MINI-REVIEW

Photo-responsive nanozymes: Mechanism, activity regulation, and biomedical applications

Chaohui Wang | Hongyu Wang | Bolong Xu | Huiyu Liu

Beijing Advanced Innovation Center for Soft Matter Science and Engineering, State Key Laboratory of Organic-Inorganic Composites, Beijing Laboratory of Biomedical Materials, Bionanomaterials & Translational Engineering Laboratory, Beijing Key Laboratory of Bioprocess, Beijing University of Chemical Technology, North Third Ring Road 15, Chaoyang, Beijing 100029, P. R. China

Correspondence
Huiyu Liu, Beijing Advanced Innovation Center for Soft Matter Science and Engineering, State Key Laboratory of Organic-Inorganic Composites, Beijing University of Chemical Technology, North Third Ring Road 15, Chaoyang, Beijing 100029, P. R. China.
Email: liuhy@mail.buct.edu.cn

Funding information
National Natural Science Foundation of China, Grant/Award Numbers: 21822802, 51772018, 2206130205; National Key Research and Development Program of China, Grant/Award Number: 2016YFA0201500; Fundamental Research Funds for the Central Universities, Grant/Award Numbers: XK1802-8, buctrc201915

Abstract
Nanozyme is defined as a nanomaterial-based artificial enzyme. It has rapidly attracted interest and been regarded as a promising alternative to natural enzymes due to its low cost, high stability, and high activity. Many researchers have recently paid attention to the optical properties of nanozymes and have found a variety of nanozymes with excellent photoactivity, called photo-responsive nanozymes. In this minireview, we briefly introduce the mechanisms of photo-responsive nanozymes, especially for the relationship between the enzyme-like activity and photoactivity. Some activity regulation strategies for improving the performance of photo-responsive nanozymes are also summarized. Moreover, the synergy of enzyme-like activity and photoactivity in biomedical applications will also be discussed, including cancer therapy, antibacteria, and biological detection. We believe this minireview will be of great significance for understanding the optical properties of nanozymes and applying them in biomedicine.

KEYWORDS antibacteria, biological detection, cancer therapy, nanomaterials, photo-responsive nanozymes

1 INTRODUCTION

Natural enzymes are limited by high preparation and purification costs, low stability, and cumbersome recovery. Nanomaterials with intrinsic enzyme-like characteristics (nanozymes) are considered as promising alternatives to mimic catalytic behavior of natural enzymes due to their high stability, excellent catalytic activity, and low cost. The “nanozymes” term is first coined by Scrimin and colleagues in 2004, by using ligand-functionalized Au nanoparticles (NPs) as an RNase-like catalyst for the transphosphorylation reaction. And since the first report of the inherent peroxidase (POD)-like activity of Fe₃O₄ NPs by Yan’s group in 2007, the nanozyme field has gained rapid development. A series of nanozymes, such as noble metal nanostructures, semiconductor
SCHEME 1  Schematic illustration for the mechanisms and biomedical applications of photo-responsive nanozymes

nanomaterials, carbon nanomaterials (CNMs), and metal-organic frameworks (MOFs), are developed and widely applied in the biomedical field.\textsuperscript{10–14}

Nanomaterials with unique photophysical and photo-chemical properties, such as tunable bandgap,\textsuperscript{15} distinct absorption spectrum,\textsuperscript{16} and localized surface plasmon resonance (LSPR),\textsuperscript{17} provide us with new perspectives for the rational regulation of nanozymes with multifunctionality. Photo-responsive nanozymes, which refer to nanozymes exhibiting photoactivity, can combine the optical performances with enzyme-like activities of nanozymes, creating a series of photo-based catalysis nanoplatorm. For example, by exploiting the nanomaterials’ optical properties to promote the catalytic activities of nanozymes, a photo-enhanced catalytic system can be formed. By synergistically increasing the treatment/detection efficiency, a photo-synergistic biological system can be constructed. Moreover, utilizing optical energy to activate catalytic activities of nanomaterials can also create a new type of nanozyme (photo-activated nanozyme). Therefore, the introduction of optical performances of nanomaterials will enlarge the connotation of nanozymes at the optical level.

Some publications have summarized the catalytic mechanisms and biomedical applications of nanozymes,\textsuperscript{3–7} but few papers have reviewed the photo-responsive nanozymes and their applications in biomedical field.\textsuperscript{18} In this minireview, we briefly discussed the action mechanisms of enzyme-like activity and photoactivity, focusing on the relationship between enzyme-like characteristics and optical performances of nanozymes (photo-enhanced, photo-activated, and photo-synergistic relation) (Scheme 1). We also summarized the activity regulation strategies for improving the performance of photo-responsive nanozymes and highlighted the synergy of enzyme-like activity and photoactivity in some biomedical applications, including cancer therapy, antibacteria, and biological detection. This minireview aims to improve the understanding of the photoactivity of various nanozymes and guide the design of photo-responsive nanozymes.

2  |  MECHANISMS OF PHOTO-RESPONSIVE NANOZYMES

With the help of theoretical calculations and experimental methods, the study of nanozymes’ catalytic mechanism has made great advances. Meanwhile, the study of nanomaterials’ optical properties is also more in-depth. Accordingly, the mechanisms of photo-responsive nanozymes can be classified into two parts: the intrinsic enzyme-like catalytic mechanisms and the photoactivity mechanisms.

2.1  |  Intrinsic enzyme-like catalytic mechanisms

The enzyme-like activities of these nanozymes commonly expressed as oxidoreductase activities, including oxidase (OXD), POD, catalase (CAT), and superoxide dismutase (SOD). In general, OXD-like nanozymes catalyze the oxidation of substrates with oxygen (O\textsubscript{2}) to generate strong oxidizing hydroxyl radical (\textbullet OH), while CAT-like nanozymes decompose H\textsubscript{2}O\textsubscript{2} to produce O\textsubscript{2} and H\textsubscript{2}O. And SOD-like nanozymes can catalyze the disproportionation reaction of superoxide.\textsuperscript{19} The catalytic mechanisms of different nanozymes vary greatly, related to the adsorption of active species, the generation of active intermediates, changes in the metal valence state, and so on. Herein, some representative types of nanozymes and their mechanisms are discussed as follows:

2.1.1  |  Noble metal-based nanozymes

Au is the most representative noble metal nanozyme. Li et al studied the pH-dependent CAT- and POD-like catalytic behavior of Au.\textsuperscript{20} This catalytic behavior is caused by the pre-adsorption of H\textsuperscript{+} or OH\textsuperscript{−} on the surface of Au, which determines the energy barrier of the H\textsubscript{2}O\textsubscript{2}
decomposition pathway. Under acidic conditions, they have POD-like activity and catalyze H₂O₂ to generate •OH (reaction: \( \text{H}_2\text{O}_2^* + \text{H}^+ \rightarrow \text{H}_2\text{O}^* + \text{OH}^* \)); while under alkaline conditions, they are similar to CAT and can decompose H₂O₂ to produce oxygen \((\text{O}_2)\) (reaction: \( \text{H}_2\text{O}_2^* + \text{OH}^* \rightarrow \text{H}_2\text{O}^* + \text{HO}^* \); \( \text{H}_2\text{O}^* + \text{HO}^* \rightarrow \text{H}_2\text{O}^* + \text{OH}^* + \text{O}_2^* \)). Asterisk (*) means the species adsorbed on the surface of Au. In addition, some noble metal nanozymes are demonstrated to exhibit facet-dependent enzyme-like activities.²¹ Chong et al reported that concave-structured palladium nanocrystals (Pd NCs) with high-index facets are more favorable for electron transfer from Pd atom to O₂ molecule than Pd NCs with low-index facets, thus resulting in higher OXD-like activity.²²

### 2.1.2 Semiconductor-based nanozymes

There are many types of semiconductor nanozymes, including Fe₃O₄, CeO₂, TiO₂, MoS₂, and so on.⁹,²³⁻²⁵ Fenton or Fenton-like reactions can generally be employed to explain the POD-like mechanism of these nanozymes, which can decompose H₂O₂ to produce •OH to oxidize substrates.¹² For other types of enzyme-like activities, the complexity of the nanostructure makes them have different catalytic mechanisms. For example, a surface defect catalytic mechanism is proposed for the CAT-like activity of CeO₂. Ce⁴⁺ is first reduced by H₂O₂ to form Ce³⁺ with the generation of H⁺ and O₂. Then, another H₂O₂ molecule can oxidize the generated Ce³⁺ to Ce⁴⁺, accompanied by the formation of a H₂O molecule.²³

### 2.1.3 Carbon-based nanozymes

The enzyme-like activities of CNMs have been widely reported, including carbon nanotubes, fullerene, carbon dots, and graphene quantum dots (GQDs).⁷,²⁶,²⁷ However, the exploration of their enzyme-like mechanisms is rare. Sun et al reported the catalytic mechanism of GQDs with POD-like activity.²⁶ According to the assessment of kinetic parameters by Lineweaver-Burk plots, they demonstrated that the H₂O₂ binding site is the carboxylic groups (O=CO–) and the active catalytic site for POD-like activity is the ketonic carbonyl groups (–C=O) during the catalytic process of GQDs.

### 2.1.4 MOFs-based nanozymes

To date, many MOFs with POD-like catalytic activity have been developed, including MIL-53, MIL-101, UiO-66, and so on.²⁸–³⁰ It has been confirmed that the mechanism of POD-like activity for MIL-53(Fe) is similar to Fenton reaction.²⁸,³¹ For other enzyme-like activity, for example, the mixed-valence state Ce-MOF (MVCM) has OXD-like activity, and the mechanism may be the “spontaneous” recycle of the Ce³⁺/Ce⁴⁺ system that the MVCM possesses in a redox reaction.³²,³³

### 2.2 Mechanisms of photoactivity

The optical properties of nanomaterials have been systematically studied, and their photophysical or photochemical processes are initiated by absorbing photons, which further causes the electrons being in an excited state.³⁴ Therefore, the photoactivity of nanozymes is related to the electronic state changes.

#### 2.2.1 Photothermal conversion

Nanomaterials with efficient photothermal properties include noble metals, semiconductors, and CNMs,³⁵⁻³⁷ which are also popular materials for nanozyme research. In noble metal nanomaterials, when the photon frequency matches the natural frequency of the electrons on the metal surface, the coherent oscillation of the electrons produces the LSPR effect, the occurrence of LSPR also results in strong light absorption and the heating effect becomes especially strong.³⁶,³⁸ Some reports have shown that semiconductor nanomaterials can also generate LSPR.³⁶

#### 2.2.2 Photocatalytic mechanisms

The principle of photocatalysis is based on the redox capacity of photocatalysts/photosensitizers under light irradiation, which always involves the production of large amounts of ROS. There are two main photocatalytic mechanisms to account for the production process of ROS. One is the charge transfer mechanism of semiconductor materials. The bandgap of semiconductor-based photocatalysts determines the wavelength of their excitation light. When the photon energy is greater than or equal to the bandgap energy, the electrons (e⁻) in the valence band (VB) of the semiconductor would be excited to the conduction band (CB), leaving holes (h⁺) in the VB.³⁹,⁴⁰ The excited e⁻ and h⁺ would propagate to the surface of the semiconductor, where they undergo an interface electron transfer reaction with a solvent or other adsorbed substance, inducing the generation of ROS.³⁹

The other one is the electron and energy transfer mechanism of photosensitizers. During this process, the ground
singlet state of electrons will be excited to its excited triplet state when the photons are absorbed by photosensitizers, and take part in two different reaction paths according to different photochemical reactions: the excited photosensitizers react with biological substrates to produce free radical intermedium through electron or proton transfer, which can further work on the surrounding ground \( \text{O}_2 \) or \( \text{H}_2\text{O} \) to produce superoxide anion (\( \text{O}_2^{-*} \)) or •OH, respectively (type I); in type II process, the excited photosensitizers can transfer the energy directly to the surrounding \( \text{O}_2 \) to generate singlet oxygen.41,42

2.3 Relationship between photoactivity and enzyme-like activity

2.3.1 Photo-enhanced enzyme-like activity

At present, there are many reports that the photothermal effect can promote the enzyme-like activity of the nanozymes, for which there are some different explanations. It is generally believed that the increase in the reaction rate is directly related to the temperature increase caused by photothermal effect.43,44 Qiu et al proved that the temperature increase caused by the photothermal conversion of Ir@Fe\(_3\)O\(_4\) NPs can accelerate their catalytic ability by the methylene blue (MB) degradation experiment.43 However, some researches have confirmed that there is an optimal reaction temperature range for nanozymes,9,19 while temperature increase caused by photothermal conversion may exceed the range. Therefore, temperature increase does not fully explain the photo-enhanced enzyme-like activity, which may also be attributed to the effect of active electrons generated by light irradiation. Christopher et al studied that Ag NPs catalyze the epoxidation reaction of ethylene to ethylene oxide. Experiments on the relationship between reaction rate and temperature were performed under thermal (without light) or photothermal (with light) conditions. The results revealed that the reaction rate in photothermal conditions increased more than thermal conditions at the same temperature. Based on the results of experiments and calculations, a possible mechanism is proposed that the excited energetic electrons of the Ag NPs populate \( \text{O}_2 \) antibonding molecular orbitals and the O–O bond is stretched, which facilitates \( \text{O}_2 \) dissociation.45

For the enzyme-like activity and photocatalytic/photosensitization activity of nanozymes, reactive oxide species (ROS) is an important marker. The ROS produced by the joint action of the two can synergistically enhance the catalytic effect of the nanozymes. FCo\(_9\)S\(_8\) nanodots (NDs) can produce •OH by POD-like activity, and they show stronger \( 3,3',5,5' \)-tetramethylbenzidine (TMB) oxidation performance in the presence of both near-infrared (NIR) light and \( \text{H}_2\text{O}_2 \). Under NIR light excitation, Co\(_9\)S\(_8\) NDs can promote both gathering and separation of charge carriers, decrease their recombination rate, and thus improve the ROS generation ability.46 Similarly, the temperature increase is not the main factor to improve the enzyme-like activities of a kind of yolk-shell structure containing an Au core and a hollow carbon shell (Au@HCNs) under NIR light irradiation. The POD- and OXD-like activities of Au@HCNs maintained almost the same level in the range of 25–45\(^\circ\)C, but there was a significant increase in activity under NIR light irradiation. Further experiments proved that NIR light irradiation can enhance the production of ROS.47

2.3.2 Photo-activated enzyme-like activity

These so-called photo-activated nanozymes show strong enzyme-like activity only under specific light excitation, which can also be regarded as a kind of photocatalyst or photosensitizer. The photo-activated mechanism is related to the transfer of electrons and energy under light stimulation.18 TiO\(_2\) NPs with the coordination of catechol (CA) exhibit OXD-like activity under light stimulation. The mechanism is that the instantaneous electrons generated by the CA-Ti(IV) complex are directly transferred from the ligand to the CB of the TiO\(_2\) under light excitation, thereby leaving holes in the CA to react with TMB directly.24

Nuclease is the basic tool of biological engineering, and photo-activated nanozymes with nuclease-like activity have attracted the interest of researchers. There have been several reports on photo-activated nanozymes for cleavage or repair of DNA.48–50 Chiral cysteine-modified CdTe NPs mimics a restriction endonuclease, whose selectivity derives from the affinity between the cysteine and a specific DNA sequence GAT’ATC (’ stands for cleavage site). The phosphodiester bonds between the T and A bases are interrupted by circularly polarized light-induced ROS oxidation.50

2.3.3 Photo-synergistic enzyme-like activity

The effect of “The whole is greater than the sum of its parts” generated by both photoactivity and the enzyme-like activity of the nanozymes is called photo-synergistic action, which is not necessarily a strong mutual influence between the two parts. Nanozymes with photothermal effect can be applied to photothermal therapy, and the
**TABLE 1** Summary of various photo-responsive nanozymes

| Nanomaterials | Enzyme-like activity | Relationship | Applications | Reference |
|---------------|----------------------|--------------|--------------|-----------|
| TiO$_2$−CA    | OXD                  | Photo-activated | Detection   | 24        |
| MoS$_2$       | POD                  | Photo-synergistic | Antibacteria | 25,53     |
| Ir@Fe$_3$O$_4$ | POD                  | Photo-enhanced, Photo-synergistic | Cancer therapy | 43        |
| PtFe@Fe$_3$O$_4$ | CAT, POD             | Photo-enhanced, Photo-synergistic | Cancer therapy | 44        |
| Co$_9$S$_8$   | POD                  | Photo-enhanced, Photo-synergistic | Cancer therapy | 46        |
| Au@HCNs       | OXD, POD             | Photo-enhanced, Photo-synergistic | Cancer therapy | 47        |
| Cu$_2$MoS$_4$ | CAT, POD             | Photo-synergistic | Cancer therapy | 51        |
| Au@Pt         | POD                  | Photo-synergistic | Detection   | 52        |
| Au@Pd         | OXD                  | Photo-enhanced  |              | 54        |
| Au−mSiO$_2$−Mn−CDs | CAT       | Photo-synergistic | Cancer therapy | 55        |
| CDs-Ag/Au     | CAT, SOD             | Photo-synergistic | Cancer therapy | 56        |
| HA-Ru (hyaluronic acid-Ru) | CAT, POD | Photo-synergistic | Cancer therapy | 57        |
| C-dots        | OXD                  | Photo-activated | Antibacteria | 58        |
| γ-C$_3$N$_4$  | OXD, POD             | Photo-activated | Detection   | 59        |
| N-SCSs (N-doped sponge-like carbon spheres) | POD | Photo-enhanced, Photo-synergistic | Antibacteria | 60        |
| Fe$_2$O$_3$   | POD                  | Photo-enhanced  | Detection   | 61        |
| Cu$_2$Se      | POD                  | Photo-enhanced, Photo-synergistic | Cancer therapy | 62        |
| Pt-CuS        | CAT                  | Photo-enhanced, Photo-synergistic | Cancer therapy | 63        |
| Co$_9$        | POD                  | Photo-enhanced, Photo-synergistic | Cancer therapy | 64        |
| CeO$_2$−PEI-MoS$_2$ | CAT, SOD, POD | Photo-synergistic | Cancer therapy | 65        |
| CeO$_3$@MnO$_2$ | OXD                  | Photo-activated | Detection   | 66        |
| BSA-IrO$_2$   | CAT                  | Photo-synergistic, Photo-enhanced | Cancer therapy | 67        |
| ABTS@MIL-100  | POD                  | Photo-synergistic | Cancer therapy | 68        |
| Cu$_2$Te      | OXD, POD             | Photo-enhanced  | Cancer therapy | 69        |

•OH produced by their POD-like activity can induced cellular poptosis, so that a high-efficiency antitumor effect can be achieved.$^{46,47,51}$ Take Au@Pt Nanozyme as an example, it combines excellent photothermal performance and POD-like activity that can simultaneously quantify protein concentration with photothermal, colorimetric, and ratiometric fluorescence immunoassay to achieve more accurate detection.$^{52}$

Here, we list some photo-responsive nanozymes, including their enzyme-like activities, photoactivity, and applications in Table 1.

### 3 ACTIVITY REGULATION STRATEGIES

The performances of nanozymes rely on their constructions (including feature size, morphology, structure), elemental doping, interaction with the ambient or other nanostructures, and so on.$^{70−73}$ Different regulation strategies would significantly impact the properties of nanozymes, so choosing an appropriate strategy can subserve the properties of photo-responsive nanozymes.

#### 3.1 Regulating size and morphology

The particle size and morphology of nanozymes have vital impacts on their photoactivity and enzyme-like activity. The theoretical calculation with Mie theory and discrete dipole approximation method indicated that the absorption and scattering of NPs were highly dependent on the size, shape, and core-shell composition.$^{74,75}$ The experimental results confirmed that the photothermal properties of Au NPs were size-tunable. When the particle size of Au NPs decreased from 50.09 ± 2.34 nm to 4.98 ± 0.59 nm, the photothermal conversion efficiency increased from 0.650 ± 0.012 to 0.803 ± 0.008, which is related to the absorption/extinction ratios.$^{76}$ In addition, for semiconductor nanozymes, particle size and morphology are also important. Zhu et al regulated the pH value of the hydrothermal reaction system to change the morphology of Fe$_2$O$_3$ NPs, which exhibited different bandgaps (1.78-2.11 eV). Additionally, in comparison, the binding affinity and maximum reaction velocity of Fe$_2$O$_3$ nanoflowers (1.78 eV) with TMB are at least 3.7 and 4.3 times higher than those of Fe$_2$O$_3$ nanocubes (2.06 eV), respectively, which shows...
FIGURE 1 (A) Relative activity of TMB-derived oxidation product, in the presence of H$_2$O$_2$, catalyzed by the Fe$_3$O$_4$ NPs with different structures or without Fe$_3$O$_4$: (a) cluster spheres, (b) triangular plates, (c) octahedra, and (d) without Fe$_3$O$_4$. Copyright 2011, Wiley-VCH. (B) Kinetic curve for OXD-, POD-, CAT-, and SOD-like activity of N-PCNSs. Reproduced with permission. Copyright 2018, Nature Publishing Group. (C) TEM and scanning TEM (STEM) images of PtFe@Fe$_3$O$_4$ NRs. Reproduced with permission. Copyright 2019, Wiley-VCH

the catalytic performance can be specifically regulated by the crystal morphology with distinct crystallographic planes. As shown in Figure 1A, Liu et al prepared Fe$_3$O$_4$ nanocrystals with three diverse structures through similar hydrothermal reactions and further studied their POD-like activities, which were structure-dependent (in the order octahedra < triangular plates < cluster spheres). Fe$_3$O$_4$ NPs with different particle sizes exhibited different levels of POD-like activity (in the order 300 nm < 150 nm < 30 nm), probably because of the larger surface-to-volume ratio of the smaller NPs. These research indicate that different sizes and morphologies of nanozymes are very important for their catalytic activity.

3.2 Elemental doping

Elemental doping is a valid way to change the optical and catalytic properties of nanomaterials. The principle behind it is to introduce an electronic state in the bandgap to generate additional transitions and affect the properties and functions of the matrix material. Doping heteroatoms into CNMs is a practical method to develop carbon-based nanozymes with great performance, and the most common doping element in carbon-based nanozymes is nitrogen (N). After N is doped into the carbon skeleton, the catalytic efficiency of carbon-based nanozymes is significantly improved. N is more electronegative than carbon, so doping N will change the electronic structure of the carbon materials. At the same time, N has one extra valence electron than C, making it a promising n-type dopant, which brings the Fermi level closer to the CB, resulting in more conductive and disordered carbon nanostructure. Fan et al synthesized N-doped porous carbon nanospheres (N-PCNSs) with different N content (N-PCNSs-3, high N; N-PCNSs-5, low N) as well as un-doped PCNSs (no N) to study the effect of N in the catalytic process. N-PCNSs-3 exhibited the best activity, and the affinity of PCNSs for substrates was significantly increased after N-doping (Figure 1B). N doping affects not only the enzyme-like activity of carbon materials, but also the photoactivity. Carbon dots (CDs) are a class of low-cost nanozymes with good photoactivity. Zhang et al developed a series of N-doped CDs, which have different optical characteristics with different N contents. The N doping level may have important significance for the photosensitivity of CDs.

In addition to the above regulation strategies, constructing nanozymes with multi-components is also a feasible way to improve catalytic activity of nanozymes. In our previous work, we constructed nanozyme PtFe@Fe$_3$O$_4$ nanorods (NRs) with CAT-like and POD-like activities (Figure 1C). Compared with Fe$_3$O$_4$ NRs, the O$_2$ production of PtFe@Fe$_3$O$_4$ NRs increased by 1.4 times, indicating that the combination of PtFe and Fe$_3$O$_4$ NRs effectively promoted the catalytic performance. After NIR light irradiation, the POD-like activity of PtFe NRs and PtFe@Fe$_3$O$_4$ NRs were significantly enhanced, while the catalytic activity of Fe$_3$O$_4$ NPs was not. Studies on the chemical composition and state of PtFe@Fe$_3$O$_4$ NRs show that the electrons from Fe atoms would transfer to Pt atoms, leading to Pt in an electron-rich state, while the
Fe atoms are mainly in the oxidation state. In addition, the electron transfer process between PtFe NRs, Fe₃O₄ NPs, and H₂O₂ molecules was also revealed. Under the NIR light irradiation, the nanozyme showed good photothermal performance and could significantly enhance the catalytic activity of PtFe@Fe₃O₄.⁴⁴

### 4 | BIOMEDICAL APPLICATIONS

#### 4.1 | Cancer therapy

Cancer is a major public health problem worldwide.⁸³ Because of the complexity, diversity, and heterogeneity of cancers, the current research on cancer monotherapy has gradually developed into combination therapy, based on the synergy between two or more therapies to enhance the therapeutic effect.⁴⁴ In recent years, many researchers have explored the combination of catalytic therapy and phototherapy for cancer therapy, and photo-responsive nanozymes are excellent nanomaterials for cancer synergy therapy.

For catalytic-photothermal therapy, Fan et al prepared a Au@HCNs nanozyme. In acidic environment, Au@HCNs exhibited POD-like and OXD-like activities, showing the ability to produce ROS. In addition, Au@HCNs not only can trigger cancer cell death by photothermal effect, but can also significantly promote the production of ROS under NIR light irradiation.⁴⁷ To better achieve the effective antitumor effect of combination therapy, Zhang et al synthesized mesoporous silica-coated cubic Au as doxorubicin (DOX) carriers, and anchored Mn-carbon dots on it to achieve controlled drug release and alleviate hypoxia in tumor tissues, and finally conjugated Arg-Gly-Asp (RGD) peptide (RGD-CCmMC/DOX) for active targeting. Under 635 nm light radiation, Mn-CDs can in situ catalyze H₂O₂ to generate O₂ by CAT-like activity, which can enhance photodynamic efficiency. In addition, the cubic Au core showed a good photothermal performance under the radiation of 808 nm light. And Mn-CDs can act as a “gate-keeper” to prevent the leakage of the packaged anticancer agent, thereby allowing the heat- and pH-sensitive anticancer agent to be accurately released at the tumor site.⁵⁵

Photo-responsive nanozymes can also be used to enhance tumor immunotherapy. Wen et al synthesized Cu₂-xTe NPs with glutathione (GSH) OXD- and POD-like activities, which can catalyze the consumption of GSH and produce ROS, thereby synergistically elevating intratumoral oxidative stress and achieving catalytic immunotherapy (Figure 2A,B). At the same time, Cu₂-xTe NPs have good photothermal effect (Figure 2C), whose enzyme-like activity was significantly reinforced under the 1064 nm light irradiation. Cu₂-xTe NPs continuously modulate immunosuppressive tumor microenvironments (Figure 2D), and accelerate the generation of systematic antitumor immunity to suppress tumor metastasis and recurrence.⁶⁹ This research exploits the application of photo-responsive nanozymes and the development of catalytic immunotherapy.

#### 4.2 | Antibacteria

Antibiotics are widely used antibacterial drugs. With the overuse or abuse of antibiotics, drug-resistant bacteria are prone to appear. The emergence of drug-resistant bacteria is one of the challenges for human health. This rapidly escalating threat has urged the discovery of new antibacterial agents and new treatment strategies to combat these highly resistant bacteria.⁸⁵ The intrinsic enzyme-like activity combined with good photothermal or photodynamic properties of photo-responsive nanozymes can achieve highly effective antibacterial activity. Xi et al synthesized N-SCSs with POD-like activity which could catalyze low concentration levels of H₂O₂ to •OH for resisting bacteria. Besides, their catalytic activity can be promoted by the generated heat under NIR light irradiation, generating more •OH to achieve better antibacterial effect.⁶⁰

Sang et al modified MoS₂ nanoflowers with L-cysteine (MoS₂-Cys) and covalently connected the MoS₂-Cys and hydrogel to construct a positively charged and porous MoS₂-hydrogel. On account of the excellent POD-like activity and photothermal characteristics, the antibacterial activity of MoS₂-hydrogel against drug-resistant Staphylococcus aureus (S. aureus) and Escherichia coli (E. coli) was evaluated. As obviously depicted in Figure 2, in the presence of H₂O₂, MoS₂-hydrogel could more effectively reduce the survival rate of E. coli and inhibit its growth compared with MoS₂-Cys. When treated by MoS₂-hydrogel + H₂O₂, the bacteria cell walls became fragmentary. Combined with the photothermal characteristics of MoS₂-Cys, the MoS₂-hydrogel + H₂O₂ + 808 nm light irradiation group has the strongest sterilization ability (Figure 2).²⁵ To solve the lack of bacterial capturing capacity and relatively low catalytic activity of nanozymes, Cao et al constructed a MoS₂ nanozyme with exposed defect-rich active edges.⁸⁶ The nanozyme has a rough surface that can effectively capture bacteria through strong adhesion, which is caused by local topological interactions between their nanoscale spikes and extracellular organelles of hairy bacteria. At the same time, the defect-rich edges show higher intrinsic POD-like activity than the original structure, combining with the photothermal properties of the nanozyme, excellent antibacterial properties are obtained in vitro and in
FIGURE 2  (A) ROS fluorescence imaging (scale bar = 50 µm) and calreticulin (CRT) and high mobility group box 1 (HMGB-1) immunostaining imaging (scale bar = 20 µm). (B) Intratumoral oxidative stress. (C) In vivo photothermal effect of Cu$_{2-x}$Te NPs under 1064 nm light irradiation. (D) Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels in serum. Conditions: (1) control, (2) 1064 nm light, (3) Cu$_{2-x}$Te, and (4) Cu$_{2-x}$Te + 1064 nm light. Reproduced with permission.\textsuperscript{69} Copyright 2019, Wiley-VCH. (E) Photographs of bacterial colonies and SEM images of E. coli samples after treated by different groups. (F) Viability of E. coli after incubated with different groups. Reproduced with permission.\textsuperscript{25} Copyright 2019, Wiley-VCH. (G) Schematic illustration of the cascade reaction with intermittent O$_2$-purging in a batch mode. (H) The concentration-response curve with the linear calibration plots and color change for glucose detection. Reproduced with permission.\textsuperscript{59} Copyright 2019, Nature Publishing Group
Biological detection

Enzymes have been widely used to design biosensors to detect substrates, but the low stability of the enzyme has stimulated the development of enzyme mimics. By integrating the photoactivity and intrinsic catalytic properties of nanomaterials, a low-cost and photoactivity-stable nanozyme can be used to construct a non-enzymatic analysis system to achieve the sensing and detection of biomarkers.

Cardiac troponin is considered as a model biomarker for acute myocardial infarction diagnosis. Jiao et al integrated three independent signal transductions based on the excellent catalytic efficiency and photothermal performance of Au@Pt nanodendrites for sensitive detection of Cardiac troponin I (cTnI). Under 808 nm light irradiation, the elevated temperature curve shows a clear concentration-dependent characteristic with the increase of cTnI. Au@Pt with POD-like activity can oxidize o-phenylenediamine (OPD) to 2,3-diaminophenazine (OX-OPD), which can cause color change and perform colorimetric detection. Because of the good affinity through hydrogen bonding and π-π stacking, OX-OPD can be anchored tightly on the surface of CDs and quench the fluorescence. This detection method makes full use of the various characteristics of Au@Pt nanodendrites, and the sensitive detection results provide a positive exploration for the application of photo-responsive nanozymes in biological detection.

Glucose detection is an important part of biological detection, and it is significant for the diagnosis of many diseases to achieve the efficient and rapid detection. Zhang et al synthesized a modified graphitic carbon nitride (GCN) with two enzyme-like activities, which was incorporated with potassium hydroxide, potassium chloride, and both, to obtain samples referred as ACN, KCN, and AKCN, respectively. Under visible light irradiation, AKCN has photocatalytic activity, which can oxidize glucose and reduce O2 to produce H2O2. Then, the in situ generated H2O2 is used in the subsequent POD-like reaction, which can oxidize TMB to realize the bifunctional enzyme-like activity to detect glucose (Figure 2G,H). Furthermore, a continuous-flow microfluidic reactor was constructed to verify the practical detection capability, and the detection limit of glucose in 30 s was downward to 0.8 µM.

5 | CONCLUSION AND PERSPECTIVES

In summary, this minireview covered recent progresses on photo-responsive nanozymes from mechanisms and activity regulation strategies to biomedical applications. Photo-responsive nanozymes exhibit improved catalytic activity and substrate selectivity due to their photoactivity, which are two of the most vital issues that call for settlement in nanozyme applications. In addition, the combination of light control strategies allows precise and dynamic control of nanozymes. Therefore, the photoresponsive nanozymes have promising applications in biomedical field. Based on the current research basis, there is still much room for development of photo-responsive nanozymes, which probably be given as follows:

As described in this review, the combination of nano-materials’ optical properties with enzyme-like activities has multiple action modalities. The complexity of action modalities makes it necessary to explore the relationship between optical properties and enzyme-like activities in depth. For example, exploring how light affects the surface electron transfer behavior of nanozymes and how it affects the generation pathway of ROS. In-depth study of these mechanisms will facilitate the de novo design of novel photo-responsive nanozymes, and help to obtain our desired photo-responsive nanozymes.

The vast majority of currently developed photo-responsive nanozymes is based on redox reaction, such as CAT-like, POD-like, SOD-like, and OXD-like reactions, etc, which severely hinders the establishment of new application systems for photo-responsive nanozymes. At present, some other photo-based natural enzymes (photolyase and fatty acid photodecarboxylase), distinct from oxidoreductases, are also utilized in chemical synthesis and biomedical fields. Therefore, it still remains a huge challenge for us to learn from nature and build a bioinspired photo-based enzymatic reaction system by optimizing the optical properties of nanomaterials and modulating the composition and structure of nanozymes.

Currently, a series of nanozymes with multi-enzymatic activities were reported, which have been demonstrated to be beneficial for some therapeutic applications, such as antitumor and antibacterial therapy. However, in certain cases, the poor catalytic specificity of photo-response nanozymes may also cause unpredictable side-effects. The rational design of controllable photo-responsive nanozymes with substrate specificity for specific requirement or function will be of great interest in some application areas, especially in biosensing and immunoassays.

A number of studies have demonstrated in vivo therapeutic effects of photo-responsive nanozymes. However,
these studies still do not elucidate the in vivo mechanism of action and toxic effect of nanozymes clearly, which may hinder the clinical translation process of nanozymes. For photo-responsive nanozymes, the toxicity has two aspects: phototoxicity and nanomaterials’ toxicity. Therefore, at the material design stage, we should consider the light absorption range, material compositions, and biodegradable properties of nanozymes as much as possible. In the therapeutic process, we need to focus on these factors such as the in vivo distribution behavior of nanozymes and the light exposure range, thus avoiding the toxicity at both materials design and application levels.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ACKNOWLEDGMENT
This work was supported by the National Natural Science Foundation of China (21822802, 5177130205), the National Key Research and Development Program of China (2016YFA0201500), and the Fundamental Research Funds for the Central Universities (XK1802-8, buctrc201915).

ORCID
Huiyu Liu https://orcid.org/0000-0003-4465-8501

REFERENCES
1. X. Wang, W. Guo, Y. Hu, J. Wu, H. Wei, Nanozymes: Next Wave of Artificial Enzymes, Springer, Berlin, Heidelberg. 2016.
2. Q. Wang, H. Wei, Z. Zhang, E. Wang, S. Dong, Trends Anal. Chem. 2018, 105, 218.
3. Y. Huang, J. Ren, X. Qu, Chem. Rev. 2019, 119, 4357.
4. H. Wei, E. Wang, Chem. Soc. Rev. 2013, 42, 6060.
5. H. Wang, K. Wan, X. Shi, Adv. Mater. 2019, 31, 1805368.
6. Y. Zhou, B. Liu, R. Yang, J. Liu, Bioconjugate Chem. 2017, 28, 2903.
7. H. Sun, Y. Zhou, J. Ren, X. Qu, Angew. Chem. Int. Ed. 2018, 57, 9224.
8. F. Manea, F. B. Houillon, L. Pasquato, P. Scrimin, Angew. Chem. Int. Ed. 2004, 43, 6165.
9. L. Gao, J. Zhuang, L. Nie, J. Zhang, Y. Zhang, N. Gu, T. Wang, J. Feng, D. Yang, S. Perretti, X. Yan, Nat. Nanotechnol. 2007, 2, 577.
10. X. Zhang, G. Li, D. Wu, X. Li, N. Hu, J. Chen, G. Chen, Y. Wu, Biosens. Bioelectron. 2019, 137, 178.
11. J. Wu, S. Li, H. Wei, Chem. Commun. 2018, 54, 6520.
12. L. Jiao, H. Yan, Y. Wu, W. Gu, C. Zhu, D. Du, Y. Lin, Angew. Chem. Int. Ed. 2020, 59, 2565.
13. X. Wang, Y. Hu, H. Wei, Inorg. Chem. Front. 2016, 3, 41.
14. S. Singh, Front. Chem. 2019, 7, 46.
15. Y. Zhang, T.-T. Tang, C. Girit, Z. Hao, M. C. Martin, A. Zettl, M. F. Crommie, Y. R. Shen, F. Wang, Nature 2009, 459, 820.
16. X. Chen, C. Burda, J. Am. Chem. Soc. 2008, 130, 5018.
17. K. A. Willets, R. P. Van Duyne, Annu. Rev. Phys. Chem. 2007, 58, 267.
18. J. Zhang, J. Liu, Nanoscale 2020, 12, 2914.
19. X. Yan, Ed., Nanozymology: Connecting Biology and Nanotechnology, Springer Singapore, Singapore, 2020.
20. J. Li, W. Liu, X. Wu, X. Gao, Biomaterials 2015, 48, 37.
21. X. Sheng, W. Liu, X. Gao, Z. Lu, X. Wu, X. Gao, J. Am. Chem. Soc. 2015, 137, 15882.
22. Y. Chong, X. Dai, G. Fang, R. Wu, L. Zhao, X. Ma, X. Tian, S. Lee, C. Zhang, C. Chen, Z. Chai, C. Ge, R. Zhou, Nat. Commun. 2018, 9, 4861.
23. I. Celardo, J. Z. Pedersen, E. Traversa, L. Ghibelli, Nanoscale 2011, 3, 1411.
24. L.-Y. Jin, Y.-M. Dong, X.-M. Wu, G.-X. Cao, G.-L. Wang, Anal. Chem. 2015, 87, 10429.
25. Y. Sang, W. Li, H. Liu, L. Zhang, H. Wang, Z. Liu, J. Ren, X. Qu, Adv. Funct. Mater. 2019, 29, 1900518.
26. H. Sun, A. Zhao, N. Gao, K. Li, J. Ren, X. Qu, Angew. Chem. Int. Ed. 2015, 54, 7176.
27. Y. Song, K. Qu, C. Zhao, J. Ren, X. Qu, Adv. Mater. 2010, 22, 2206.
28. L. Ai, L. Li, C. Zhang, J. Fu, J. Jiang, Chem. Eur. J. 2013, 19, 15105.
29. D. Chen, B. Li, L. Jiang, D. Duan, Y. Li, J. Wang, J. He, Y. Zeng, RSC Adv. 2015, 5, 97910.
30. Z. Hu, X. Jiang, F. Xu, J. Jia, Z. Long, X. Hou, Talanta 2016, 158, 276.
31. W. Dong, X. Liu, W. Shi, Y. Huang, RSC Adv. 2015, 5, 17451.
32. Y. Xiong, S. Chen, F. Ye, L. Su, C. Zhang, S. Shen, S. Zhao, Chem. Commun. 2015, 51, 4635.
33. R. Dalapati, B. Sakthivel, M. K. Ghosalay, A. Dhakshinamoorthy, S. Biswas, CrystEngComm 2017, 19, 5915.
34. V. Balzani, P. Ceroni, A. Juris, Photochemistry and Photophysics: Concepts, Research, Applications, Wiley-VCH, Weinheim, 2014.
35. B. Han, Y.-L. Zhang, Q.-D. Chen, H.-B. Sun, Adv. Funct. Mater. 2018, 28, 1802235.
36. M. Gao, L. Zhu, C. K. Peh, G. W. Ho, Energy Environ. Sci. 2019, 12, 841.
37. X. Huang, W. Zhang, G. Guan, G. Song, R. Zou, J. Hu, Acc. Chem. Res. 2017, 50, 2529.
38. M. L. Brongersma, N. J. Halas, P. Nordlander, Nat. Nanotechnol. 2015, 10, 25.
39. X. Meng, L. Liu, S. Ouyang, H. Xu, D. Wang, N. Zhao, J. Ye, Adv. Mater. 2016, 28, 6781.
40. S. Linic, P. Christopher, D. B. Ingram, Nat. Mater. 2011, 10, 911.
41. W. Fan, P. Huang, X. Chen, Chem. Soc. Rev. 2016, 45, 6488.
42. S. Kwiatkowski, B. Knip, D. Przystupski, J. Saczko, E. Kędzier- ska, K. Knap-Czop, J. Kotlińska, O. Michel, K. Kotowski, J. Kulbacka, Biomed. Pharmacother. 2018, 106, 1098.
43. K. Qiu, J. Wang, T. W. Rees, L. Ji, Q. Zhang, H. Chao, Chem. Commun. 2018, 54, 14108.
44. S. Li, L. Shang, B. Xu, S. Wang, K. Gu, Q. Wu, Y. Sun, Q. Zhang, H. Yang, F. Zhang, L. Gu, T. Zhang, H. Liu, Angew. Chem. Int. Ed. 2019, 58, 12624.
45. P. Christopher, H. Xin, S. Linic, Nat. Chem. 2011, 3, 467.
46. S. Lin, Y. Wang, Z. Chen, L. Li, J. Zeng, Q. Dong, Y. Wang, Z. Chai, ACS Sustainable Chem. Eng. 2018, 6, 12061.
47. L. Fan, X. Xu, C. Zhu, J. Han, L. Gao, J. Xi, R. Guo, ACS Appl. Mater. Interfaces 2018, 10, 4502.
48. J. Zhang, S. Wu, L. Ma, P. Wu, J. Liu, Nano Res. 2020, 13, 455.
49. Z. Tian, Y. Yao, C. Qu, S. Zhang, X. Li, Y. Qu, Nano Lett. 2019, 19, 8270.
50. M. Sun, L. Xu, A. Qu, P. Zhao, T. Hao, W. Ma, C. Hao, X. Wem, F. M. Colombari, A. F. de Moura, N. A. Kotov, C. Xu, H. Kuang, Nat. Chem. 2018, 10, 821.
AUTHOR BIOGRAPHIES

Chaohui Wang received his bachelor’s degree from Beijing University of Chemical Technology in 2019. Currently, he is pursuing his master’s degree under the supervision of Prof. Huiyu Liu from Beijing University of Chemical Technology. His research interests mainly include the preparation and structural control of inorganic nanomaterials and the construction of nanocarriers for drug delivery.

Hongyu Wang received his master’s degree from Beijing University of Chemical Technology in 2020. Currently, he is pursuing his Ph.D. degree under the supervision of Prof. Huiyu Liu from Beijing University of Chemical Technology. His research interests mainly include the preparation of nanomaterials and their applications in cancer therapy.

Bolong Xu received his bachelor’s degree from Beijing University of Chemical Technology in 2017. He is now pursuing his Ph.D. under the supervision of Prof. Huiyu Liu in Beijing University of Chemical Technology. Currently, his research focuses on the design, preparation, and biological application of multifunctional nanomaterials.

Huiyu Liu is currently a professor at Beijing University of Chemical Technology. She received her Ph.D. degree from the Technical Institute of Physics and Chemistry (TIPC), the Chinese Academy of Sciences (CAS) in 2007. There-
after, she worked as an associate professor at TIPC. Dr. Liu moved to the current position at the end of 2015. Her research mainly focuses on nanomedicine and nanobiology, including the safe design of smart nanoparticle-based platforms for cancer therapy and the characterization and understanding of the biological effects of nanomaterials with important implications in human health.

How to cite this article: Wang C, Wang H, Xu B, Liu H. Photo-responsive nanozymes: Mechanism, activity regulation, and biomedical applications. VIEW. 2021;2:20200045. https://doi.org/10.1002/VIW.20200045