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## Review

# Fenton metal nanomedicines for imaging-guided combinatorial chemodynamic therapy against cancer



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## ABSTRACT

Chemodynamic therapy (CDT) is considered as a promising modality for selective cancer therapy, which is realized via Fenton reaction-mediated decomposition of endogenous H<sub>2</sub>O<sub>2</sub> to produce toxic hydroxyl radical (•OH) for tumor ablation. While extensive efforts have been made to develop CDT-based therapeutics, their *in vivo* efficacy is usually unsatisfactory due to poor catalytic activity limited by tumor microenvironment, such as anti-oxidative systems, insufficient H<sub>2</sub>O<sub>2</sub>, and mild acidity. To mitigate these issues, we have witnessed a surge in the development of CDT-based combinatorial nanomedicines with complementary or synergistic mechanisms for enhanced tumor therapy. By virtue of their bio-imaging capabilities, Fenton metal nanomedicines (FMNs) are equipped with intrinsic properties of imaging-guided tumor therapies. In this critical review, we summarize recent progress of this field, focusing on FMNs for imaging-guided combinatorial tumor therapy. First, various Fenton metals with inherent catalytic performances and imaging properties, including Fe, Cu and Mn, were introduced to illustrate their possible applications for tumor theranostics. Then, CDT-based combinatorial systems were reviewed by incorporating many other treatment means, including chemotherapy, photodynamic therapy (PDT), sonodynamic therapy (SDT), photothermal therapy (PTT), starvation therapy and immunotherapy. Next, various imaging approaches based on Fenton metals were presented in detail. Finally, challenges are discussed, and future prospects are speculated in the field to pave way for future developments.

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## 1. Introduction

Cancer, as one of the major causes of diseases-related death throughout the world, is severely threatening the

human health [1]. Over the past few decades, extensive efforts have been made for the development of advanced treatment modalities to improve therapeutic outcomes, and chemotherapy, radiotherapy and surgery have become

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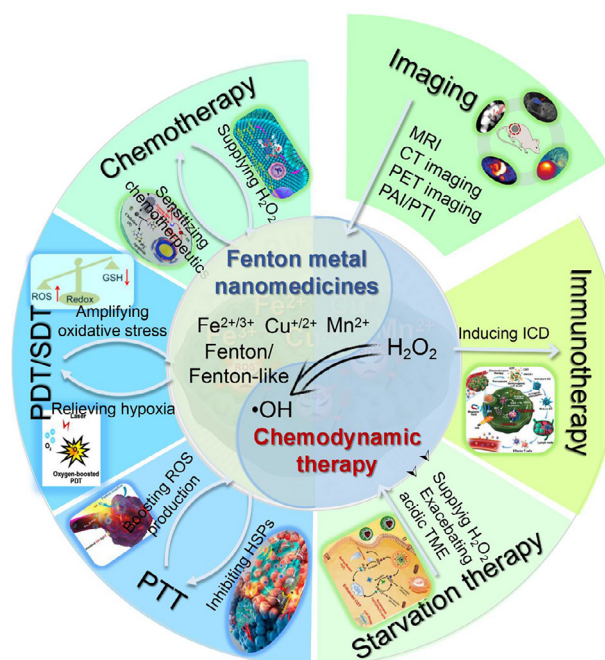
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the standard-of-care for clinical cancer management [2–4]. However, these conventional treatment approaches often suffer from the risk of recurrence, treatment resistance, severe side effects and high-cost [5]. Alternatively, several novel therapeutic modalities based on energy conversion, such as photodynamic therapy (PDT), photothermal therapy (PTT) and sonodynamic therapy (SDT), have gained particular interest, showing great potential for tumor therapy [6,7]. For example, PDT employs photosensitizers to transfer oxygen molecules into singlet oxygen ( $^1O_2$ ) upon light stimulation, thereby inducing cancer cell apoptosis and necrosis [8]. This light triggered therapy is advantageous for temporal- and spatial-controlled specificity with minimized side-effects, while its efficacy is often limited by tumor hypoxia, leading to low reactive oxygen species (ROS) generation efficiency. What's more, the oxygen consumption during photodynamic process would worsen the tumor microenvironment (TME) to further compromise treatment outcomes [9,10]. Similarly, the efficacy of PTT and SDT is usually limited by the poor tissue penetration of light [11] and tumor hypoxia [12], respectively.

In addition to hypoxia, TME is also pathologically characterized by high level of  $H_2O_2$  [13,14], which can be used as an endogenous substance to generate toxic ROS *in situ* for selective tumor ablation with minimal harmfulness to normal tissues. With such purpose, chemodynamic therapy (CDT) has emerged as a promising therapeutic mean for its unique pattern of ROS generation. It is based on Fenton or Fenton-like reaction, which utilizes Fenton metals (such as Fe, Cu, Mn) to convert endogenous  $H_2O_2$  into highly biocidal hydroxyl radical ( $\cdot OH$ ) with no need for external stimulation [15–17]. This process causes irreversible oxidative damage of biomolecules, such as lipid peroxidation, DNA and protein damage [18]. The acidic condition could facilitate Fenton reaction efficacy, which matches the TME. In comparison with other energy-driven cancer-therapeutic modalities, CDT exhibits several unique superiorities, including endogenous energy activation, high TME selectivity, and capacity for TME modulation [19]. In addition, the such metal-based nanomedicines possess multifunctional imaging capability [20–22], based on which imaging-guided tumor therapy can be achieved to dynamically monitor the *in vivo* fate of the nanoparticles and their therapeutic outcomes.

However, while varieties of Fenton metal nanomedicines (FMNs) have been demonstrated for effective CDT *in vitro*, their efficacy is far from satisfactory *in vivo* for complete tumor ablation. Possible limitations include un abundant intratumoral  $H_2O_2$  for  $\cdot OH$  production, the mild acidity of TME that is not optimal for Fenton reaction, as well as the anti-oxidative systems in tumor to scavenge ROS [19,23,24]. To mitigate these issues, multimodal systems that combine CDT with other therapeutics are suggested to complement each other for synergistic tumor therapy (Fig. 1). For example, therapeutic benefit can be improved by combining with PTT. On one hand, PTT-induced hyperthermia promotes  $\cdot OH$  generation and accelerates ROS oxidation of biological molecules [25]. Meanwhile, the oxidative stress alleviates heat resistance of tumor cells to some extent by inhibiting heat shock proteins (HSPs), thereby improving the PTT efficacy [25,26]. Another typical example is glucose oxidase (GOx)-



**Fig. 1 – Schematic illustration of the imaging-guided combinatorial CDT strategies for cancer therapy. Reproduced from [28]. Copyright 2018 American Chemical Society. Reproduced from [29]. Copyright 2019 American Chemical Society. Reproduced from [30]. Copyright 2018 American Chemical Society. Reproduced from [31]. Copyright 2020 American Chemical Society. Reproduced from [32]. Copyright 2018 2019 Elsevier. Reproduced from [26]. Copyright 2019 American Chemical Society. Reproduced from [33]. Copyright 2018 American Chemical Society. Reproduced from [34]. Copyright 2020 John Wiley & Sons.**

mediated starvation therapy to synergize CDT via  $H_2O_2$  generation and acidification of TME [27].

In this review article, we first introduced diverse FMNs for CDT, and their mechanisms were elucidated in detail for theranostic applications. Then, the recent development of multi-modal strategies combining CDT with other treatments, such as chemotherapy, PTT, PDT, SDT, starvation therapy and immunotherapy, is discussed. Afterwards, various imaging-guided systems were described, including magnetic resonance imaging (MRI), computed tomography (CT) imaging, positron emission tomography (PET) imaging, photothermal imaging (PTI), photoacoustic imaging (PAI). Finally, challenges and future perspectives of FMNs in biomedical applications are summarized for further development.

## 2. FMNs for CDT

The basic requirement of CDT is the integration of Fenton metal to trigger Fenton or Fenton-like reactions in tumor [19,35]. Currently, the nanomaterials containing redox-active transition metal, such as  $Fe^{2+}/Fe^{3+}$ ,  $Cu^+/Cu^{2+}$ ,  $Mn^{2+}$ ,  $Co^{2+}$ ,  $Ce^{3+}$  and  $Ag^+$ , are widely explored as Fenton catalysts for CDT

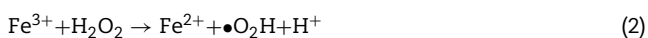
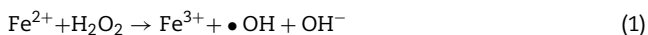
**Table 1 – Summary of types and properties of various FMNs for CDT.**

Fenton metal	Types	Properties for CDT
Fe	Iron oxide, iron sulfide, MOFs, Prussian blue	<ul style="list-style-type: none"> <li>∅ Along with TAMs polarization and ferroptosis</li> <li>∅ Guiding by T<sub>1</sub>/T<sub>2</sub>-weighted MR imaging</li> <li>∅ Strong acidic conditions are required</li> <li>∅ Relatively low catalytic efficiency of Fe-mediated Fenton reaction</li> </ul>
Cu	Copper oxide, copper sulfide, CuSe, MOFs, CuETs	<ul style="list-style-type: none"> <li>∅ Broader reactive pH range and higher Fenton efficiency</li> <li>∅ Guiding by PET imaging and CT imaging</li> <li>∅ More toxic to normal organs</li> <li>∅ Promoting tumor angiogenesis and metastasis</li> </ul>
Mn	Manganese oxides	<ul style="list-style-type: none"> <li>∅ Along with oxygen generation and GSH depletion</li> <li>∅ Guiding by T<sub>1</sub>-weighted MR imaging</li> <li>∅ <i>In vivo</i> potential of immunoreactions are still under exploration</li> </ul>

[15,36]. The types and properties of various FMNs for CDT are summarized (Table 1), and each type of metal species were reviewed in the following section.

### 2.1. Fe-based nanomaterials

Since the initial attempt of using amorphous Fe as Fenton agent in breast cancer cells in 2016 [37], various Fe-containing nanomaterials, such as iron oxide, iron sulfide, Fe-based metal-organic frameworks (MOFs), Prussian blue, have been developed for CDT against malignant tumor [30,38–42]. Under acidic condition, Fe<sup>2+</sup>/Fe<sup>3+</sup> reacts with H<sub>2</sub>O<sub>2</sub> to generate ROS, and the reactions were shown below (Eqs. 1 and 2) [43].



Besides CDT, other biological functions of Fe-based nanomaterials were also explored. For example, ferroptosis, a type of nonapoptotic programmed cell death caused by accumulation of lipid hydroperoxides, is closely related to the iron-dependent intracellular oxidative stress, and Fe-based FMNs could induce ferroptosis via the Fenton-like reaction of Fe<sup>2+</sup> and lipid peroxidation [44,45]. Ferroptosis has attracted great research interest for tumor therapy owing to its non-apoptotic pathway to bypass the treatment resistances. In addition, it is also reported recently that Fe<sup>2+</sup>/Fe<sup>3+</sup> could polarize tumor-related macrophages (TAMs) and reprogram TME to synergize CDT [46,47]. Moreover, Fe-based nanomaterials can act as imaging agents for tumor diagnosis and imaging. For instance, iron oxide nanoparticles (IONPs) have been applied in T<sub>1</sub>/T<sub>2</sub>-weighted MR imaging [48,49]. Despite these functionalities, there are still two critical issues of the Fe-based nanomaterials, i.e., insufficient acidity in TME and low H<sub>2</sub>O<sub>2</sub> concentration that limits the CDT efficacy [50,51].

### 2.2. Cu-based nanomaterials

Cu-based nanomaterials are compared favorably over Fe-based nanomaterials for CDT owing to their broader reactive

pH range and higher Fenton reactivity (Eq. 3, the catalytic rate of Cu<sup>+</sup> is ~160-fold higher than that of Fe<sup>2+</sup>) [36].



As such, Cu-based nanomaterials have been extensively attempted as Fenton reagent, including copper oxide, copper sulfide, CuSe and Cu-based MOF [32,52–54]. For example, Cu-tannic acid networks (Cu-TA) could effectively convert H<sub>2</sub>O<sub>2</sub> into toxic •OH, exhibiting robust CDT efficacy with high biosafety [55]. Meanwhile, the inherent biological activity of Cu<sup>2+</sup> and photothermal conversion capability of several Cu-based oxides and sulfides endow the nanomaterials with versatile applications for combinatorial therapy [21,56], and they also possess the capability for imaging-guided therapies, such as PAI, PTI, PET and CT performance [21].

### 2.3. Mn-based nanomaterials

Mn-based nanomaterials have also been employed as the Fenton-like metal for chemodynamic conversion [57]. Manganese oxides (MnO<sub>x</sub>) were the most commonly used Mn-based Fenton nanomaterials for cancer theranostics, and combinatorial therapy can be easily realized since this type of nanomaterials has been extensively used as carriers to deliver small molecular drugs and gene therapeutics. [22,40] Compared with many other FMNs, these nanomaterials possess additional function to relieve tumor hypoxia via their catalase-mimicking activity to produce oxygen, and the generated Mn<sup>2+</sup> from MnO<sub>x</sub> decomposition triggers the Fenton-like chemical reaction for CDT [58]. Moreover, MnO<sub>x</sub> were able to deplete intracellular GSH to promote the efficacy of CDT. For bioimaging, Mn-based nanomaterials have been demonstrated as excellent contrast agent for tumor T<sub>1</sub>-weighted MR imaging, and their capabilities for PTI, PAI and ultrasonic imaging (USI) were also demonstrated [59,60].

### 2.4. Other metal-based nanomaterials

Other transition metals, such as Co<sup>2+</sup>, Ce<sup>3+</sup> and Ag<sup>+</sup>, also showed the potential as Fenton agents for CDT [61–63],

while their biological applications are limited by biosafety issues caused by metal poisoning [64]. For example, Co or Ag-contained nanomaterials could cause DNA mutations or damage, induce genotoxicity and carcinogenicity [65]. Moreover, the cerium oxides (CeO<sub>2</sub>) have intrinsic pulmonary toxicity [66].

### 3. CDT-based combinatorial therapy

Although CDT is considered as a new type of “green” cancer therapy, its efficacy is not good *in vivo* due to the poor catalytic activity and intrinsic resistance of tumor [67]. Therefore, combination strategies have been developed to optimize the therapeutic outcomes, and we have witnessed the incorporation of various treatments into CDT systems, including chemotherapy, PDT, SDT, PTT, starvation therapy and immunotherapy, for multi-modal tumor therapy (Table 2) [43].

#### 3.1. CDT combined with chemotherapy

Chemotherapy is one of the most prevailing treatment of various cancer, and hundreds of chemotherapeutic drugs have been discovered. However, the nonspecific distribution, rapid clearance and multidrug chemoresistance cause the undesirable therapeutic efficiency and severe side effects of chemotherapy [88–90]. ROS, as an important part of redox balance and cell signaling pathway in biological processes, exhibits outstanding synergistic effect with chemotherapy. Integrating chemotherapy drugs with FMNs into one nanoplatform is highly desirable for combinational therapy [91]. For instance, Shi et al. fabricated Cu<sup>2+</sup>-doped PEGylated hollow mesoporous silica nanoparticles (HMSNs) to encapsulate disulfiram (DSF) [29]. DSF, as a Cu<sup>2+</sup>-dependent chemotherapy drug, could chelate Cu<sup>2+</sup> released from HMSNs in acidic TME to generate toxic CuETs for chemotherapy. Meanwhile, Cu<sup>+</sup> converted from Cu<sup>2+</sup> triggered Fenton-like reaction to produce ROS in presence of endogenous H<sub>2</sub>O<sub>2</sub> condition, improving the therapeutic outcomes of CuETs (Fig. 2A and 2B). With these synergistic effects, tumor tissue was remarkably inhibited.

Interestingly, several typical chemotherapeutic drugs, such as doxorubicin (DOX) [68], cisplatin, [70] and  $\beta$ -lapachone [92], can activate some enzymes to generate H<sub>2</sub>O<sub>2</sub>, which in turn supply the substrate of Fenton reaction to enhance CDT, thereby achieving synergistic chemotherapy/CDT to overcome chemoresistance of cancer. Capitalized on this fact, Wu et al. designed a DEN-DOX@TA-Fe<sup>III</sup> nanocomplex (namely DDTF) by mixing metal-phenolic network (MPN) with DOX-loaded dendrimer (DEN) [68]. After intracellular internalization, the released DOX induced cell apoptosis and elevated the H<sub>2</sub>O<sub>2</sub> level to sensitize Fe<sup>2+/3+</sup>-mediated CDT (Fig. 2C). The nanoplatform provides a novel solution to surmount multidrug-resistance of cancer.

#### 3.2. CDT combined with PDT or SDT

PDT is a ROS-mediated treatment modality. It employs photosensitizers to convert molecular oxygen into singlet

oxygen (<sup>1</sup>O<sub>2</sub>) under light irradiation, which causes cancer cells death via apoptosis and necrosis [93,94]. As a non-invasive therapeutics, PDT has the advantages of low systemic toxicity, spatiotemporal selectivity and the lack of resistance mechanisms [95,96]. However, the treatment outcome of PDT was often limited by poor tissue penetration and hypoxic TME [97]. Combining PDT with CDT is a powerful strategy to employ multiple antitumor mechanisms for amplified tumor oxidative stress. Li et al. constructed a sorafenib-loaded hemoglobin (Hb)-Ce6 nanoplatform (namely SRF@Hb-Ce6) for oxygen-boosted PDT/CDT (Fig. 3A) [31]. Fe-containing hemoglobin (Hb) simultaneously furnished oxygen for enhanced PDT and triggered Fenton reaction to synergize with sorafenib for enhanced ferroptosis. Moreover, PDT/CDT-induced tumor immunogenic cell death (ICD) activated robust immune response, which further improved the efficacy of ferroptosis via interferon- $\gamma$  (IFN- $\gamma$ ) secretion. Notably, several nanosystems release Fenton metal ions in a GSH-dependent manner, and the concurrent depletion of GSH could amplify ROS-mediated PDT/CDT therapy. For example, Zhang et al. utilized cancer cell membrane to coat mesoporous copper/manganese silicate nanospheres (namely mCMSNs) for homotype-targeted CDT/PDT therapy (Fig. 3B) [71]. The catalase-mimic activity of mCMSNs converted H<sub>2</sub>O<sub>2</sub> into O<sub>2</sub> to relieve the hypoxia TME, and thus enhanced O<sub>2</sub>-dependent PDT. Meanwhile, GSH-mediated mCMSNs decomposition produced Cu<sup>+</sup> and Mn<sup>2+</sup> to trigger Fenton reaction, and oxidation stress was further enhanced via GSH depletion. This study demonstrated a multifunctional nanosystem with oxygen supply, tumor response and TME regulation capabilities for enhanced CDT/PDT.

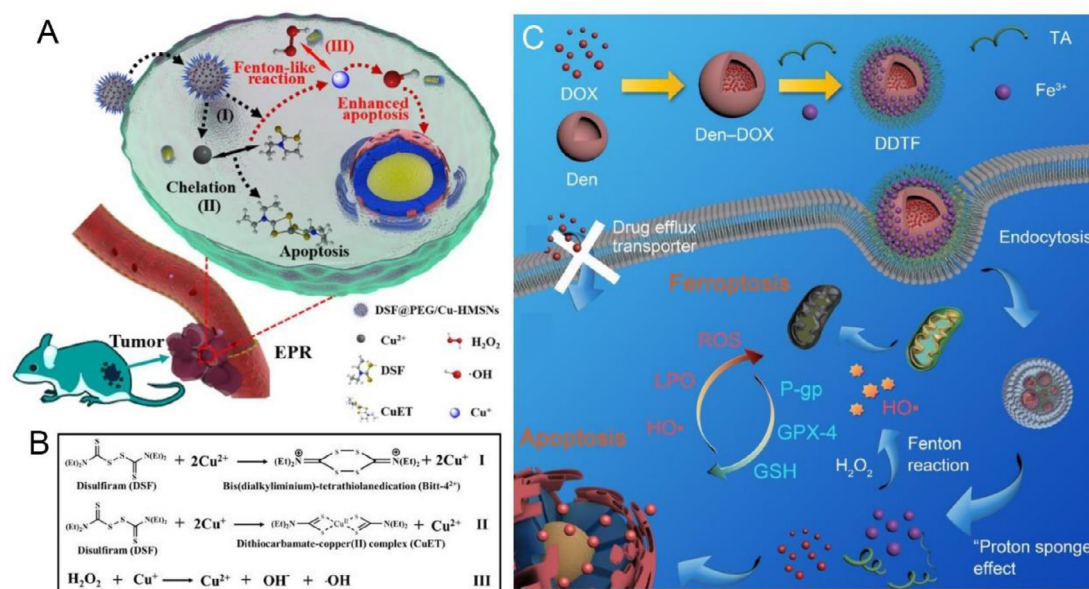
SDT, which utilizes sonosensitizers to produce ROS under ultrasound irradiation to ablate tumor, could also synergize with CDT, and a notable advantage is the deep penetration of ultrasound [98]. In one example, Yang et al. prepared Janus Au-MnO nanoparticles coated with PEG and ROS-responsive polymer for deep-seated tumor CDT/SDT (Fig. 3C) [73]. After ultrasound to generate ROS, this nanosystem was disassembled into small Au-MnO NPs, and then degraded into Au NPs and Mn<sup>2+</sup>. Au NPs served as sonosensitizer for SDT, which amplified oxidative stress and facilitated Mn<sup>2+</sup>-mediated CDT.

#### 3.3. CDT combined with PTT

Among various CDT combinatorial therapy, integrating PTT with CDT into one system is most attractive owing to their multiple synergistic mechanism. First, some nanomaterials, such as copper oxide [81], copper sulfide [32], ferric oxide [99], MPN [74], and Prussian blue [40], can simultaneously induce photothermal conversion for PTT and release Cu<sup>2+</sup> or Fe<sup>2+/3+</sup> for CDT, offering simple platforms to combine these two modalities. Second, hyperthermia is capable of facilitating drug release, thus realizing triggered release of Fenton-based agents [100]. Third, the photothermal effect not only causes tumor cells death but also increases the yield of ROS and accelerates the ROS oxidation of biological molecules, thereby improving efficiency of CDT [25,101]. Finally, heat shock proteins (HSPs), which cause thermoresistance via

**Table 2 – Summary of representative FMNs for imaging-guided combinatorial tumor therapy.**

Name of the nanomaterials	Fenton metals	Theranostic modalities	Performance	Refs.
DEN-DOX@TA-Fe <sup>III</sup>	Fe <sup>3+</sup> /Fe <sup>2+</sup>	Chemotherapy /CDT	CDT sensitization by DOX-mediated apoptosis	[68]
DSF@PEG/Cu-HMSNs	Cu <sup>2+</sup> /Cu <sup>+</sup>	Chemotherapy /CDT	Cu <sup>2+</sup> released from HMSNs in acidic TME to form toxic CuETs, or converse into Cu <sup>+</sup> by endogenous H <sub>2</sub> O <sub>2</sub> to produce ROS.	[29]
DDMON-IONP-CUR	Fe <sup>3+</sup> /Fe <sup>2+</sup>	Chemotherapy /CDT	Cancer-cell-specific Ca <sup>2+</sup> and GSH depletion, •OH generation, thioredoxin reductase inhibition, and tumor ICD.	[69]
UCNPs@MnO <sub>2</sub> -Pt-PEG	Mn <sup>2+</sup>	MRI/UCL imaging-guided chemotherapy /CDT	GSH depletion- and cisplatin-activation-enhanced •OH generation, along with TME-triggered MRI/UCL imaging.	[70]
SRF@Hb-Ce6	Fe <sup>2+</sup>	CDT/PDT	Sorafenib/Fe-induced ferroptosis combining with PDT	[31]
mCMSNs	Cu <sup>2+</sup> /Cu <sup>+</sup> , Mn <sup>2+</sup>	MRI-guided PDT/CDT	Programing TME via hypoxia relief and GSH depletion to enhance PDT/CDT.	[71]
Cu <sub>2-x</sub> Se-CD-Ce6	Cu <sup>2+</sup> /Cu <sup>+</sup>	PAI-guided CDT/PDT	Fenton-like Haber-Weiss catalyst for ICD and M <sub>1</sub> -macrophages polarization.	[72]
Au-MnO@PEG/PPADT	Mn <sup>2+</sup>	FI/MRI-guided CDT/ST	ROS and GSH-triggered Au NPs release as numerous cavitation nucleation for sonodynamic conversion, and Mn <sup>2+</sup> production for Fenton-like reaction.	[73]
EA-Fe@BSA	Fe <sup>3+</sup> /Fe <sup>2+</sup>	MRI-guided CDT/PTT	Endogenous H <sub>2</sub> S triggered Fe <sup>3+</sup> /Fe <sup>2+</sup> conversion and PTT-enhanced •OH generation.	[74]
Au@MSN@IONP	Fe <sup>3+</sup> /Fe <sup>2+</sup>	MRI-guided PTT-enhanced CDT	Heat-triggered intracellular H <sub>2</sub> O <sub>2</sub> production to fuel Fenton reaction, and PI3K/Akt/FoxO axis inhibition.	[75]
Cu(I) phosphide nanocrystals	Cu <sup>+</sup>	PAI/MRI/PTI guided CDT/PTT	GSH depletion and NIR II photothermal conversion to increase •OH generation, along with in situ T <sub>1</sub> -MR imaging.	[76]
FP NRs	Fe <sup>3+</sup> /Fe <sup>2+</sup>	PAI/MRI-guided CDT/PTT	Ultrasound and photothermal-enhanced Fenton reaction, along with PA/MR imaging.	[77]
MnO <sub>x</sub> @silicene-BSA	Mn <sup>2+</sup>	PAI/MRI-guided CDT/PTT	Hyperthermia-augmented Fenton-like catalytic activity, along with TME-responsive T <sub>1</sub> -MRI and PAI.	[78]
Co-Fc@GOx	Fe <sup>2+</sup>	Starvation therapy/CDT	Promoting intracellular acidity and H <sub>2</sub> O <sub>2</sub> production by GOx to boost the Fenton reaction.	[79]
GOx@ZIF@TA-Fe <sup>III</sup>	Fe <sup>3+</sup> /Fe <sup>2+</sup>	MRI-guided starvation therapy enhanced CDT	GOx-mediated H <sub>2</sub> O <sub>2</sub> generation and TA-induced Fe <sup>3+</sup> /Fe <sup>2+</sup> conversion for enhanced CDT.	[33]
Fe <sub>5</sub> C <sub>2</sub> -GOx@MnO <sub>2</sub>	Fe <sup>2+</sup>	T <sub>1</sub> /T <sub>2</sub> MRI-guided starvation therapy /CDT	MnO <sub>2</sub> decomposition and GOx release under acidic TME for starvation therapy to enhance CDT, along with MR imaging.	[80]
MnO <sub>x</sub> -TF	Mn <sup>2+</sup>	MRI/PAI-guided immunotherapy /CDT	TME-responsive capability and tumor ICD.	[34]
Cu <sub>2</sub> O@CaCO <sub>3</sub> @HA	Cu <sup>2+</sup> /Cu <sup>+</sup>	PTT/PDT/CDT/ immunotherapy	Hyperthermia and oxidative stress induced by acidic and H <sub>2</sub> S-overexpressed TME to reprogram macrophages and facilitate immunotherapy.	[81]
HSA-GOx-TPZ@TA-Fe <sup>III</sup>	Fe <sup>3+</sup> /Fe <sup>2+</sup>	starvation therapy enhanced CDT/ chemotherapy	GOx-mediated H <sub>2</sub> O <sub>2</sub> generation and hypoxia exacerbation, as well as TA-accelerated Fe <sup>3+</sup> /Fe <sup>2+</sup> conversion for cascade cancer therapy.	[82]
GOx-MnCaP-DOX	Mn <sup>2+</sup>	MRI-guided starvation therapy CDT/chemotherapy	Acidic-responsive NPs degradation, GOx-mediated glucose elimination and Mn <sup>2+</sup> -mediated Fenton-like reaction for cascade-enhanced anti-tumor therapy.	[83]
Fe <sup>III</sup> -TPPS@Bis (DPA-Zn)-RGD /SOD2 siRNA	Fe <sup>3+</sup>	FI/MRI-guided SDT/gene therapy/CDT	Enhanced ROS production via SOD <sub>2</sub> downregulation, GSH depletion and Fenton reaction.	[84]
TCPP-Fe <sup>III</sup> @DHA@CaCO <sub>3</sub>	Fe <sup>3+</sup> /Fe <sup>2+</sup>	Oncosis therapy /CDT/PDT	Acidic TME- and GSH-triggered DHA release, Ca <sup>2+</sup> and Fe <sup>2+</sup> supply, and TCPP activation for combinatorial therapy.	[85]
GOx@Cu <sub>2</sub> MoS <sub>4</sub>	Cu <sup>2+</sup> /Cu <sup>+</sup> Mo <sup>6+</sup> /Mo <sup>6+</sup>	CDT/starvation therapy/PDT/PTT/ immunotherapy	GSH peroxidase mimicking activity to deplete GSH, and O <sub>2</sub> /H <sub>2</sub> O <sub>2</sub> supply.	[86]
PtCu <sub>3</sub> -PEG	Cu <sup>2+</sup> /Cu <sup>+</sup>	FI/PAI/CT imaging-guided SDT/CDT	GSH peroxidase mimicking activity to deplete GSH, along with FI/PAI/CT imaging.	[87]
HMON-Au-Col@Cu-TA-PVP	Cu <sup>2+</sup> /Cu <sup>+</sup>	FI/PET imaging-guided PDT/CDT	Au NPs catalysis-based H <sub>2</sub> O <sub>2</sub> supply, along with PET imaging by <sup>64</sup> Cu <sup>2+</sup> labeling.	[55]



**Fig. 2 – (A) Schematic showing the construction of DSF@PEG/Cu-HMSNs for synergistic CDT/chemotherapy. (B) Mechanisms of DSF/Cu<sup>2+</sup> interaction for chemo/CDT combination. Reproduced from [29]. Copyright 2019 American Chemical Society. (C) Schematic illustration of the construction of DDTF nanocomplexes and their application for chemotherapy/CDT cancer therapy. Reproduced from [68]. Copyright 2019 American Chemical Society.**

resisting heat damage, were inhibited by ROS in cancer cell, thus enhancing hyperthermia-induced tumor ablation [26].

Ling et al. fabricated core-shell-satellite nanomaterials (namely Au@MSN@IONP) composed of Au nanorod, mesoporous silica nanoshell and ultrasmall iron oxide nanoparticles (IONP) for triple-negative breast cancer (TNBC) therapy. The Au nanorod core could transform near infrared (NIR) light into heat to increase ROS generation, thus fueling IONP-mediated Fenton reaction for robust CDT (Fig. 4A) [75]. Meanwhile, the Au@MSN@IONP was found to inhibit PI3K/Akt/FoxO signaling pathways, which is related to redox regulation and survival of TNBC. Therefore, this system could realize self-enhanced and PTT-fueled CDT against TNBC. To improve tissue penetration and energy conversion efficiency, Yang et al. synthesized copper phosphide nanocrystals, which combined NIR II laser-mediated PTT and CDT for deep tumor elimination (Fig. 4B) [76]. These nanocrystals depleted endogenous GSH to enhance ·OH accumulation, and induced NIR II photothermal conversion under 1064 nm laser irradiation to promote the penetration of nanoparticle into deep-seated tumor. In another work, ferrous phosphide nanorods (namely FP NRs) were developed by Yang et al. for ultrasound and photothermal-enhanced CDT (Fig. 4C) [77]. The prepared FP NRs, as an “all-in-one” Fenton agent, facilitated the production of ROS under ultrasound and NIR II laser irradiation, showing high therapeutic effect with high maximum permissible exposure and deep tissue penetration.

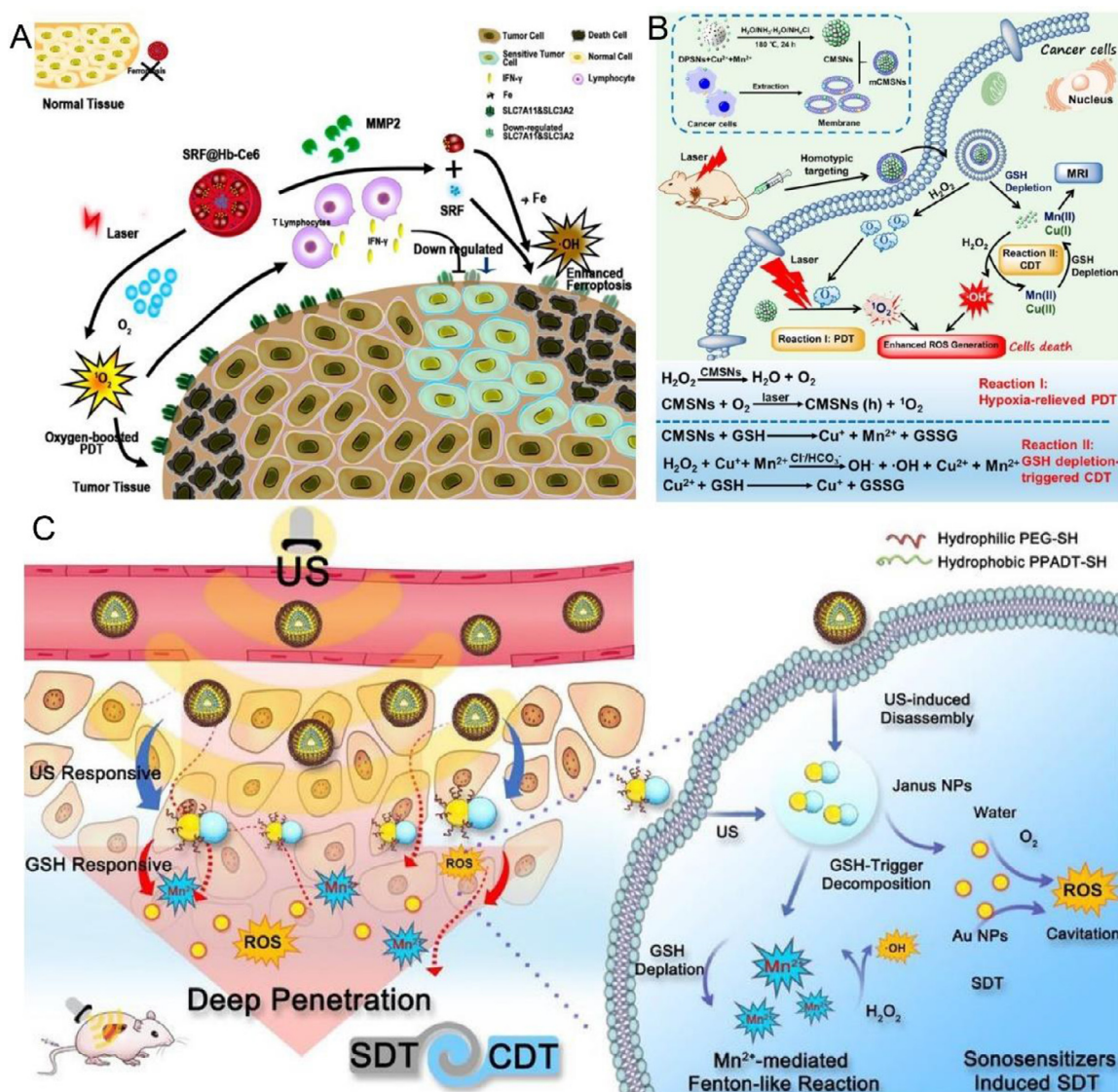
### 3.4. CDT combined with starvation therapy

Starvation therapy kill cancer cells via exhausting nutrients or blocking the energy supply. GOx, a type of oxidoreductase, can effectively catalyze glucose oxidation into gluconic acid and H<sub>2</sub>O<sub>2</sub>, and oxygen is consumed during

this process. GOx-mediated glucose depletion provides a noninvasive strategy for cancer starvation therapy [27,102]. More interestingly, the generated H<sub>2</sub>O<sub>2</sub> and gluconic acid can provide sufficient H<sub>2</sub>O<sub>2</sub> and acidifies TME to boost Fenton reaction. Therefore, combining GOx-mediated starvation with CDT has outstanding synergistic therapeutic effects. Han et al. synthesized a cascade enzymatic/Fenton catalytic nanoplateform (namely Co-Fc@GOx) by incorporating GOx into Co-ferrocene metal-organic framework to achieve enhanced Fenton reaction with intracellular anabolic acidity and self-supplied H<sub>2</sub>O<sub>2</sub> production (Fig. 5A) [79]. Once internalization into cancer cells, GOx exhausted endogenous glucose to kill the cells, and provided enough intracellular acidity and H<sub>2</sub>O<sub>2</sub> for the subsequent Fenton reaction (Fig. 5B). Consequently, enhanced CDT was achieved both *in vitro* and *in vivo*, resulting in significant tumor growth inhibition in 4T1-tumor-bearing mice. While this pioneering work demonstrated the benefits of CDT/GOx combination, the catalytic activity of GOx is limited by the hypoxic TME. To mitigate this issue, a TME-responsive and oxygen self-supplied nanocatalyst composed of iron carbide (Fe<sub>5</sub>C<sub>2</sub>), GOx and MnO<sub>2</sub> was constructed by Feng et al. (Fig. 5C) [80]. After cellular internalization, MnO<sub>2</sub> was decomposed into Mn<sup>2+</sup> accompanied by O<sub>2</sub> generation in acidic TME, and GOx was concomitantly released. The *in situ* generated O<sub>2</sub> elevated the catalytic effect of GOx to synergize Fe<sub>5</sub>C<sub>2</sub>-mediated CDT. Such oxygen supply-enhanced CDT/starvation combinatorial therapy provides a promising strategy for selective tumor ablation with amplified treatment outcomes and minimized side effects.

### 3.5. CDT combined with immunotherapy

Immunotherapy, which activates patient's own immune system to fight cancer, hold great promise to inhibit both



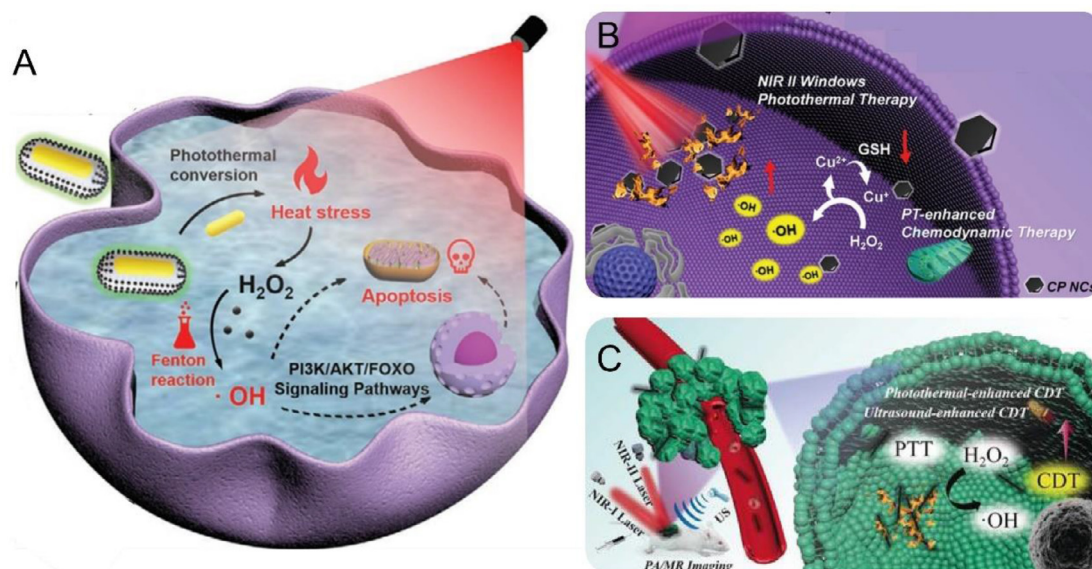
**Fig. 3 – (A)** The schematic showing the mechanisms of SRF@Hb-Ce6 for synergistic tumor therapy. Reproduced from [31]. Copyright 2020 American Chemical Society. **(B)** Schematic illustration showing the therapeutic mechanism of mCMSNs for synergistic CDT/PDT. Reproduced from [71]. Copyright 2019 American Chemical Society. **(C)** Illustration of the Janus Au-MnO<sub>x</sub> nanosystem for CDT/SDT against deep tumor. Reproduced from [73]. Copyright 2020 John Wiley & Sons. Abbreviations; MMP-2: matrix metalloproteinase-2; Hb: hemoglobin; SRF: sorafenib; IFN- $\gamma$ : interferon- $\gamma$ ; US: ultrasound.

primary and metastatic tumor, as well as tumor recurrence [103]. Among them, cancer vaccines, cytokine therapy and immune checkpoint blockade therapy have recently received more and more attention owing to high efficiencies and minimal side effects [104,105]. Nevertheless, various immune-suppressive mechanisms of tumor lead to poor lymphocytes infiltration, thus inhibiting immune response [106]. Toward this issue, CDT can strengthen the antitumor immune response via inducing ICD, indicating the potential advantages of CDT/immunotherapy combination [69,107]. ICD is characterized by secretion of danger associated molecular patterns (DAMPs) and tumor-associated antigens (TAAs), which promotes antigens presentation and elicits robust immune response [108]. For instance, Lin et al. constructed manganese oxide nanomaterials-based nanovaccines (namely MnO<sub>x</sub>-TF) for cancer immunotherapy (Fig. 6) [34].

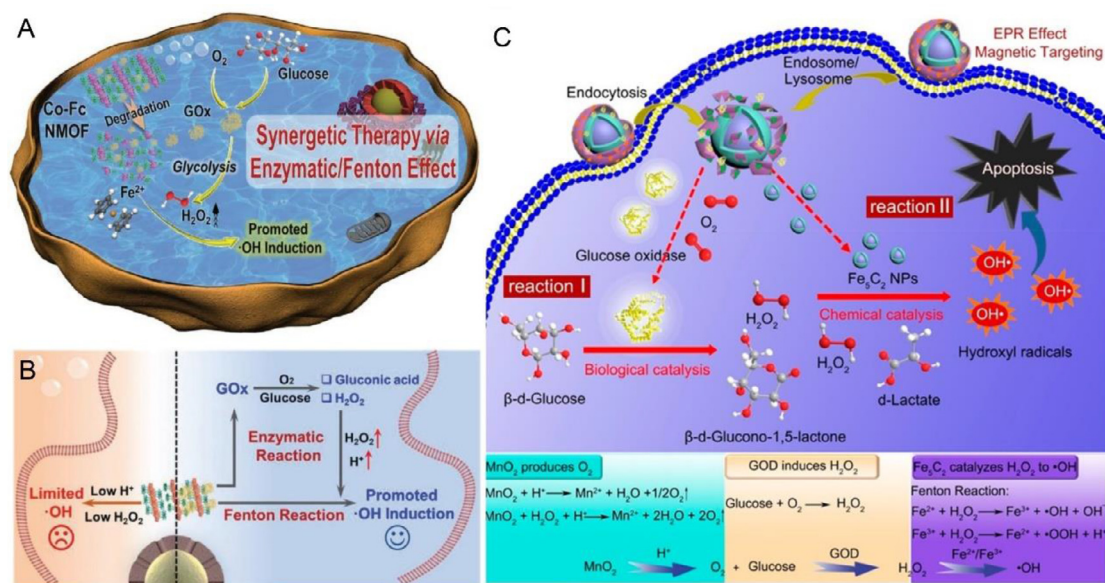
After intratumoral injection, the Fenton-like reaction can be triggered for CDT and ferroptosis, which induced ICD with the release of tumor-associated antigens. Subsequently, the cascade immune responses were activated to produce an immunogenic TME. Consequently, MnO<sub>x</sub>-TF not only inhibited the primary tumor, but also suppressed distal tumor growth and tumor metastasis.

### 3.6. Multimodal therapy

In addition to binary combination, multimodal systems that integrate more than two therapeutics were also developed to further improve the treatment outcomes [109]. For example, with the fact that Fenton reaction-induced oxidative stress is insufficient to elicit robust ICD for immunotherapy, Lin et al. have fabricated a core-shell nanostructure



**Fig. 4 – (A)** Schematic illustration showing the Au@MSN@IONP as photothermal-triggered self-fueling Fenton agents for TNBC ablation. Reproduced from [75]. Copyright 2020 John Wiley & Sons. **(B)** Schematic illustration of the copper phosphide nanocrystals for PTT-enhanced CDT to treat deep-seated tumor. Reproduced from [76]. Copyright 2019 John Wiley & Sons. **(C)** Schematic showing the FP NRs for enhanced CDT/PTT treatment. Reproduced from [77]. Copyright 2019 John Wiley & Sons. Abbreviations; US: ultrasonic.

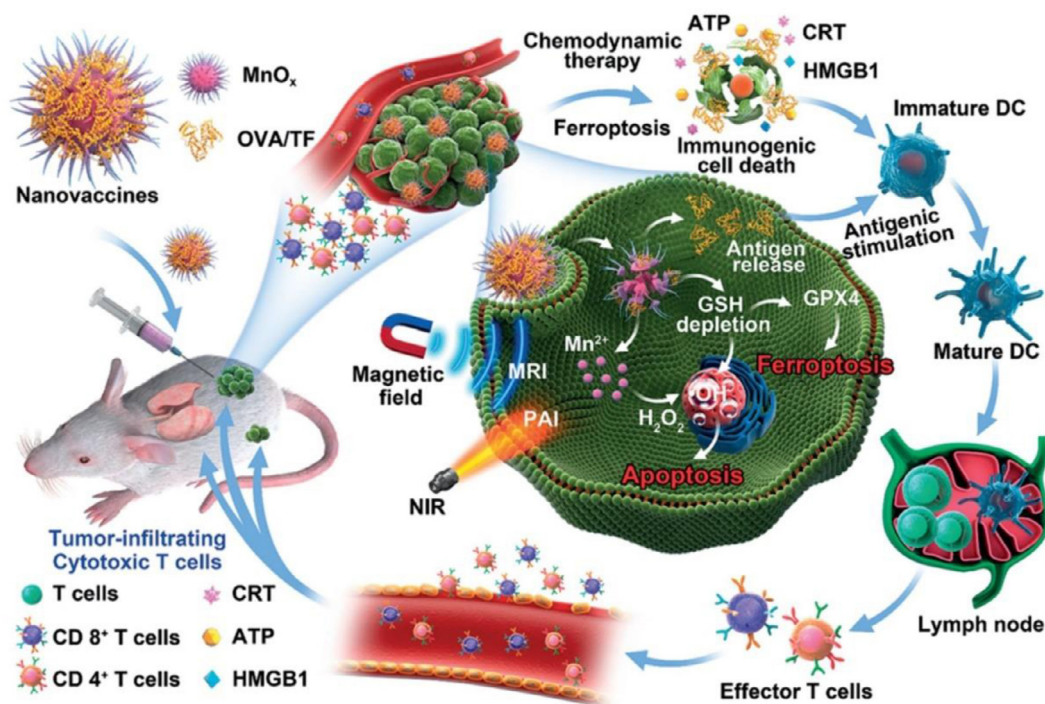


**Fig. 5 – (A)** The scheme of Co-Fc@GOx as a GOx-enhanced Fenton reaction platform for CDT/starvation therapy. **(B)** Schematic showing the mechanism of synergistic effect between GOx-based starvation therapy and CDT. Reproduced from [79]. Copyright 2020 John Wiley & Sons. **(C)** Schematic diagram of catalytic therapeutic mechanism of Fe<sub>5</sub>C<sub>2</sub>-GOx@MnO<sub>2</sub> for cancer therapy. Reproduced from [80]. Copyright 2018 American Chemical Society.

(namely Cu<sub>2</sub>O@CaCO<sub>3</sub>@HA) for multimodal therapy against colorectal cancer (Fig. 7A) [81]. The acidic colorectal TME facilitated CaCO<sub>3</sub> shell decomposition to generate Ca<sup>2+</sup> for intracellular calcium overload. Subsequently, the Cu<sub>2</sub>O core was sulfuretted by overexpressed H<sub>2</sub>S in tumor for in-situ generation of copper sulfide nanocrystals

(Cu<sub>31</sub>S<sub>16</sub>). The produced Cu<sub>31</sub>S<sub>16</sub> increased oxidative stress via Fenton reaction, and also possessed photodynamic and photothermal capabilities, displaying outstanding CDT/PTT/PDT effect under NIR laser irradiation. More importantly, this Cu<sub>2</sub>O@CaCO<sub>3</sub>@HA-mediated calcification and multimodal therapies repolarized tumor-associated





**Fig. 6 – Schematic presentation of the  $MnO_x$ -TF nanovaccines for cancer CDT/immunotherapy. Reproduced from [34]. Copyright 2020 John Wiley & Sons.**

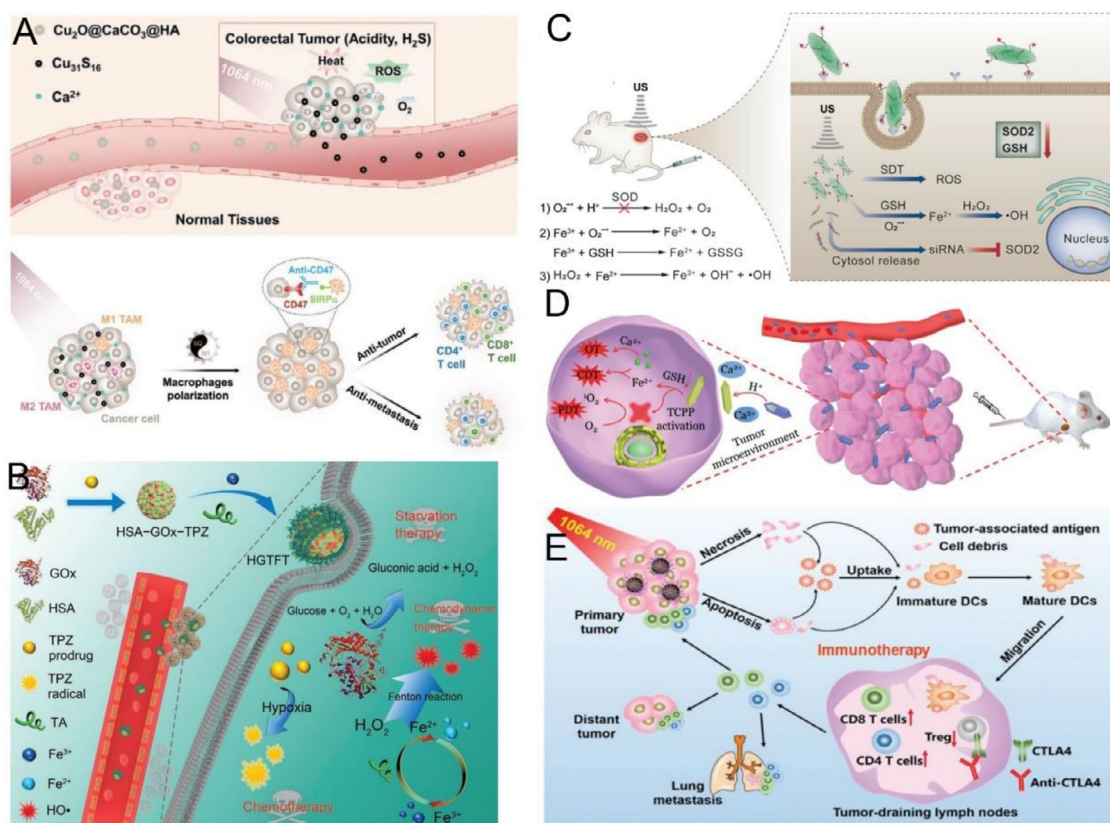
macrophages and strengthened immunotherapy. By further combining with CD47 blockade, this nanostructure not only ablated primary/distant tumor, but also suppressed cancer recurrence and metastasis, showing unprecedented potency for cancer therapy.

Given the various TME modulation effects of GOx, including  $H_2O_2$  generation, acidification and hypoxia exacerbation, GOx has been incorporated into multimodal tumor therapy. For instance, Wu et al. fabricated a self-amplified MPN-based nanoreactor composed of tirapazamine (TPZ), human serum albumin (HSA) and GOx for sustainable and cascade therapy (Fig. 7B) [82]. The starvation therapy induced by GOx obviously increased the intracellular  $H_2O_2$  for  $Fe^{2+/3+}$ -mediated Fenton reaction and aggravated hypoxia to activate TPZ (a hypoxic prodrug) for chemotherapy. The nanosystem achieved high tumor accumulation and synergistic anticancer effect for effective tumor ablation.

Multi-modal systems have also been explored to enhance ROS production to improve CDT. In one design, Liu and coworkers developed a  $Fe^{III}$ -porphyrin nano-sonosensitizer anchored with Bis(DPA-Zn)-RGD and superoxide dismutase 2 (SOD2) siRNA for SDT/gene therapy/CDT therapy (Fig. 7C) [84]. This nano-sonosensitizer effectively delivered siRNA into tumor cells for SOD2 silencing, and ROS generation can be enhanced via porphyrin-mediated SDT,  $Fe^{3+}$ -induced GSH depletion and  $Fe^{2+}$ -triggered Fenton reaction, which collectively leads to amplified intracellular oxidative stress. In another case, Tang et al. fabricated a dihydroartemisinin (DHA)-loaded  $Fe$ -TCPP MOF with  $CaCO_3$  mineralized coating

for synergistic oncosis therapy/CDT/PDT (Fig. 7D) [85]. This nanoplatform released DHA in response to acidic and GSH-overexpressed TME, accompanied with  $Ca^{2+}/Fe^{2+}$  generation and photosensitizer activation. The anticancer mechanism of DHA is to act on cell membrane and  $Ca^{2+}$  pump ATPase, leading to oncosis-like cell death, which can be enhanced by introducing exogenous  $Ca^{2+}$ . Meanwhile, the produced  $Fe^{2+}$  reacted with DHA to generate free radicals, causing cell apoptosis. Therefore,  $Ca^{2+}$ -DHA-mediated oncosis therapy and TCPP-mediated PDT synergized with  $Fe^{2+}$ /DHA-mediated CDT, resulting in high cancer therapeutic efficiency and negligible side effects.

We noticed that the most complicated system has combined five different modalities for tumor therapy, which integrated CDT, starvation therapy, PDT, PTT and immunotherapy [86]. They fabricated the GOx-loaded hollow mesoporous  $Cu_2MoS_4$  as multifunctional cascade bioreactor (Fig. 7E), which realized efficient cancer therapy through a variety of synergistic mechanisms. (I) the multivalent elements ( $Cu^{+2+}$ ,  $Mo^{4+/6+}$ ) triggered Fenton-like reaction and depleted GSH for CDT. (II) Converting  $H_2O_2$  into  $O_2$  via catalase-like catalysis to enhance GOx-induced starvation therapy. (III) Effective photothermal conversion and superoxide anion production under 1064 nm laser irradiation. (IV) Robust immune responses elicited by multiple treatments that can combine with checkpoint blockade therapy to eliminate both primary and metastatic tumor. However, while such system is robust enough for tumor therapy, the contribution of each treatment modality is rather elusive.



**Fig. 7 – (A) Schematic diagram showing the  $\text{Cu}_2\text{O}@Ca\text{CO}_3@HA$  combined with CD47 blockade for combinatorial tumor therapy. Reproduced from [81]. Copyright 2020 John Wiley & Sons. (B) Scheme of the synthetic route of the MPN-based nanoreactors and their applications for combinatorial therapy. Reproduced from [82]. Copyright 2020 John Wiley & Sons. (C) Schematic diagram showing the multifunctional sonotheranostics for synergistic tumor therapy. Reproduced from [84]. Copyright 2019 John Wiley & Sons. (D) Schematic illustration showing the TCPP- $\text{Fe}^{\text{III}}@DHA@Ca\text{CO}_3$  for synergistic tumor therapy. Reproduced from [85]. Copyright 2019 John Wiley & Sons. (E) Schematic illustration showing the anti-tumor mechanisms of  $\text{GOx}@Cu_2\text{MoS}_4$  when combining with checkpoint blockade therapy. Reproduced from [86]. Copyright 2019 John Wiley & Sons.**

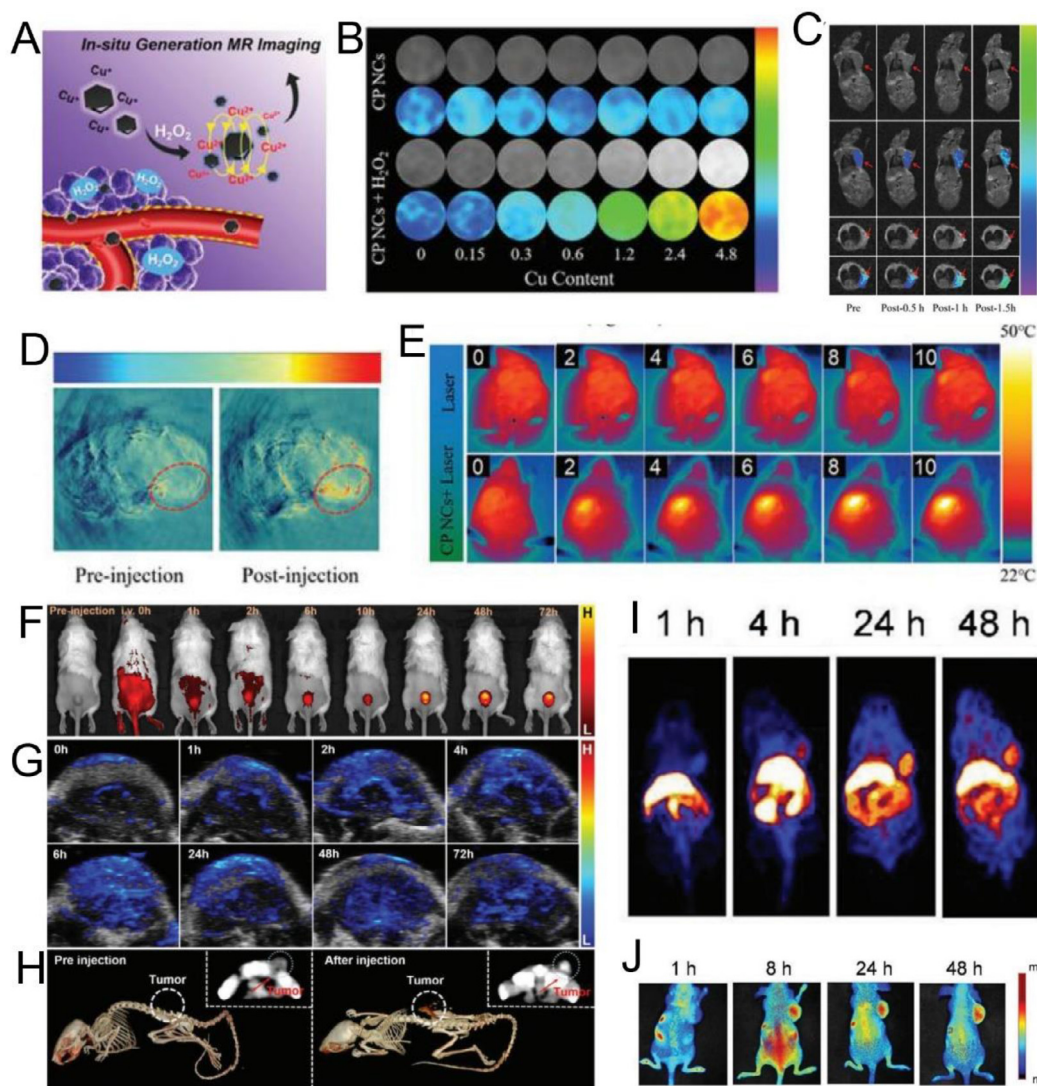
#### 4. Imaging-guided CDT-based therapy

Precise diagnosis is vital for the management of various diseases, particularly when the cancer is involved. The imaging-guided therapy is a theranostic approach to visualize the location of the tumors and dynamically monitor the drug delivery [110,111]. Fenton metals could serve as versatile nanoplatforms for tumor bioimaging, such as MRI, PET imaging, CT imaging, PAI and PTI. These Fenton metal-based imaging modalities, as well as multimodal imaging-guided therapy have been summarized in Table 2, and will be introduced in the following section.

##### 4.1. Fenton metals for bioimaging

Fenton metals, including Fe, Cu, Mn, not only show Fenton-like catalytic activity to produce  $\cdot\text{OH}$ , but also serve as contrast agents (CAs) for bioimaging. As clinically approved diagnostic  $T_1$ -weighted MR imaging CAs, Mn-based nanomaterials act as  $T_1$ -positive agents of paramagnetic species to produce hyperintense regions on the MR image. By virtue of the five

unpaired electrons,  $\text{Mn}^{2+}$  shows longer electronic relaxation time and higher spin number than  $\text{Mn}^{4+}$  [59]. Therefore, the TME-responsive disassembly behavior (from  $\text{MnO}_2$  to  $\text{Mn}^{2+}$ ) for contrast-enhanced MRI promotes their applications in theranostics [22].  $\text{Fe}^{2+}/\text{Fe}^{3+}$  can also be applied in  $T_1$ -weighted MR imaging. Superparamagnetic iron oxide nanoparticles (SPIONs), which can induce magnetization on the perpendicular plane disappearing by the dephasing of the spins, are excellent  $T_2$ -weighted MRI CAs for imaging-guided CDT [112]. The SPIONs have been demonstrated as MRI CAs for liver tumor imaging and metastasis monitoring [113]. Moreover, Positron-emitting isotope  $^{64}\text{Cu}$ -labeled Fenton-based nanomaterials exhibit powerful PET imaging capability with sufficient tissue penetration [55]. As a high Z value element, Cu displays large X-ray attenuation coefficient, making it ideal X-ray computed tomography contrast agent for CT imaging [21]. The FMNs with photothermal conversion performance (CuO, CuS, MPN, Prussian blue et al.) induce tissue thermoelastic expansion and hyperthermia under NIR light irradiation, which can be utilized for noninvasive PAI and PTI [114,115].



**Fig. 8 – (A)** Schematic illustration showing in situ self-generation of Cu<sup>2+</sup> for MR imaging. **(B)** T<sub>1</sub>-MR imaging of CP NCs solution with different concentrations in absence or presence of 100 μM H<sub>2</sub>O<sub>2</sub>. **In vivo** T<sub>1</sub>-MRI **(C)**, PAI **(D)** and PTI **(E)** of tumor-bearing mice. Reproduced from [76]. Copyright 2019 John Wiley & Sons. **(F)** Fluorescence images of 4T1 tumor-bearing mice by intravenous injection of Cy5.5-labeled nanocages. PAI **(G)** and CT imaging **(H)** of 4T1 tumor-bearing mice. Reproduced from [87]. Copyright 2020 John Wiley & Sons. **(I)** PET imaging of tumor-bearing mice after intravenous injection with the <sup>64</sup>Cu-labeled nanoreactor. **(J)** Fluorescence images of tumor-bearing mice after intravenous injection with the nanoreactor. Reproduced from [55]. Copyright 2020 John Wiley & Sons.

#### 4.2. Multimodal imaging-guided combinatorial CDT

Integrating multiple imaging means into one nanoplatform was prevailing in imaging-guided combinatorial CDT, which overcomes drawbacks of each singular imaging signal to provide complementary information of cancer. As an example, Yang et al. fabricated a highly efficient CDT agent (namely CP NCs) for PAI/MRI/PTI-guided CDT/PTT [76]. Unlike other hybrid nanomaterials, The CP NCs represent simple and multifunctional Cu-based FMNs, which can realize multiple imaging-guided therapy with a singular nanosystem. In response to H<sub>2</sub>O<sub>2</sub>, the CP NCs generated MRI contrast agent of paramagnetic Cu<sup>2+</sup> via in-situ oxidation (Fig. 8A), which produced strong T<sub>1</sub>-weighted MRI signal (Fig. 8B). After in vivo

injection, the MRI signal increased at tumor site overtime (Fig. 8C), owing to gradual generation of Cu<sup>2+</sup>. Benefiting from the photothermal capability, the applications of CP NCs for PAI and PTI were also explored, and PA signals were significantly boosted at the tumor site at 12 h post-injection in contrast to that of before injection (Fig. 8D). Meanwhile, the photothermal imaging showed a rapid temperature elevation of tumor within 10 min under laser illumination (Fig. 8E). Combining all these signals, this CDT-based nanoplatform provided abundant information for precise cancer theranostics. As a complementary example, Yang et al. reported PtCu<sub>3</sub> nanocages serving as sonosensitizer for FI/PAI/CT imaging-guided SDT/CDT [87]. The in vivo behavior was monitored by labeling the nanocages with Cyanine 5.5 for FI, and obvious

fluorescence was observed in the tumor regions more than 72 h post-injection (Fig. 8F). The similar results were also obtained from PA imaging with amplified and sustained signal at tumor site within 72 h (Fig. 8G). More importantly, these nanocages might serve as CT imaging contrast agent, exhibiting stronger X-ray attenuation than commercially used Iohexol (Fig. 8H). In addition, a  $^{64}\text{Cu}$ -labeled biocatalysis nanoreactor was fabricated by Chen et al. for FI/PET imaging-guided PDT/CDT [55]. An obviously stronger PET imaging signal was observed at the tumor site over a long time after intravenous injection (Fig. 8I), meanwhile the fluorescence imaging agreed well with the PET imaging result (Fig. 8J). This imaging performance was demonstrated to be robust enough to guide the ROS-mediated therapy.

## 5. Conclusion and future perspective

As a catalysis-driven cancer-therapeutic modality, CDT has obtained increased interest owing to its tumor selectivity. Especially, CDT-based combinatorial systems with imaging-guided therapy are highly encouraging for cancer theranostics attributing to precise tumor treatment with robust therapeutic outcomes. In this review, we have introduced the typical Fenton metals and their catalytic mechanisms, and summarized the recent development of FMNs for imaging-guided combinatorial CDT. Overall, the research in the field is still in its infancy, and there needs a lot of work to be done for potential clinical translation. To make real clinic impact, several crucial issues and challenges are remained to be addressed as listed below.

- (I) **Mechanism:** The Fenton/Fenton-like catalytic reaction-mediated ROS production has been widely explored, whereas the catalytic mechanism and ROS-induced molecular damage have not yet been fully revealed, making it difficult to rationally improve and optimize catalytic efficiency. Deep exploration of *in vivo* CDT process and its relevant mechanisms is important to guide cancer treatment. For example, techniques that can monitor Fenton reaction *in vivo* are necessary to better elucidate the real contribution of CDT for tumor therapy.
- (II) **Efficacy:** CDT performance is limited by unamiable TME, and both of the exogenous  $\text{H}_2\text{O}_2$  and the acidity in the cancer cell are not enough to initiate traditional Fenton reaction. Meanwhile, the intratumoral overexpressed GSH also passivates Fenton-induced ROS via antioxidation [116]. Although numerous FMNs have been designed to overcome the above obstacles, the more smart and versatile combinatorial nanoplatforms, which can overcome multiple limitations of TME, are desired in the future.
- (III) **Delivery:** Nanoscale delivery systems can be utilized to load Fenton metal for targeted delivery via EPR effect. However, this passive targeting is usually not sufficient [117]. Active targeting can be realized by further modification of specific ligands on particle surface to selectively recognize tumor. Moreover, the CDT-based combinatorial systems are powerful solution

to improve the tumor treatment outcomes, while effective integration CDT with various therapeutics into one set usually requires complicated preparation procedures with sophisticated materials design. The development of simple, cost-effective and robust multimodal nanoplatforms are still deemed necessary to realize combinatorial therapy with synergistic effects.

- (IV) **Biosafety:** The biosafety of Fenton metals is another important issue that need to be taken into consideration for their potential clinical applications. Although their biocompatibility has been widely investigated in animal model during the treatment period, the long-term toxicity is rather unclear and needs further research. For FMNs, their biodegradation is important, which is the pre-requisite for body elimination of the Fenton metals. Hence, intensive studies on ADME (absorption, distribution, metabolism, and excretion) performances of FMNs should be conducted for further applications.

Taken together, CDT represents a highly promising strategy for tumor theranostic applications, which have garnered significant research interest to contribute the rapid progress of the field. Since the first attempt of CDT five years before, nearly 500 papers have been published by searching the ISI Web of Knowledge database, and various FMNs have been constructed with excellent anti-tumor efficacy at animal models. However, as mentioned above, to reach a clinical impact, substantial work has to be done both fundamentally and at animal/clinical levels, which may fuel the growth of the field in the future.

## Conflicts of interest

The authors declare no conflict of interest.

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