smll.202400919.
[187] B. Li, Z. Li, Y. Qian, N. Xiao, C. Fan, Y. Huang, A. Zhou, X. Ning, The convergence of sonodynamic therapy and cuproptosis in the dual-responsive biomimetic cytonano for precision mitochondrial intervention in cancer treatment, Nano Lett. 24 (26) (2024) 8107–8116, https://doi.org/10.1021/acs.nanolett.4c01864.
[188] L. Ren, Y. Sun, J. Zhang, L. Nie, A. Shavandi, K.E. Yunusov, U.E. Aharodnikau, S. O. Solomevich, G. Jiang, Red blood cell membrane-coated functionalized Cu-doped metal organic framework nanoformulations as a biomimetic platform for improved chemo-/chemodynamic/photothermal synergistic therapy, Int. J. Pharm. 652 (2024) 123811, https://doi.org/10.1016/j.ijpharm.2024.123811.
[189] L. Ren, J. Zhang, L. Nie, A. Shavandi, K.E. Yunusov, U.E. Aharodnikau, S. O. Solomevich, Y. Sun, G. Jiang, Platelet membrane-camouflaged copper doped CaO(2) biomimetic nanomedicines for breast cancer combination treatment, ACS Biomater Sci. Eng. 10 (12) (2024) 7492–7506, https://doi.org/10.1021/acsbiomaterials.4c01362.
[190] Y. Zhang, Q. Chen, Y. Zhu, M. Pei, K. Wang, X. Qu, Y. Zhang, J. Gao, H. Qin, Targeting inorganic nanoparticles to tumors using biological membrane-coated technology, MedComm 3 (4) (2022) e192.
[191] J. Lan, X. Chu, L. Xie, B. Li, Y. Song, L. Lei, C. Ouyang, Z. Meng, P. Liu, S. Li, Q. Liu, Biomimetic nanoparticles with dual targeting for hepatocellular carcinoma promote tumor immune system activation by enhancing extracellular ATP homeostasis, ACS Appl. Mater. Interfaces 17 (32) (2025) 45382–45397, https://doi.org/10.1021/acsami.5c04278.
[192] J. Liang, J. Ling, X. Zhang, X.K. Ouyang, A.M. Omer, G. Yang, pH/glutathione dual-responsive copper sulfide-coated organic mesoporous silica for synergistic chemo-photothermal therapy, J. Colloid Interface Sci. 657 (2024) 1–14, https://doi.org/10.1016/j.jcis.2023.11.146.
[193] L. Qiao, W. Xuan, Y. Ou, L. Li, S. Wu, Y. Guo, M. Liu, D. Yu, Q. Chen, J. Yuan, M. Zuo, C. Wei, C. Ou, H. Li, D. Cheng, Z. Yu, Z. Li, Tumor microenvironment activation amplify oxidative stress promoting tumor energy remodeling for mild photothermal therapy and cuproptosis, Redox Biol. 75 (2024) 103260, https://doi.org/10.1016/j.redox.2024.103260.