RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2025, **15**, 47648

Bimetallic and multimetallic nanozymes: synergistic catalysis for advanced biomedical and health applications

Qian He and Liyun Zhang*

Nanozymes are a class of nanomaterials with enzyme-mimetic catalytic activities. Owing to their high stability, tunable catalytic performance, and ease of preparation, they have emerged as important alternatives to natural enzymes. However, single-metal nanozymes often face challenges such as insufficient active sites, low catalytic efficiency, and limited functionality. The introduction of a second or multiple metals into nanozymes significantly boosts their catalytic efficiency and multifunctionality through intermetallic electronic coupling and synergy. This review systematically summarizes the latest research progress on nanozymes composed of Fe, Mn, Cu, Pt, Au, Pd, Ga, Mo, Ni, and multi-metallic systems. It focuses on their applications in therapeutic interventions and health monitoring strategies, which encompass not only highly sensitive biosensing for disease biomarkers but also the detection and degradation of environmental pollutants that pose significant risks to human health. Finally, we outline key challenges and future prospects in critical areas ranging from atomically-precise synthesis and mechanistic studies to the development of smart systems and clinical translation.

Received 22nd October 2025
Accepted 26th November 2025

DOI: 10.1039/d5ra08106h

rsc.li/rsc-advances

1 Introduction

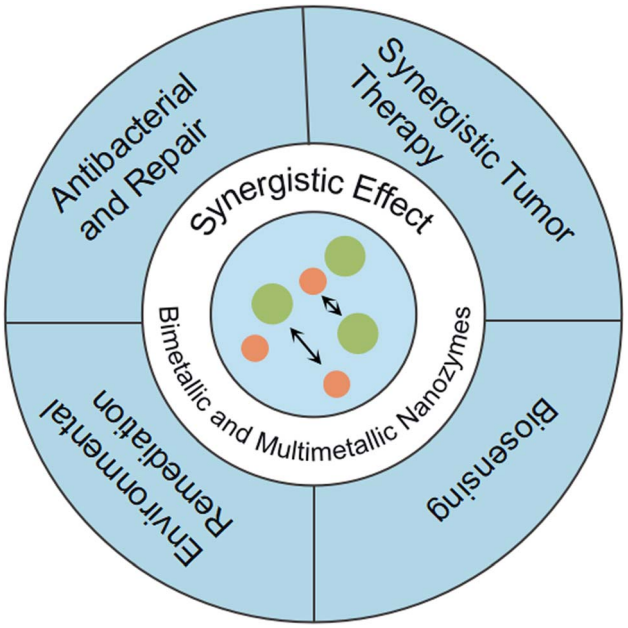
Nanozymes, as a class of nanomaterials with intrinsic enzyme-mimetic activities, have rapidly developed into a vibrant interdisciplinary frontier since the first report in 2007 that Fe_3O_4 nanoparticles exhibit peroxidase (POD)-like activity.[1–3] They integrate the unique physicochemical properties of nanomaterials (*e.g.*, high specific surface area, tunable size and morphology, and ease of functional modification) with the efficient catalytic characteristics of biological enzymes.[4] Consequently, they demonstrate significant advantages in terms of stability, cost-effectiveness, and large-scale preparation, making them highly promising alternatives to natural enzymes.[5–7] However, first-generation single-metal nanozymes face practical limitations. These include scarce active sites, slow reaction kinetics, poor substrate specificity, and a tendency to deactivate in complex biological or environmental media. These bottlenecks severely restrict the further improvement of their performance and the expansion of their application scope.

To overcome these limitations, research strategies have gradually shifted from single-metal components to multi-metal systems.[8] By deliberately introducing a second or multiple metal elements, bimetallic and multimetallic nanozymes achieve a leap in performance through electronic interactions, lattice strain effects, and synergistic catalytic mechanisms between different metals.[9,10] This "1 + 1 > 2" synergy significantly boosts catalytic activity, primarily by lowering reaction energy barriers through enhanced electron transfer. Additionally, it improves stability and introduces novel functions such as photothermal properties, magnetism, or stimulus responsiveness. Furthermore, incorporating multiple metals allows for precise, atomic-level regulation of the active centers' local coordination environment and electronic structure. This capability opens the door to mimicking the complex multi-center catalytic mechanisms of natural enzymes.[11]

Despite rapid progress, a timely, systematic review is still lacking. This review should categorize nanozymes by metal type, explore the mechanistic basis for their enhanced performance through metal synergy, and expand the application horizon to include the burgeoning field of environmental biomedicine. Most existing reviews tend to focus on a single metal or a specific application area, failing to provide a holistic and comparative perspective. This review is therefore motivated by the need to bridge this gap and offer a comprehensive knowledge framework that connects material design, synergistic catalysis, and multifaceted applications.

This review comprehensively surveys the latest advances in bimetallic and multimetallic nanozymes, encompassing systems from transition (*e.g.*, Fe, Mn, Cu) and noble metals (*e.g.*, Pt, Au, Pd) to those incorporating Ga, Mo, Ni, and even more complex multi-metallic systems (≥3 metals). We will delve into their diverse design and synthesis strategies, enhanced catalytic mechanisms (*e.g.*, POD-like, oxidase-like (OXD), catalase-like

Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University, Tongji Shanxi Hospital, Shanxi Province Engineering Research Center of Translational Drugs for Immune Diseases, Taiyuan, 030032, China. E-mail: zhangly@sxbqeh.com.cn



Scheme 1 Schematic illustration of the synergistic catalysis in bimetallic/multimetallic nanozymes and their cutting-edge applications. The core concept involves integrating two or more distinct metal elements (represented by green and orange spheres) within a single nanostructure. This integration induces electronic coupling and synergistic effects, which significantly enhance the catalytic activity and functionality of the nanozyme. These advanced nanozymes are then engineered for diverse applications aimed at improving health. This includes direct therapeutic applications such as targeted antibacterial therapy and tissue repair, and synergistic tumor therapy. It also encompasses health monitoring and preventive applications, which include highly sensitive biosensing for point-of-care diagnostics and environmental health monitoring through the detection and degradation of pollutants, thereby addressing health threats at their source.

(CAT), superoxide dismutase-like (SOD) activities), and focus on their innovative applications across the entire spectrum of health science. This includes direct therapeutic interventions (such as antibacterial therapy, anti-tumor therapy, tissue engineering, and immune regulation) as well as preventive and diagnostic strategies. The latter extends to environmental health, where the detection and degradation of pollutants serve as a crucial first line of defense against environmentally-induced diseases, thereby closing the loop between environmental quality and human health outcomes (Scheme 1). By summarizing general rules, analyzing challenges, and envisioning the future, this review intends to provide valuable references for researchers in related fields and promote the broader practical application of these intelligent catalytic materials.

1.1 Fe-based nanozymes

Nanozymes are a class of nanomaterials with enzyme-mimetic catalytic activities. Owing to their advantages such as high stability, tunability, and ease of large-scale preparation, they have become important alternatives to natural enzymes. Among various nanozymes, Fe-based nanozymes have attracted considerable attention due to their excellent POD-like activity and good biocompatibility. However, single-metal nanozymes often face challenges including insufficient active sites and low electron transfer efficiency. In recent years, the construction of Fe-based bimetallic nanozymes by introducing a second metal has significantly enhanced catalytic performance *via* electronic coupling and synergistic effects between metals, thereby expanding their applications in biosensing, antibacterial therapy, tumor therapy, and other fields.

Fe-based nanozymes exhibit great potential in biomedical fields, attributed to their natural enzyme-mimetic catalytic centers, favorable biocompatibility, and versatile valence transitions (Fe^{2+}/Fe^{3+}). The construction of bimetallic systems by incorporating a second metal (*e.g.*, Co, Ce, Mn, Cu, Pt) can significantly optimize the electronic structure of Fe active centers, enhance catalytic efficiency, and expand functional diversity. Fe-based bimetallic nanozymes have achieved a series of important advances in antibacterial therapy, synergistic tumor therapy, environmental remediation, and highly sensitive biosensing.

1.1.1 Applications in antibacterial therapy and tissue repair. Fe-based bimetallic nanozymes offer innovative strategies to treat drug-resistant bacterial infections and aid tissue repair. They function by catalyzing reactive oxygen species (ROS) production and modulating the immune microenvironment.

Fe–Co@D-Arg@PDA nanozymes significantly enhance Fenton-like catalytic activity through valence transitions and synergistic effects between Fe and Co. When integrated with a thermosensitive hydrogel and near-infrared (NIR)-triggered photothermal/nitric oxide (NO) gas therapy, this nanozyme forms a multifunctional platform for deep-tissue antibacterial action. This system effectively overcomes low bioavailability and drug resistance in treating bacterial corneal ulcers.[12] Fe/Cu-BBDC metal–organic framework (MOF) nanozymes are integrated into microneedle patches for infected wound treatment. Boronic acid modification enhances their specific recognition of sugars on bacterial surfaces. Utilizing the weakly acidic microenvironment of wounds and excessive H_2O_2, the nanozymes catalyze the generation of hydroxyl radicals ($^{\bullet}OH$) to achieve efficient bactericidal effects, significantly promoting wound healing.[13]

1.1.2 Applications in synergistic tumor therapy and immune regulation. Fe-based bimetallic nanozymes achieve efficient tumor suppression and immune microenvironment remodeling through the synergy of catalytic therapy with immunotherapy, photothermal therapy, and other modalities.

MET-CMS@FeTA (MCMSFT) nanozymes use hollow Cu_2MoS_4 as the core to load immune adjuvants, with an outer shell composed of an Fe^{3+}-tannic acid network. They possess triple enzyme activities (CAT, POD, and GPx), which can synergistically induce tumor cell apoptosis/ferroptosis/immunogenic cell death (ICD) by consuming GSH, generating $^{\bullet}OH$, and alleviating hypoxia. Additionally, they downregulate PD-L1 expression to reverse the immunosuppressive microenvironment.[14] The dis-SAzyme-Dox@M nanocomposite is based

on a single-atom nanozyme with dual Fe^{3+}/Cu^{2+} ionic sites, loaded with doxorubicin and coated with cancer cell membranes. This system can synergistically induce ferroptosis/cuproptosis, promote ROS generation and GSH consumption, polarize M1-type macrophages, and induce ferroptosis in M2-type macrophages. Combined with immune checkpoint blockade therapy, it significantly inhibits hepatocellular carcinoma growth.[15]

1.1.3 Applications in environmental health and safety. The impact of nanozymes extends beyond the clinic into the realm of public health and preventive medicine. Fe-based bimetallic nanozymes are being actively explored to mitigate health risks originating from environmental pollution, ensuring a safer ecosystem. The high catalytic activity and stability of Fe-based bimetallic nanozymes enable them to play an important role in environmental pollution control.

Fe–Mn dual-atom nanozymes (FeMn-DSAzymes) optimize the electronic configuration through strong electronic coupling between Fe and Mn dual atoms, significantly improving POD-like activity and catalytic degradation efficiency of paracetamol (PCM). This system is immobilized on melamine foam to construct a continuous flow reactor, realizing long-term and stable removal of pharmaceutical residues in water (Fig. 1a).[16] Fe–Ce-MOL two-dimensional nanozymes enhance the adsorption and activation capacity of H_2O_2 *via* electron transfer between Fe and Ce (dual variable-valence metals). Their POD-like activity is significantly superior to that of natural horseradish POD, and they have been successfully applied in bactericidal processes and the detection of antioxidants in fruits and vegetables (Fig. 1b).[17]

1.1.4 Applications in highly sensitive biosensing. The enhanced catalytic activity of Fe-based bimetallic nanozymes provides a powerful tool for constructing highly sensitive, multimodal sensing platforms.

Zr-MOFFe/CuPh bimetallic MOF nanozymes exhibit enhanced POD-like activity. Using this nanozyme as a single

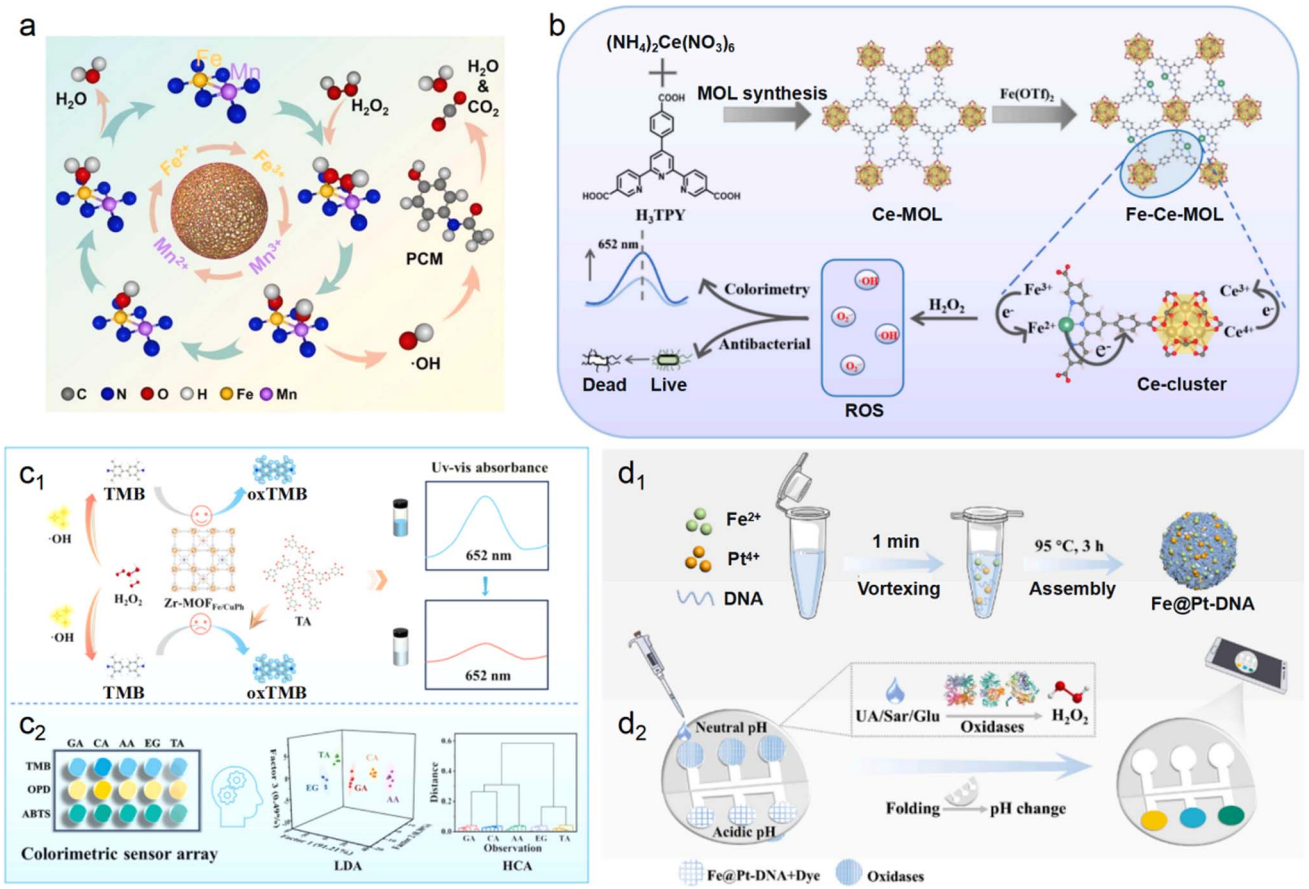


Fig. 1 (a) Schematic illustration of the continuous flow reactor based on FeMn dual-atom nanozymes (FeMn-DSAzymes) for long-term and stable degradation of PCM. Reproduced from ref. 16 with permission from Elsevier, copyright 2025; (b) the synthetic procedures of Fe–Ce-MOL nanozymes and their applications in bactericidal processes and antioxidant detection. Reproduced from ref. 17 with permission from Elsevier, copyright 2024; (c_1) schematic diagram of colorimetric detection of tannic acid based on the POD-like activity of Zr-MOFFe/CuPh bimetallic MOF nanozymes. (c_2) Colorimetric sensor array for the identification of five antioxidants using linear discriminant analysis (LDA) and hierarchical clustering analysis (HCA). (Abbreviations: TA: tannic acid, TMB: 3,3′,5,5′-tetramethylbenzidine, OPD: *o*-phenylenediamine, ABTS: 2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) ammonium salt, GA: gallic acid, CA: catechol, AA: ascorbic acid, EG: epigallocatechin gallate). Reproduced from ref. 18 with permission from Elsevier Ltd, copyright 2025; (d_1 and d_2) schematic illustration of the foldable paper-based analytical device (PAD) integrated with Fe@Pt-DNA nanozymes for the multi-target POCT of UA, sarcosine, and glucose. Reproduced from ref. 19 with permission from Elsevier, copyright 2025.

sensing receptor, a three-channel colorimetric sensor array is constructed by combining three chromogenic substrates (TMB, OPD, ABTS), enabling high-throughput identification of tannic acid and other antioxidants (Fig. 1c$_1$ and c$_2$).[18] Fe@Pt-DNA nanozymes precisely regulate the synergistic effect between Fe and Pt *via* a DNA programming strategy, showing excellent POD-like activity. Integrated into a foldable paper-based device and combined with smartphone readout, they realize multi-target point-of-care testing (POCT) of uric acid (UA), sarcosine, and glucose (Fig. 1d$_1$ and d$_2$).[19]

1.2 Mn-based nanozymes

As an important transition metal, Mn has attracted significant attention in nanozyme design due to its multi-valence (Mn^{2+}/Mn^{3+}/Mn^{4+}) transition properties and excellent biocompatibility. Mn-based nanozymes can mimic multiple enzyme activities, such as SOD, POD, CAT, and OXD. To regulate the electronic structure of Mn, optimize active sites, and enhance catalytic stability and specificity, a second metal can be introduced to construct bimetallic nanozymes. These materials thus hold broad prospects in disease therapy, biosensing, and environmental governance.

1.2.1 Applications in disease therapy. Mn-based bimetallic nanozymes play a crucial role in the treatment of tumors and inflammation-related diseases by catalyzing ROS metabolism, inducing cell death, or alleviating oxidative stress. In terms of tumor therapy, $MnFe_2O_4$ (MF) bimetallic nanozymes not only possess dual enzyme activities (CAT and POD) but also achieve dual targeting of CD44 and integrin αVβ3 through surface

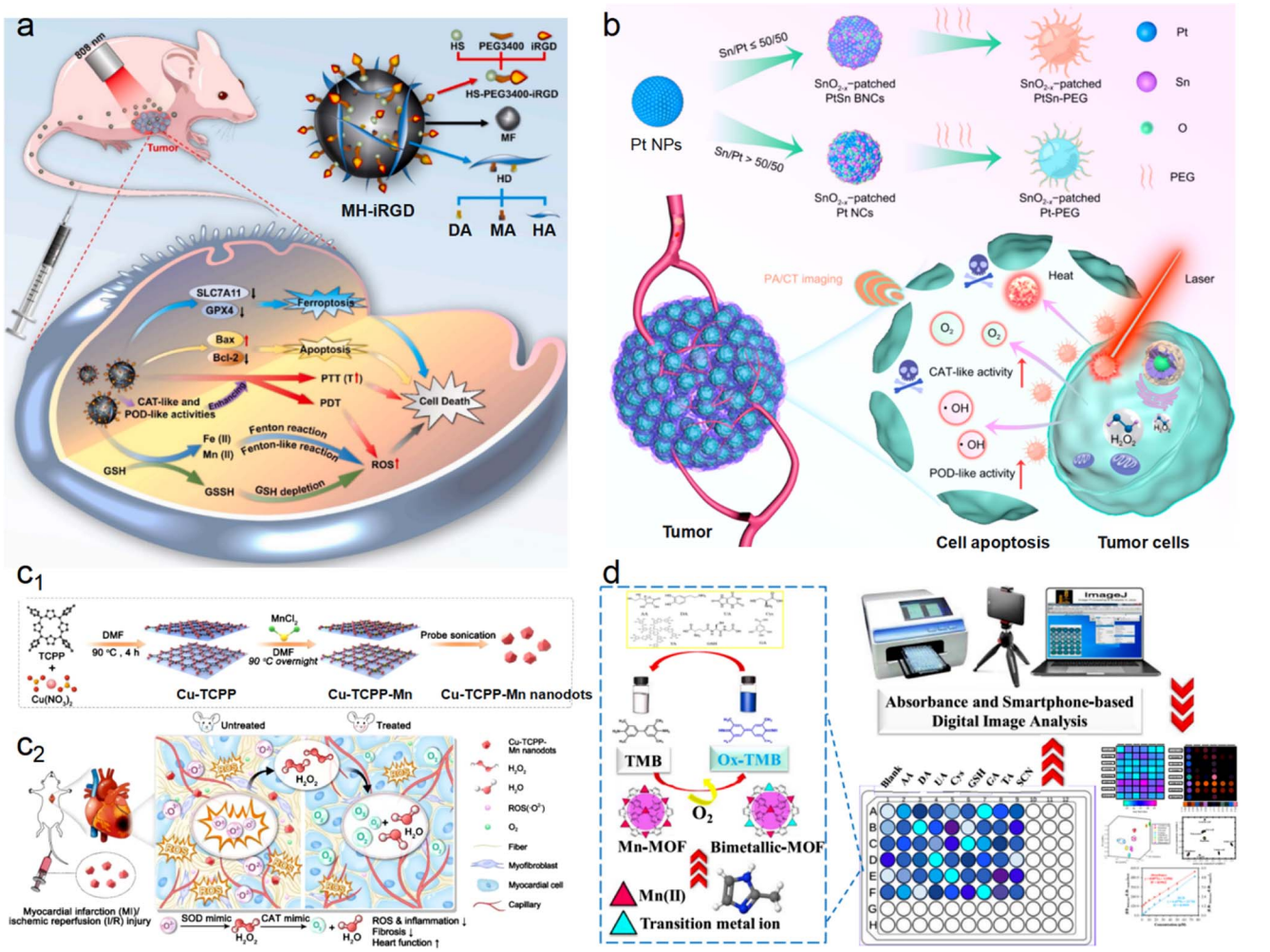


Fig. 2 (a) Schematic illustration of the composition of the MH-iRGD nanozyme ($MnFe_2O_4$ modified with iRGD and HA) and its application in dual-targeting, NIR-enhanced ferroptosis–apoptosis synergistic anti-tumor therapy for lung adenocarcinoma. Reproduced from ref. 20 with permission from Elsevier Science, copyright 2025; (b) schematic illustration of PtSn BNCs for phototheranostics and photothermal-enhanced catalytic therapy. Reproduced from ref. 21 with permission from American Chemical Society, copyright 2023; (c$_1$) fabrication process of the bimetallic Cu-TCPP-Mn nanozyme *via* a solvothermal method and subsequent sonication into nanodots. (c$_2$) Mechanism of the Cu-TCPP-Mn nanozyme in treating myocardial injury through ROS scavenging, inflammation inhibition, fibrosis reduction, and promotion of constructive remodeling and vascularization in MI and I/R injury models. Reproduced from ref. 22 with permission from Ivyspring International Publisher, copyright 2023; (d) schematic illustration of the dual spectral-RGB colorimetric sensor array constructed using Mn-based bimetallic MOF nanozymes with enhanced OXD-like activity for the simultaneous discrimination and determination of multiple antioxidants. Reproduced from ref. 24 with permission from American Chemical Society, copyright 2025.

modification with iRGD peptide and hyaluronic acid (HA). Under NIR light excitation, this system can synergistically induce ferroptosis/apoptosis and enhance photothermal/photodynamic therapeutic effects, providing a novel strategy for lung adenocarcinoma treatment (Fig. 2a).[20] On the other hand, PtSn bimetallic nanoclusters (PtSn BNCs), relying on their efficient photothermal conversion performance and dual enzyme catalytic activity, can catalyze H_2O_2 to generate ROS and O_2 under 808 nm laser excitation. This enables photothermally enhanced catalytic therapy while integrating CT/photoacoustic imaging functions, offering a new tool for integrated tumor diagnosis and treatment (Fig. 2b).[21]

In the field of myocardial protection, Cu-TCPP-Mn MOF nanozymes efficiently scavenge ROS by mimicking SOD/CAT cascade activities. In models of myocardial infarction (MI) and ischemia–reperfusion (I/R) injury, they exhibit excellent anti-inflammatory and antioxidant capabilities. These functions enable them to inhibit early inflammation, promote angiogenesis, and improve cardiac function, demonstrating long-term myocardial protective potential (Fig. 2c_1 and c_2).[22] Additionally, Ce–O–Mn asymmetric dual-atom nanozymes enhance electron transfer through oxygen-bridge-mediated heteronuclear active centers. After loading epigallocatechin gallate (EGCG) and modifying with HA, they achieve multimodal synergistic tumor catalytic therapy, highlighting the unique advantages of dual-atom centers in catalytic regulation.[23]

1.2.2 Applications in sensing and detection. Owing to their high catalytic activity and substrate diversity, Mn-based bimetallic nanozymes are widely used to construct highly sensitive, multimodal biochemical sensing platforms.

In one study, six types of Mn-based bimetallic MOF nanozymes (*e.g.*, Mn/Co, Mn/Zn, Mn/Fe, Mn/Ni) were synthesized. By regulating the metal ratio, their OXD-mimetic activity was significantly enhanced, enabling the catalytic color development of TMB. Based on this, a dual-mode (absorption spectroscopy/RGB imaging) sensor array was constructed. Combined with chemometric analysis, it realized high-throughput identification and detection of multiple antioxidants (Fig. 2d).[24] In environmental monitoring, Cu–Mn MOF nanozymes mimic the multi-copper active center of natural laccase. Their bimetallic synergistic effect significantly accelerates electron transfer, exhibiting superior catalytic activity and stability compared to natural laccase. This nanozyme has been used for the degradation of phenolic pollutants (*e.g.*, 2,4-dichlorophenol) and further integrated into a smartphone-assisted visual sensing platform. It enables portable, highly sensitive detection of phenol, showing promising application potential in the monitoring of pollutants in environmental water bodies.[25]

1.3 Cu-based nanozymes

Cu, an essential trace element in the human body, serves as the core active center of various natural enzymes (*e.g.*, SOD, tyrosinase). Cu-based nanozymes not only exhibit favorable catalytic activity and biocompatibility but also facilitate participation in redox reactions *via* their multi-valence (Cu^+/Cu^{2+}) transitions. The construction of bimetallic nanozymes by introducing a second metal can effectively regulate the local coordination environment and electron distribution of Cu, significantly enhancing its catalytic performance and stability. These nanozymes demonstrate broad potential in wound repair, tumor therapy, biosensing, and protein hydrolysis.

1.3.1 Applications in wound repair and anti-infection. Cu-based bimetallic nanozymes play a critical role in chronic wound treatment by scavenging ROS, alleviating inflammation, and promoting tissue regeneration. Cu/Mg-MOF nanozymes were combined with a thermosensitive hydrogel to construct an injectable wound dressing. This system not only promotes angiogenesis and collagen deposition but also effectively regulates the hyperoxidative stress and inflammatory microenvironment of diabetic wounds, significantly accelerating wound healing (Fig. 3a).[26] Another study reported CuBi-TA@BSA artificial metalloproteinases, where Bi regulates the electronic state of Cu to enhance its broad-spectrum RONS (reactive oxygen and nitrogen species) scavenging capacity. These nanozymes exhibit excellent biocompatibility in blood and cells, effectively protecting cells from oxidative damage and significantly promoting diabetic wound healing.[27]

1.3.2 Applications in tumor catalytic therapy. Leveraging the enzyme-mimetic activity and photothermal properties of Cu, Cu-based bimetallic nanozymes perform prominently in synergistic tumor therapy. CuPt bimetallic nanozymes were loaded into sulfonamide-modified dendrimers to construct an intelligent nanotheranostic platform (CPL@G5-BS). This system not only consumes GSH and generates $^{\bullet}OH$ to enhance chemodynamic efficacy but also possesses excellent photothermal conversion performance. Combined with the glycolysis inhibitor lonidamine, it can effectively alleviate tumor hypoxia, enabling synergistic therapy integrating photothermal, catalytic, and metabolic regulation (Fig. 3b).[28]

1.3.3 Applications in catalysis and sensing detection. Cu-based bimetallic nanozymes exhibit unique advantages in protein hydrolysis and highly sensitive biosensing. $CuCoO_2$ nanoproteases can efficiently catalyze peptide bond hydrolysis at room temperature, with an activity that is 100 000 times higher than previously reported nanoproteases. Surface Co^{3+} is responsible for activating peptide bonds, while Cu^+–OH acts as a nucleophilic group to attack the carbonyl carbon. The bimetallic synergy enables highly selective hydrolysis of peptide bonds containing hydrophobic amino acids, showing significant potential in the processing of insoluble proteins (*e.g.*, membrane proteins).[29]

In terms of sensing, Ag–Cu bimetallic nanozymes possess POD-like activity, which can be used for colorimetric detection of H_2O_2 (limit of detection, LOD = 13.3 μM) and electrochemical detection of glucose (LOD = 0.1 μM). This material can be immobilized on PTFE membranes or activated carbon fibers to construct reusable catalytic membranes, finding wide applications in environmental monitoring and biosensing (Fig. 3c_1 and c_2).[30] Additionally, core–shell structured Cu@MnO nanozymes exhibit excellent OXD-like activity, capable of catalyzing TMB color development within 1 minute. The UA detection method developed based on this nanozyme achieves over 90% sensitivity and specificity, making it suitable for clinical blood sample analysis (Fig. 3d).[31]

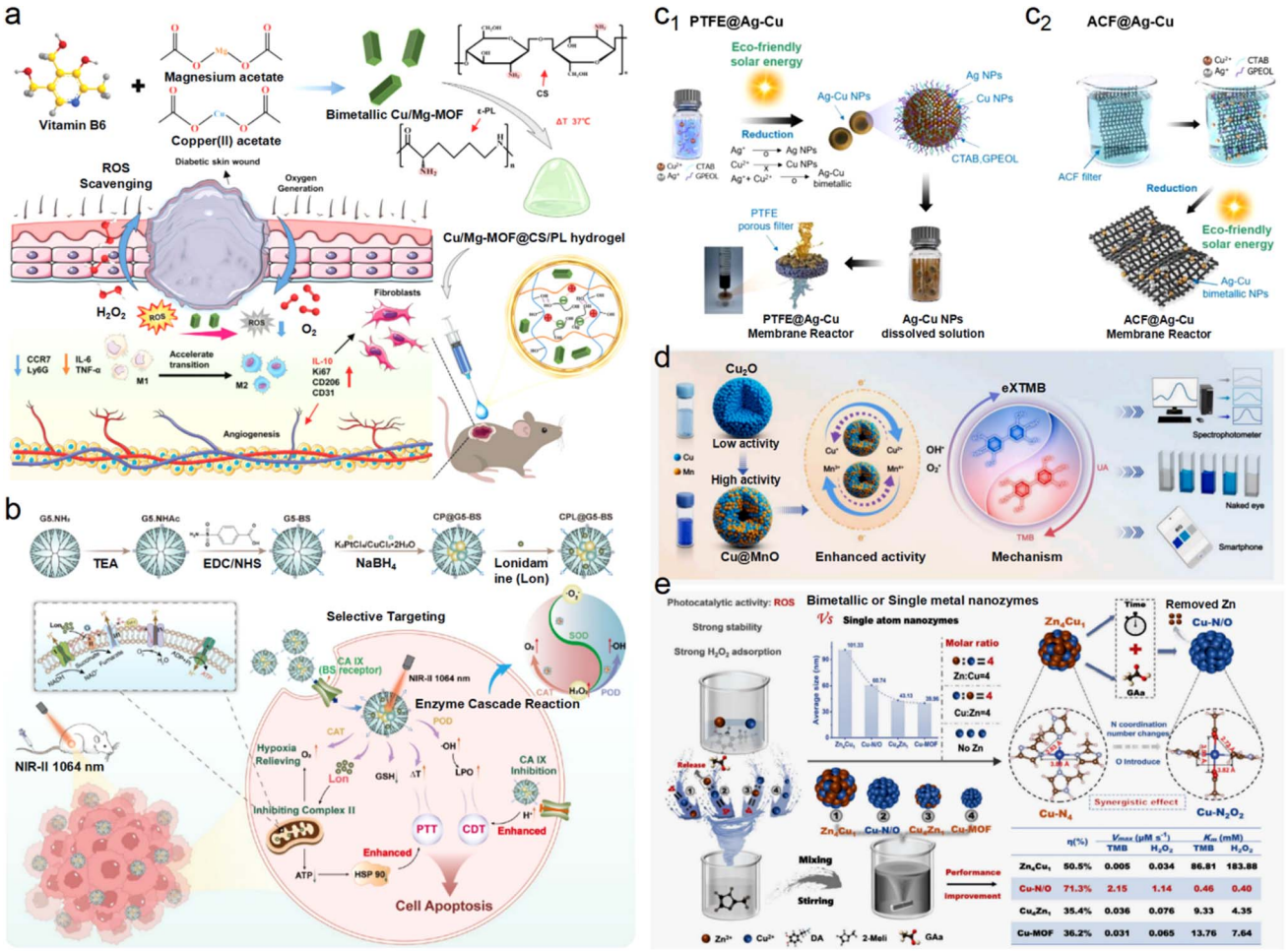


Fig. 3 (a) Preparation of a temperature-sensitive injectable hydrogel incorporating Cu/Mg bimetallic MOFs and its mechanism in modulating local angiogenesis and the inflammatory microenvironment in diabetic wounds. Reproduced from ref. 26 with permission from Wiley-VCH Verlag, copyright 2025; (b) schematic illustration of the therapeutic mechanism of the CPL@G5-BS nanoplatform (CuPt nanozymes loaded in sulfonamide-modified dendrimers) for lonidamine-assisted photothermal therapy and enhanced nano-enzymatic catalytic therapy. Reproduced from ref. 28 with permission from American Chemical Society, copyright 2025; (c_1) sunlight-mediated synthesis of Ag–Cu bimetallic nanostructures and their immobilization on a PTFE membrane to construct a catalytic filter. (c_2) Sunlight-mediated synthesis of an ACF@Ag–Cu catalytic membrane for industrial wastewater treatments. Reproduced from ref. 30 with permission from Wiley-VCH Verlag, copyright 2025; (d) schematic description of the core–shell Cu@MnO nanozyme as a colorimetric biosensor for the rapid detection of UA. Reproduced from ref. 31 with permission from Elsevier, copyright 2025; (e) schematic diagram of the synthesis and structural optimization process for Cu single-atom nanozymes (Cu–N/O) *via* a cascade competition strategy using different volumes of GAa and etching times. Reproduced from ref. 32 with permission from Wiley-VCH Verlag, copyright 2025.

1.3.4 Novel synthesis strategies and structural regulation. Precise regulation of the coordination structure of Cu is key to improving its catalytic performance. A study adopted a cascade competition strategy, using glacial acetic acid (GAa) as the medium to synthesize single-atom nanozymes with a Cu–N_2O_2 coordination structure in one step from a Zn_4Cu_1 precursor. This strategy enables selective etching of Zn sites and precise reconstruction of the local environment of Cu, significantly enhancing its POD activity and photothermal properties (Fig. 3e).[32]

1.4 Pt-based nanozymes

Pt-based nanozymes have attracted significant attention in biomedical and environmental detection fields due to their outstanding catalytic activity, stability, and nearly 100% atomic utilization efficiency. The construction of bimetallic systems by introducing a second metal (*e.g.*, Ir, Re, Pd, Cu) can effectively regulate the electronic structure of Pt, enhance its catalytic selectivity, and reduce costs. These nanozymes exhibit unique advantages in the treatment of cardiovascular and cerebrovascular diseases, synergistic tumor therapy, pesticide detection, and tumor microenvironment (TME) regulation.

1.4.1 Applications in the treatment of cardiovascular and cerebrovascular diseases. Pt-based bimetallic nanozymes provide innovative therapeutic strategies for diseases such as MI by efficiently scavenging ROS and regulating the immune microenvironment. PtIr bimetallic nanozymes possess an ultrasmall size (<5 nm) and dual enzyme-mimetic activities (SOD/CAT), enabling efficient ROS scavenging and protection of mitochondrial function in cardiomyocytes. In a rat MI model,

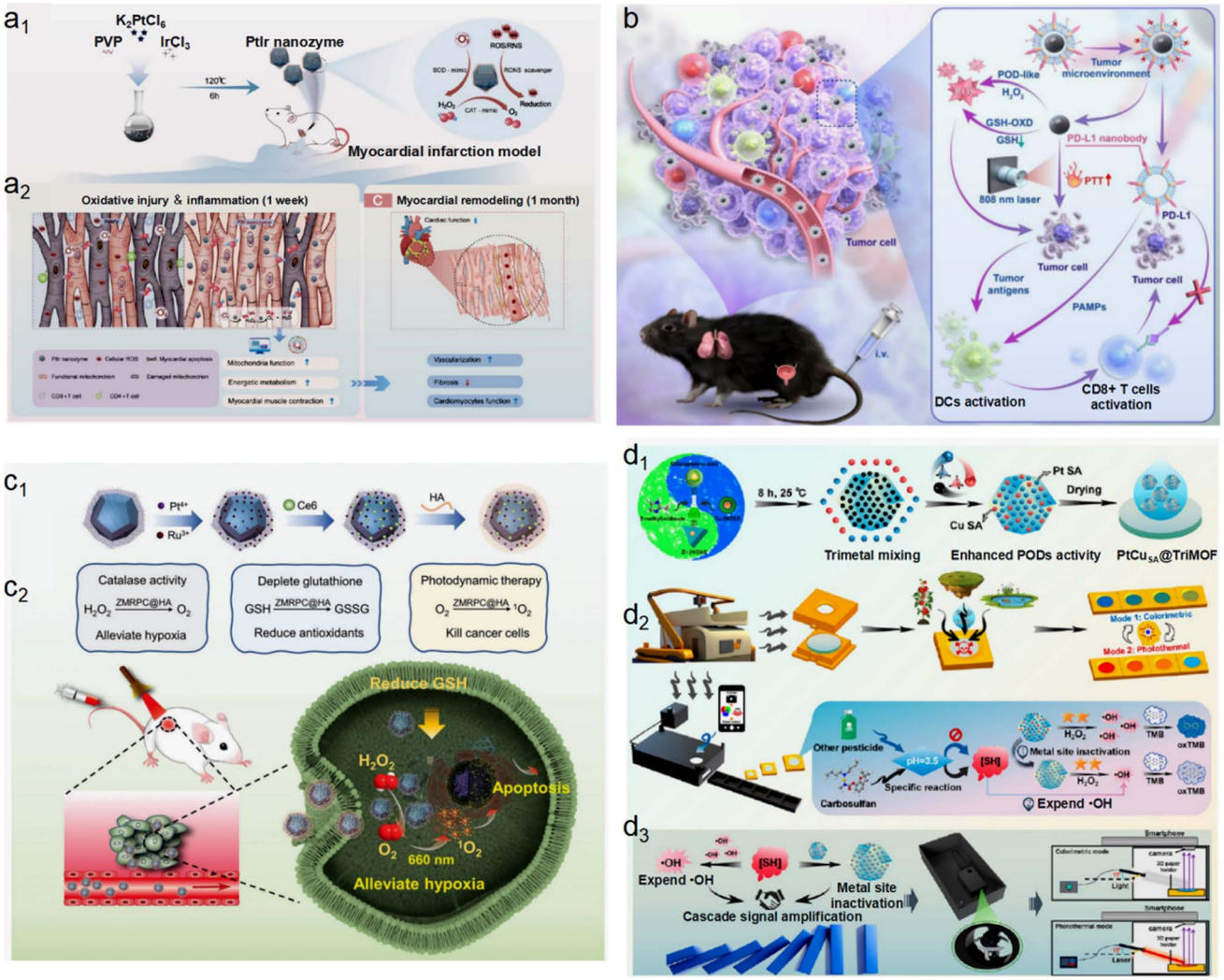


Fig. 4 (a) Synthesis and therapeutic mechanism of ultrasmall PtIr bimetallic nanozymes for treating MI *via* ischemic/inflammatory cardiac microenvironment remodeling. Reproduced from ref. 33 with permission from American Chemical Society, copyright 2025; (b) schematic illustration of the preparation of RePd@OMVs$^{PD\text{-}L1\ nb}$ biomimetic immune organoids and the combined nanozyme-catalyzed photothermal-immunotherapy strategy for effective tumor eradication. Reproduced from ref. 35 with permission from Wiley, copyright 2025; (c_1) fabrication process of the ZMRPC@HA nanozyme (Ru^{3+} and Pt^{4+} loaded into Zr^{4+}-MOFs and modified with HA). (c_2) Mechanism of ZMRPC@HA nanoparticle-triggered PDT for hypoxic tumors, accompanied by O_2 generation and GSH depletion. Reproduced from ref. 36 with permission from John Wiley and Sons Ltd, copyright 2023; (d_1) synthesis procedure of the PtCuSA@TriMOF derived from a trimetallic MOF. (d_2) Specific detection mechanism of carbosulfan by the PCSSIF sensor. (d_3) Cascade signal sensitization diagram for pesticide residue detection. Reproduced from ref. 37 with permission from American Chemical Society, copyright 2025.

these nanozymes significantly improved cardiac contractile function, reduced infarct size and fibrosis by inhibiting neutrophil extracellular trap (NET) formation, decreasing cell apoptosis and inflammatory responses, and activating energy metabolism pathways such as fatty acid β-oxidation. This realizes multi-target remodeling of the ischemic/inflammatory microenvironment (Fig. 4a).[33]

1.4.2 Applications in synergistic tumor therapy and TME regulation. Pt-based bimetallic nanozymes significantly enhance anti-tumor efficacy through the synergy of catalytic therapy with immunotherapy, photothermal therapy, and other modalities, while simultaneously regulating the TME to overcome therapeutic resistance. The modulation of the TME by alleviating hypoxia, consuming glutathione (GSH), and disrupting antioxidant defenses is pivotal for amplifying synergistic effects and achieving long-term tumor suppression.[34] For instance, Re–Pd bimetallic nanozymes exhibit remarkably enhanced POD-like and glutathione oxidase (GSHOx) activities *via* orbital hybridization between Re and Pd. These nanozymes are encapsulated in bacterial outer membrane vesicles (OMVs) expressing PD-L1 nanobodies, constructing biomimetic immune organoids (RePd@OMVs$^{PD\text{-}L1\ nb}$). This system releases nanozymes in the TME to consume GSH and enhance oxidative stress, while PD-L1 nanobodies block immunosuppressive signals. Combined with photothermal effects to induce ICD, it effectively eliminates bladder cancer metastases and inhibits recurrence (Fig. 4b).[35]

Similarly, ZMRPC@HA nanozymes, a typical example of bimetal-functionalized MOFs, simultaneously load Ru^{3+} and

Pt^{4+} into Zr^{4+}-MOFs and are further modified with HA. These nanozymes not only catalyze the decomposition of H_2O_2 to generate O_2, alleviating hypoxia, but also consume GSH to disrupt the tumor antioxidant defense system. This dual action significantly enhances the efficacy of photodynamic therapy (PDT) against hypoxic tumors, providing new insights for the design of multifunctional nanozymes (Fig. $4c_1$ and c_2).[36]

By unifying the discussions on synergistic therapy and TME regulation, this section emphasizes how Pt-based bimetallic nanozymes holistically address key challenges in tumor treatment, such as immunosuppression, metabolic adaptation, and oxidative stress resilience. This integrated perspective not only clarifies the mechanistic links between different application strategies but also underscores the versatility of Pt-based nanozymes in advancing precision oncology.

1.4.3 Applications in sensing and detection. The high catalytic activity and stability of Pt-based bimetallic nanozymes make them ideal platforms for highly sensitive sensing and detection. PtCu diatomic nanozymes (PtCuSA@TriMOF) are derived from trimetallic MOF. The synergistic effect between Pt–Cu diatomic sites significantly reduces the energy barrier for H_2O_2 reduction, enabling efficient oxidation of TMB to generate colorimetric/photothermal dual-mode signals. This system establishes a highly specific dual-inhibition detection mechanism, where the acidic hydrolysis product of fenitrothion inhibits hydroxyl radical generation and enzyme activity. A portable flexible sensor developed based on this mechanism, combined with smartphone readout, realizes *in situ* and highly sensitive detection of pesticide residues (LOD = 4.2 nM) (Fig. $4d_1$–d_3).[37]

1.5 Au-based nanozymes

Au nanomaterials are ideal platforms for constructing high-performance nanozymes due to their excellent biocompatibility, easy modifiability, and unique optical properties. The formation of bimetallic nanozymes by introducing a second metal (*e.g.*, Pt, Ru, Os, Pd) can effectively regulate the surface electronic structure and local coordination environment of Au, significantly enhancing its catalytic activity, stability, and functional diversity. Au-based bimetallic nanozymes exhibit broad application prospects in tissue regeneration, disease therapy, biosensing, and synergistic tumor therapy.

1.5.1 Applications in tissue regeneration. Au-based bimetallic nanozymes play a key role in the treatment of chronic diseases by regulating the pathological microenvironment, scavenging ROS, and promoting tissue repair. Au@Pt nanozymes were encapsulated in GelMA hydrogel microspheres for diabetic bone regeneration. These nanozymes possess dual enzyme-mimetic activities (glucose oxidase-like (GOx) and CAT-like), enabling simultaneous glucose consumption and ROS scavenging. This effectively protects the proliferation and osteogenic differentiation capabilities of bone marrow mesenchymal stem cells (BMSCs) in a high-glucose environment. In a rat model of diabetic bone defects, this system significantly promoted angiogenesis and bone tissue regeneration.[38] Another study developed a cardiac-targeting bimetallic cluster nanozyme (ATBMzyme) with an AuRu core modified with atrial natriuretic peptide (ANP). This nanozyme has ultra-strong antioxidant activity and can specifically target cardiac tissue. By alleviating ferroptosis and PANoptosis, it effectively mitigated doxorubicin-induced cardiomyopathy (DIC), providing an innovative strategy for cardiac protection (Fig. $5a_1$ and a_2).[39]

1.5.2 Applications in biosensing and environmental detection. The high catalytic activity and stability of Au-based bimetallic nanozymes make them ideal tools for constructing highly sensitive, multi-modal sensing platforms. Au@Pt, Au@Os, and Au@Pd nanozymes exhibit excellent POD-like activity, with stability superior to that of natural enzymes. Based on the differential inhibition of their enzyme activity after interaction with phenolic acids, combined with chemometric algorithms, a colorimetric sensor array was successfully constructed. This array enables highly sensitive identification of 7 phenolic acids (*e.g.*, chlorogenic acid, gallic acid) and their mixtures (LOD = 0.005–0.01 mM), and its reliability was verified in the detection of actual water samples (Fig. $5b_1$ and b_2).[40]

In terms of sensing mechanism research, DNA-programmed Au/Pt bimetallic nanozymes achieve precise regulation of nanozyme morphology and POD-like activity by using DNA with different sequences (*e.g.*, polyT) to mediate the *in situ* growth of Pt on the surface of gold nanorods (AuNRs). A colorimetric sensor array constructed based on this system can efficiently distinguish 5 biological thiols (*e.g.*, GSH, cysteine), providing a new method for biomarker detection (Fig. $5c_1$ and c_2).[41]

1.5.3 Applications in synergistic tumor therapy and nanomotors. Au-based bimetallic nanozymes achieve deep tumor penetration and synergistic therapy through the combination of catalytic therapy, photothermal therapy, and dynamic propulsion. Parachute-like Au_2Pt@PMO@ICG Janus nanomotors (APIJNs) integrate bimetallic nanozymes with the photosensitizer ICG, and possess dual-source propulsion capabilities (autonomous catalysis and photothermophoresis). Their Au_2Pt core has dual POD/CAT enzyme activities, which can catalyze H_2O_2 to generate ROS and O_2 while producing a photothermal effect. Under NIR laser irradiation, this system enables deep tumor penetration and synergistic triple therapy (photothermal/photodynamic/chemodynamic therapy, PTT/PDT/CDT), significantly enhancing anti-tumor effects (Fig. 5d).[42]

1.5.4 Structure–activity relationship research and rational design. In-depth understanding of the structure–activity relationship of Au-based bimetallic nanozymes is key to realizing their rational design. A study synthesized Au–Pt bimetallic aerogels with three structures (alloy, core–shell, and heterojunction), and systematically revealed their structure–performance relationship. Among them, the heterojunction structure exhibited the highest glucose cascade catalytic activity due to its abundant Au–Pt interfaces and synergistic effects. Based on this, a highly sensitive and portable glucose detection kit was developed.[43] Another study adopted a DNA programming strategy, achieving precise regulation of the growth process and enzyme-mimetic activity of Au/Pt nanozymes by adjusting DNA sequences (*e.g.*, T15). This was further applied to the highly sensitive detection of ascorbic acid (AA) and alkaline phosphatase (ALP).[44]

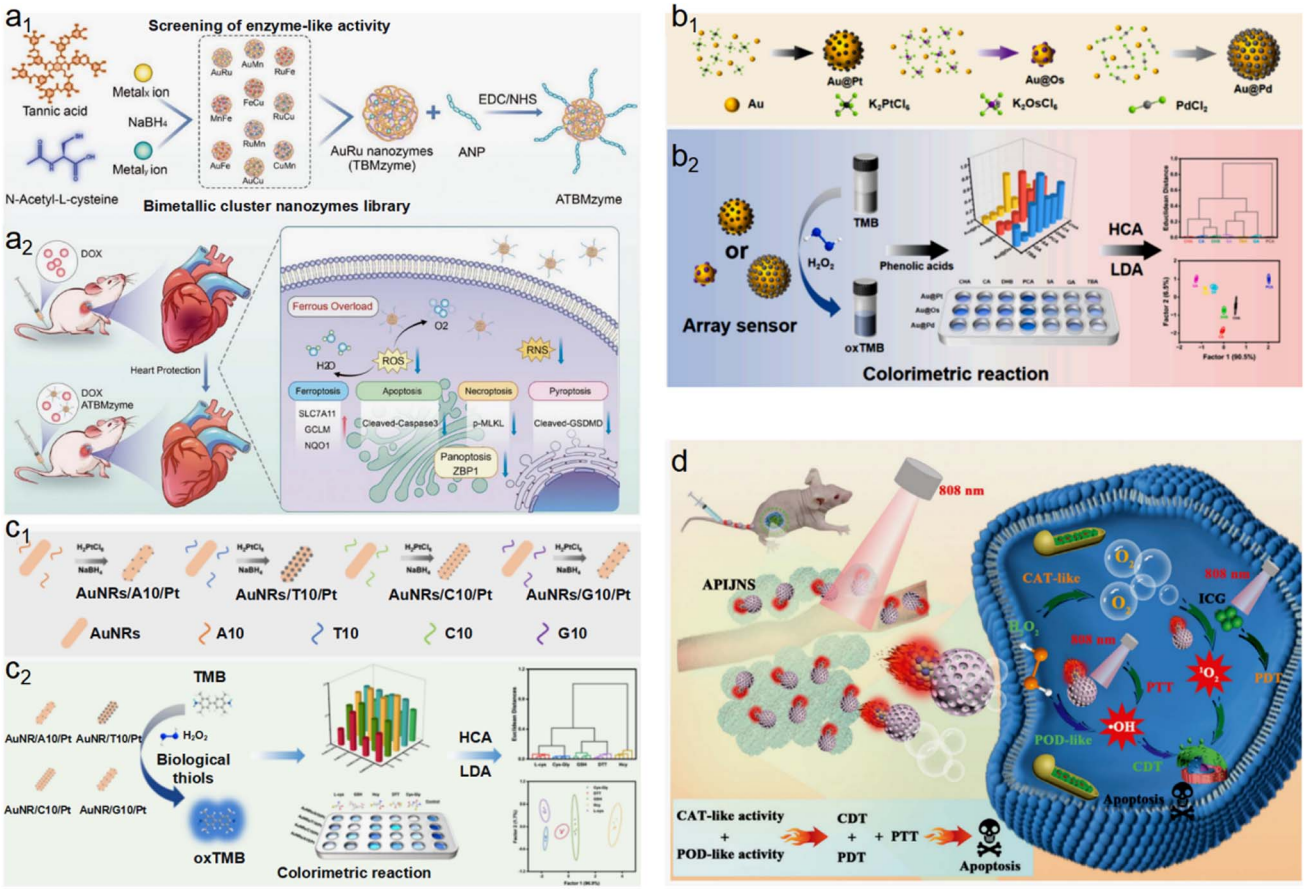


Fig. 5 (a_1) Preparation of the bimetallic cluster nanozyme library and the cardiac-targeted ATBMzyme (AuRu core modified with atrial natriuretic peptide). (a_2) Application of the cardiac-targeted ATBMzyme for the treatment of DIC by alleviating ferroptosis and PANoptosis. Reproduced from ref. 39 with permission from Wiley-VCH Verlag, copyright 2025; (b) schematic diagram showing the fabrication of the colorimetric sensor array for phenolic acids detection using Au-based bimetallic nanozymes (Au@Pt, Au@Os, Au@Pd), assisted by machine learning. Reproduced from ref. 40 with permission from Elsevier, copyright 2024; (c_1) synthesis of the DNA-programmed Au/Pt bimetallic nanozyme. (c_2) Schematic of the colorimetric sensing system for identifying various biological thiols. Reproduced from ref. 41 with permission from American Chemical Society, copyright 2024; (d) schematic illustration of the parachute-like APIJNs for synergistic CDT/PTT/PDT cancer therapy. Reproduced from ref. 42 with permission from Wiley-VCH Verlag, copyright 2024.

1.6 Pd-based nanozymes

Pd-based nanozymes have attracted widespread attention in the biomedical field due to their unique electronic structure, tunable redox properties, and favorable catalytic activity. The construction of bimetallic nano-systems by introducing a second metal (*e.g.*, Ir, Re, Sn) can effectively optimize the catalytic sites of Pd, enhance electron transfer efficiency, and improve its biocompatibility. Pd-based bimetallic nanozymes exhibit significant advantages in ultra-sensitive diagnosis, synergistic tumor therapy, and immune regulation, serving as an important platform for cutting-edge biomedical applications.

1.6.1 Applications in ultra-sensitive biomedical diagnosis. Leveraging their outstanding enzyme-mimetic activity, Pd-based bimetallic nanozymes are widely used in *in vitro* diagnostic fields, significantly improving detection sensitivity and accuracy. Pd@Ir core–shell nanozymes possess excellent POD-like activity, and their bimetallic synergistic effect remarkably enhances catalytic efficiency. The research team innovatively combined them with *in situ* catalyzed reporter deposition (ISCRD) technology and applied the combination to a lateral flow immunoassay (LFIA) platform, enabling ultra-sensitive detection of gastric cancer biomarkers (PG I and PG II). This method achieves a visual LOD of 10 pg mL^{-1}, with a sensitivity 200 times higher than that of traditional methods. It has also been successfully validated for accurate identification in clinical serum samples, providing a powerful tool for early cancer diagnosis.[45]

1.6.2 Applications in synergistic tumor therapy and immune regulation. Through the multimodal synergy of catalytic therapy, photothermal therapy, and immunotherapy, Pd-based bimetallic nanozymes achieve efficient tumor inhibition and immune microenvironment remodeling. A study reported homologous cell membrane-modified PdSn@mSiO_2 nanozymes. This system possesses triple enzyme activities (POD, CAT, and GPx) and can generate a photothermal effect (photothermal conversion efficiency of 30.9%) under NIR laser excitation, realizing photothermally enhanced catalytic therapy. Mouse 4T1 tumor models demonstrated that these nanozymes can be efficiently enriched at tumor sites, and through the synergy of multi-ROS regulation and hyperthermia, they

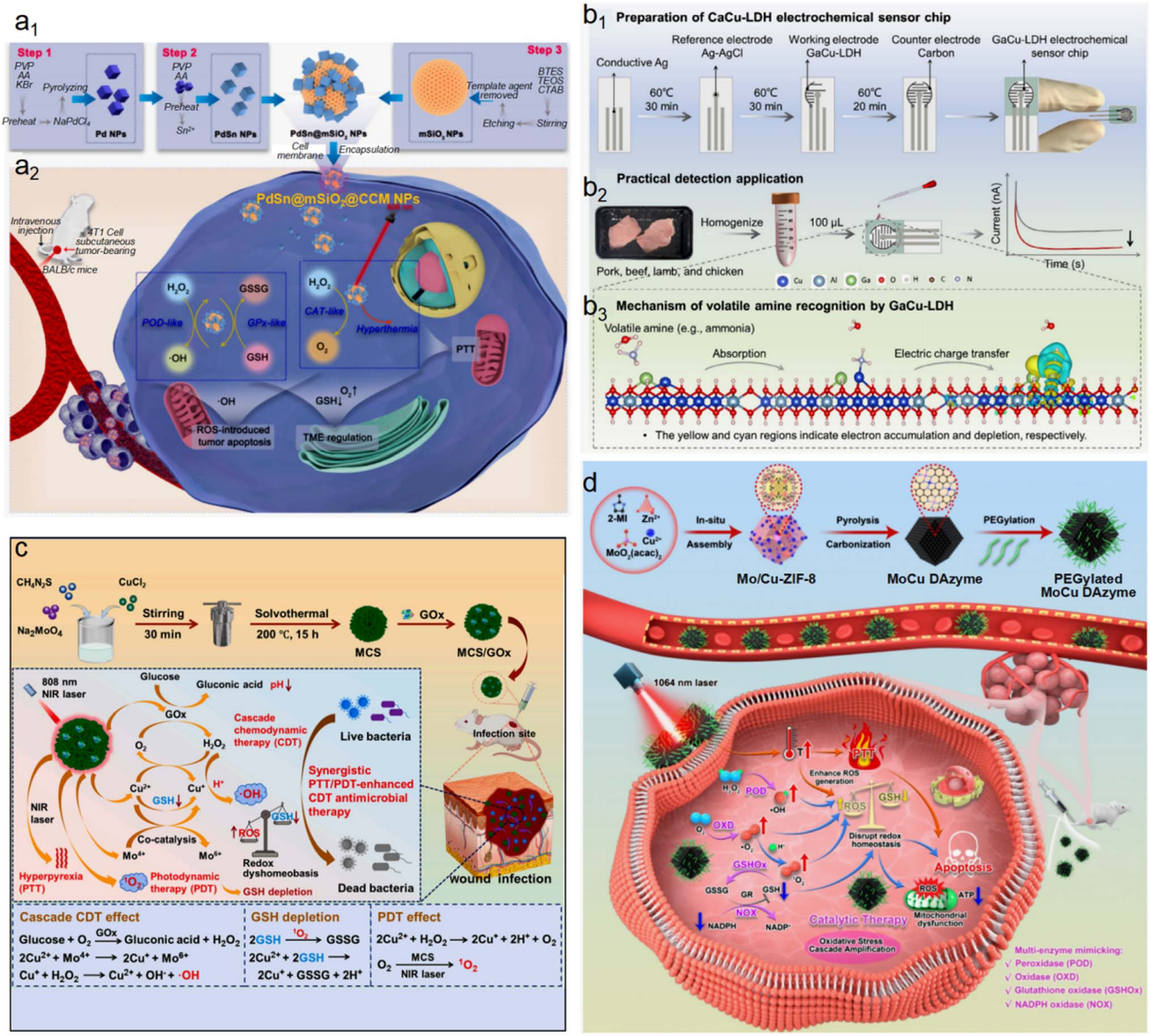


Fig. 6 (a_1) Schematic diagram of the synthesis process of homologous cell membrane-modified PdSn@mSiO$_2$ nanozymes. (a_2) Schematic illustration depicting the photothermal effect and photothermal-enhanced catalytic therapy mediated by PdSn@mSiO$_2$ NPs. Reproduced from ref. 46 with permission from Elsevier, copyright 2025; (b) preparation and practical detection application of the Ga–Cu dual single-atom nanozyme (GaCu-LDH) electrochemical sensing chip for rapid amine detection in meat freshness monitoring. Reproduced from ref. 48 with permission from Wiley-VCH Verlag, copyright 2025; (c) schematic illustration of the synthesis of the MoCuS$_x$/GOx cascade nanozyme and its applications in treating wound infections *via* synergistic photothermal/photodynamic/chemodynamic antimicrobial therapy. Reproduced from ref. 49 with permission from Elsevier, copyright 2024; (d) schematic illustration of the fabrication process and the multi-enzyme mimetic activities of the PEGylated MoCu DAzyme for synergistic catalytic and photothermal cancer therapy. Reproduced from ref. 50 with permission from John Wiley and Sons Ltd, copyright 2025.

significantly inhibit tumor growth and exhibit good biocompatibility (Fig. 6a_1 and a_2).[46]

1.7 Ga-based nanozymes

As an emerging class of enzyme-mimetic catalysts, Ga-based nanozymes exhibit significant potential in the biomedical field, leveraging the multi-valence properties of Ga, excellent biocompatibility, and its unique "pseudo-iron" biological effect. The construction of diatomic or dual single-atom nanozymes by introducing a second metal (*e.g.*, Zn, Cu) enables precise regulation of the electronic structure and coordination environment of active sites, achieving synergistic catalysis and dynamic functional transformation. Important progress has been made in applications such as tumor therapy and biosensing.

1.7.1 Applications in tumor catalytic therapy and ferroptosis induction. Ga-based bimetallic nanozymes realize synergistic catalytic and metabolic therapy for tumors by mimicking multiple enzyme activities and releasing ions to interfere with metabolism. Ga/Zn diatomic nanozymes (Ga/Zn-NC) possess

well-defined geometric and electronic structures, and can mimic POD and GSHOx activities. The Ga–Zn metal bond significantly accelerates electron transfer and reduces reaction energy barriers. In the TME, these nanozymes induce oxidative damage by catalyzing the production of ROS and consuming GSH, rendering tumor cells sensitive to ferroptosis. More uniquely, the Ga^{3+} ions released during catalysis exert a "pseudo-iron" effect, which competitively interferes with cellular iron metabolism and activates a self-amplifying ferroptosis pathway. This action synergizes with catalytic therapy to significantly inhibit tumor growth.[47]

1.7.2 Applications in biosensing and rapid detection. The multi-enzyme activity and electronic regulation capability of Ga-based bimetallic nanozymes provide a new platform for highly sensitive and rapid biosensing. Ga–Cu dual single-atom nanozymes are constructed using a two-dimensional layered double hydroxide (LDH) support, exhibiting multiple enzyme-mimetic activities (POD-like, OXD-like, CAT-like, and GPx-like). The synergistic doping of Ga and Cu enhances material stability and catalytic efficiency, among which the formation of Cu–N bonds significantly improves the recognition ability for volatile amines. A portable electrochemical sensor developed based on this nanozyme enables the detection of amine substances within 4 seconds, with a linear range of 0.05–0.4 mM and a LOD as low as 5.9 μM, along with good repeatability and stability. This sensor has been successfully applied to the rapid freshness detection of meat products, such as pork and beef, and the results are highly consistent with standard methods. It thus provides an efficient solution for on-site food monitoring (Fig. 6b_1–b_3).[48]

1.8 Mo-based nanozymes

Mo-based nanozymes exhibit enormous potential in catalysis and biomedical fields, attributed to the rich valence states (Mo^{4+}/Mo^{5+}/Mo^{6+}) of Mo and its excellent electron transfer capability. The construction of bimetallic systems by introducing a second metal (*e.g.*, Cu) can effectively optimize the local coordination environment of Mo, generate significant synergistic effects, and greatly enhance its enzyme-mimetic activity and functional diversity. Mo-based bimetallic nanozymes have achieved important progress in antibacterial therapy and synergistic tumor therapy.

1.8.1 Applications in antibacterial therapy and wound healing. Through cascade catalysis and multimodal synergy, Mo-based bimetallic nanozymes effectively address the challenges of substrate deficiency and microenvironmental limitations in antibacterial therapy. The $MoCuS_x$/GOx cascade nanozyme constructs a high-efficiency catalytic-therapeutic platform by integrating natural GOx with bimetallic sulfide $MoCuS_x$ nanozymes. GOx consumes glucose in the local wound area, simultaneously generating H_2O_2 and acidifying the microenvironment. This provides both the necessary substrate and a suitable pH for the POD-like activity of $MoCuS_x$, enabling the cascade generation of $^{\bullet}OH$. The co-catalytic effect of Mo^{4+}/Mo^{6+} and Cu^{+}/Cu^{2+} redox couples further enhance catalytic efficiency. Under 808 nm NIR laser irradiation, this system can also generate a photothermal effect and singlet oxygen ($^1O_2$), synergizing PDT and CDT, while efficiently consuming the antioxidant GSH. *In vitro* and *in vivo* experiments show that this platform exerts efficient combined bactericidal effects against *Staphylococcus aureus* and *Escherichia coli*, significantly promotes the healing of infected wounds, and demonstrates good biosafety (Fig. 6c).[49]

1.8.2 Applications in synergistic tumor therapy. By virtue of multi-enzyme mimetic activities and photothermal properties, Mo-based bimetallic nanozymes achieve efficient catalytic-photothermal synergistic tumor therapy. The MoCu dual-atom nanozyme (MoCu DAzyme) possesses well-defined dual-atom active sites and exhibits multiple enzyme-mimetic activities (including POD-like, OXD-like, CAT-like, *etc.*). Compared with Mo single-atom nanozymes, the introduction of Cu atoms forms a synergistic catalytic center, which significantly enhances substrate adsorption capacity and reduces reaction energy barriers. This nanozyme can not only generate ROS in a diversified manner but also efficiently consume GSH and block its regeneration pathway, thereby triggering a cascade amplification effect of oxidative stress. In addition, its amorphous nitrogen-doped carbon matrix endows it with excellent photothermal conversion performance. Through the synergy of enzyme-mimetic catalytic therapy and photothermal therapy, MoCu DAzyme realizes efficient tumor inhibition, providing new insights into nano-catalytic cancer therapy (Fig. 6d).[50]

1.9 Ni-based nanozymes

Ni-based nanozymes have attracted widespread attention in biosensing, environmental monitoring, and medical diagnosis due to their low cost, variable valence states (Ni^{2+}/Ni^{3+}), and favorable catalytic activity. The construction of bimetallic systems by introducing a second metal (*e.g.*, Os, Co, Fe, Pt) can effectively regulate the electronic structure of Ni, generate synergistic effects, and significantly enhance its enzyme-mimetic activity, stability, and substrate specificity. Ni-based bimetallic nanozymes demonstrate important value in highly sensitive detection, cancer screening, and environmental pollution control.

1.9.1 Applications in highly sensitive biosensing and immunoassays. Leveraging their enhanced POD-like activity, Ni-based bimetallic nanozymes are widely used for the highly sensitive detection of disease biomarkers. HA-Ni_2/Os nanozymes are synthesized by incorporating Ni and osmium (Os) into HA. Their POD-like activity (1224 U mg^{-1}) is more than twice that of single-metal Os nanozymes. Theoretical calculations indicate that Ni doping enhances the adsorption of H_2O_2 and accelerates the oxidation of TMB. After cross-linking with antibodies, this nanozyme is used to detect the lung cancer marker squamous cell carcinoma antigen (SCCA), exhibiting better stability than natural horseradish peroxidase (HRP) and providing a reliable alternative for immunoassays.[51]

NiCo Prussian blue analog (PBA) nanozymes, through bimetallic doping and the introduction of oxygen vacancies, show 30.08-fold and 4.83-fold increases in POD and CAT activities compared to single-metal materials, respectively. Based on

the cascade catalysis principle where GOx generates H_2O_2 and NiCo PBA catalyzes color development or decomposes it, this system enables dual-mode detection of carcinoembryonic antigen (CEA), achieving LOD of 0.061 ng mL^{-1} in POD mode and 0.028 ng mL^{-1} in CAT mode, which significantly improves detection sensitivity.[52]

1.10 Applications in environmental health monitoring

Monitoring hazardous substances in the environment is a critical aspect of public health protection. Ni-based bimetallic nanozymes, with their high catalytic activity and stability, serve as effective tools for the early detection of such health threats. The high catalytic activity and stability of Ni-based bimetallic nanozymes make them effective tools for monitoring hazardous substances in the environment. Ni–Pt@PAM nanozymes significantly enhance POD-like activity through surface ligand engineering (modified with polyacrylamide hydrochloride, PAM). Based on the specific reaction between penicillin (PCN) and $^{\bullet}OH$, this system develops a colorimetric and fluorescent dual-mode sensing platform, enabling rapid detection of PCN in water samples with a linear range of 0.5–10 μM and an LOD as low as 13.5 nM.[53]

NiFe bimetallic hydrogels (3-QW-NiFe) possess both POD-like and OXD-like activities, with their catalytic mechanisms based on the generation of $^{\bullet}OH$ and superoxide anions ($O_2^{\bullet-}$), respectively. A colorimetric sensor constructed based on POD-like activity enables specific detection of resorcinol (LOD = 0.033 μM), while OXD-like activity is used for hydroquinone detection. Combined with a smartphone-assisted platform, this system realizes on-site rapid detection of phenolic pollutants without the need for large-scale instruments.[54]

1.10.1 Progress in catalytic mechanism research and biosensor design. In-depth research on the catalytic mechanism of Ni-based bimetallic nanozymes provides an important basis for their rational design and performance optimization. Fe_3Ni-MOF nanozymes exhibit significantly enhanced POD-like activity after the introduction of Ni. Mechanistic studies show that Ni doping not only enhances the electron transfer capability between TMB and H_2O_2 but also promotes the Fe^{2+}/Fe^{3+} cycle and the generation of $^{\bullet}OH$, forming a dual enhancement mechanism of electron transfer and free radical generation. Based on this, the developed Fe_3Ni-MOF/GOx integrated system is successfully applied to one-step colorimetric detection of glucose in human serum, demonstrating its potential in biosensing.[55]

1.11 Multi-metal-based nanozymes

Multi-metal (≥3 metals) nanozymes achieve significant improvements in catalytic performance and functional diversification by integrating the unique physicochemical properties of three or more metal elements. The synergistic effects between multiple metals not only enhance electron transfer efficiency and optimize the distribution of active sites but also endow materials with multifunctional properties (*e.g.*, optical, electrical, magnetic), exhibiting enormous potential in cutting-edge fields such as self-powered sensing, synergistic tumor therapy, and detection and degradation of environmental pollutants.

Beyond the enhanced performance seen in bimetallic systems, multimetallic nanozymes offer a qualitatively higher level of functionality and design space. Their primary distinction lies in the creation of interconnected synergistic networks and the emergence of novel, often unpredictable, properties that are not merely the sum of individual metal contributions. This complexity allows for the simultaneous modulation of multiple catalytic pathways and the integration of complementary non-catalytic functions within a single nanostructure, enabling solutions to biomedical and environmental challenges that are beyond the reach of simpler bimetallic counterparts.

1.11.1 Distinguishing advantages and complex synergistic networks. The incorporation of a third metal often goes beyond linear improvement, enabling non-linear synergistic effects. For instance, while a bimetallic system might optimize a single catalytic cycle, a trimetallic system can orchestrate two or more parallel or sequential catalytic cycles. One metal might be specialized for substrate adsorption, a second for efficient electron transfer, and a third for the stabilization of high-energy intermediates, resulting in a concerted catalytic pathway with superior efficiency and robustness. Furthermore, the combination of metals with disparate properties (*e.g.*, a plasmonic metal, a catalytically active noble metal, and a magnetic transition metal) can lead to emergent properties. These are new functionalities that arise from the interactions within the ternary system, such as unique plasmonic resonances enabling novel photothermal effects, or complex electronic structures that yield unprecedented substrate selectivity.

1.11.2 Synthesis and characterization: navigating increased complexity. The formidable advantages of multimetallic nanozymes are counterbalanced by significantly heightened challenges in their synthesis and characterization. Achieving precise control over the composition, spatial distribution, and coordination environment of three or more distinct metals within a single nanoparticle is a monumental synthetic task. The differing reduction potentials and nucleation kinetics of each metal component make conventional co-reduction methods prone to phase segregation, leading to inhomogeneous structures with compromised synergistic effects. Advanced synthesis strategies, such as multi-step seeded growth, template-assisted methods, and the use of specific capping agents, are often required to achieve the desired architectural control.

Similarly, the characterization of these complex materials demands a more sophisticated arsenal of techniques. Probing the local coordination environment of each metal, identifying the true nature of the multi-metallic active sites, and deconvoluting their individual contributions to the overall catalytic mechanism require a combination of advanced *in situ*/*operando* spectroscopy and high-resolution microscopic analysis. The path to rational design of multimetallic nanozymes is therefore contingent upon overcoming these significant synthetic and analytical hurdles to establish clear structure–activity relationships.

1.11.3 Applications in self-powered biosensing and accurate detection. Multi-metal nanozymes, with their multi-enzyme activities and switchable catalytic functions, provide a new platform for constructing intelligent, portable self-powered sensing systems. CoMn–CeO_2 nanospheres possess both GOx-like and POD-like activities, serving as natural catalytic switches. Utilizing this principle, a substrate-switched dual-signal self-powered biosensor (EBFC-SPB) enables accurate, convenient detection of aflatoxin B1 (AFB1) *via* competitive recognition reactions without additional equipment, thereby offering an innovative food safety monitoring solution.[56]

Another study reported NiCoFe-MOF-74 trimetallic nanozymes, where Ni, Co, and Fe atoms synergize with organic ligands to provide abundant recognition sites and POD-like activity. Combining its fluorescent properties and hollow structure, this material enables fluorescent/colorimetric dual-mode detection and efficient adsorption removal of tetracycline antibiotics (TCs), showing good application potential in practical samples such as honey.[57]

1.11.4 Applications in synergistic tumor therapy and immune regulation. By integrating catalytic therapy, photothermal therapy, and immune regulation functions, multi-metal nanozymes achieve efficient synergistic tumor therapy and long-term inhibition. Au@Pt@Rh trimetallic nanozymes have a large mesoporous structure, which can load a TGF-β inhibitor (LY2157299) and be coated with homologous tumor cell membranes (CM) to form LY-Au@Pt@Rh-CM nanocomposites. This system can continuously catalyze endogenous H_2O_2 to generate $^{\bullet}OH$ and O_2, alleviate tumor hypoxia, and improve the immunosuppressive microenvironment. Its photothermal effect can further enhance catalytic efficiency, realizing immunomodulation-enhanced tumor catalytic therapy.[58] Mn/Fe-MIL-101/CuS/DOX@FA trimetallic nanozymes integrate Mn/Fe-MOF, CuS, the chemotherapeutic drug doxorubicin, and the targeting molecule folic acid (FA), possessing GPx-like and POD-like activities, photothermal properties, and T_1/T_2 dual-modal MRI functions. By amplifying the ICD effect, consuming GSH, and generating ROS, this system realizes synergistic photothermal chemodynamic chemotherapy, effectively inhibiting tumor growth and metastasis, and constructing a "trinity" platform for diagnosis, treatment, and metastasis prevention.[59]

RuPdNi trimetallic nanosheets (TMNSs) obtain excellent RONS scavenging capabilities and photothermal conversion performance through the introduction of Ru and Ni atoms and the design of surface atomic vacancies. This material can effectively alleviate colonic inflammation and inhibit colon cancer growth through photothermal therapy, providing a new integrated anti-inflammatory-anti-tumor therapeutic strategy for intestinal diseases.[60]

1.11.5 Applications in environmental pollutant detection and degradation. The high catalytic activity and versatility of multi-metal nanozymes make them effective tools for environmental pollutant monitoring and control. Au@PtPd multimetal nanozymes are used to enhance colorimetric biosensors on finger-actuated microfluidic chips. Through efficient microfluidic control and immune signal amplification, they enable rapid and highly sensitive detection of *Salmonella*, providing a portable solution for food safety monitoring.[61]

In terms of pollutant degradation, metal ion-doped ZIF-67-derived composites (*e.g.*, doped with Ni^{2+}, Cu^{2+}, or Fe^{2+}) exhibit triple catalytic activities: POD-like, OXD-like, and pollutant reductive degradation. Metal doping increases the pollutant degradation rate by more than 13.3 times, and this enhancement reaches 96.3 times after high-temperature pyrolysis. This material generates reactive oxygen intermediates ($^1O_2$ and $O_2^{\bullet-}$), which are utilized to construct a sensor array for the efficient identification and quantification of 9 phenolic pollutants and 5 biomolecules, thus revealing significant potential in environmental monitoring and disease diagnosis.[62]

Table 1 Summary of representative bimetallic/multimetallic nanozymes

Nanozymes	Methods	Catalytic activity	Parameter-POD	Application	Ref.
Fe–Co	Solvothermal method	POD-like	K_m (165 ± 1.7 μM), V_{max} (0.7 ± 0.1 × 10^{-8} M s^{-1}) H_2O_2	Subcutaneous abscess in mice, bacterial corneal ulcer in rats	12
Pt–Sn	Solvothermal method	POD-like, CAT-like	K_m (0.24 mM), V_{max} (1.67 × 10^{-8} M s^{-1}) TMB	Tumor-bearing mice	21
Ce–Mn	Hydrothermal method	POD-like, CAT-like, OXD-like	K_m (27.7 mM), V_{max} (3.21 × 10^{-7} M s^{-1}) H_2O_2	Tumor-bearing mice	23
Cu–Pt	*In situ* reduction method	SOD-like, POD-like, CAT-like	K_m (3.83 mM), V_{max} (11.43 × 10^{-8} M s^{-1}) H_2O_2	Tumor-bearing mice	28
Au–Ru	Chemical co-reduction method	SOD-like, CAT-like	—	Tumor-bearing mice	39
Pd–Ir	Seed-mediated growth method	POD-like	K_m (0.246 mM), K_{at} (4.36 × 10^5 s^{-1}) TMB	Detection of gastric pepsinogen I and II in gastric cancer	45
Ni–Co–Fe	Solvothermal method	POD-like	K_m (0.35 mM) TMB, K_m (0.45 mM) H_2O_2	Detection of tetracycline antibiotics in honey	57
Ru–Pd–Ni	Wet chemical method	SOD-like, CAT-like $^{\bullet}OH$ scavenging	—	Colitis and colon cancer treatment	60

1.12 General principles and structure–activity relationships

To compare the key performance of different bimetallic/polymetallic nanozymes more clearly, we systematically summarized the key parameters of various materials in terms of catalytic activity, parameter, and application (Table 1). Beyond the extensive catalog of specific applications, the collective progress in bimetallic and multimetallic nanozymes reveals a set of overarching principles and structure–activity relationships that transcend individual metal compositions. Synthesizing these insights is crucial for transitioning from serendipitous discovery to rational design. The enhanced performance and multifunctionality observed across diverse systems are fundamentally rooted in several interconnected mechanistic and strategic paradigms.

1.12.1 Universal synergistic mechanisms underlying enhanced catalysis. The catalytic supremacy of multi-metal nanozymes is universally governed by a confluence of electronic, geometric, and dynamic synergistic effects. Electronic modulation, arising from the electronegativity difference between heterometals, facilitates interfacial electron transfer, which optimizes the adsorption strength of reaction intermediates and effectively lowers the activation energy barriers for key catalytic steps, such as H_2O_2 dissociation. This electronic "pull–push" effect is a cornerstone of enhanced activity across numerous nanozyme families. Concurrently, the introduction of a second metal induces geometric and strain effects, altering the lattice parameters and local coordination geometry of the primary active sites. This structural distortion can create uniquely configured catalytic pockets that stabilize transition states and enhance substrate specificity. Furthermore, in systems featuring multiple redox-active metals, synergistic catalytic cycles can be established. Here, the different metals engage in complementary valence transitions, creating a more efficient and continuous electron transfer pathway that accelerates the regeneration of the active species and prevents catalyst passivation, thereby sustaining high catalytic turnover.

1.12.2 Rational design strategies for function-oriented nanozymes. The empirical successes documented in the literature converge into several high-level design strategies for engineering next-generation nanozymes. The pursuit of atomic-level precision, exemplified by single-atom and dual-atom architectures, represents a paradigm shift towards emulating the well-defined active centers of natural enzymes. By meticulously engineering the primary coordination environment of the metal centers, designers can precisely fine-tune catalytic selectivity and efficiency. Parallel to this, strategic interface engineering in core–shell, alloy, and heterojunction structures is critical. Each architecture presents distinct interfacial microenvironments and electronic communication channels, with heterojunctions often yielding superior performance due to enhanced charge separation and the creation of highly active interfacial sites. The integration of catalytic activity with ancillary functions, including photothermal conversion, magnetism, or specific targeting, embodies a holistic "multimodal synergy" strategy. This approach enables the construction of sophisticated theranostic platforms that tackle complex pathophysiological contexts more effectively than monofunctional agents. Lastly, the design of microenvironment-responsive systems marks the frontier of "intelligent" nanozymes. By embedding responsiveness to specific biological or chemical cues into the material's design, catalytic activity can be spatially and temporally controlled, maximizing therapeutic or sensing efficacy while minimizing off-target effects.

In summary, the evolution from single-metal to multi-metal nanozymes is underpinned by a deeper understanding of these general principles. The deliberate exploitation of electronic coupling, geometric strain, and synergistic cycles, guided by rational design strategies focused on atomic precision, interface control, functional integration, and smart responsiveness, provides a comprehensive framework for the future development of advanced nanozyme technologies. Internalizing these concepts empowers researchers to move beyond compositional screening and towards the predictive design of tailored nanocatalysts.

2 Conclusion

This review systematically summarizes the latest research progress in bimetallic and multimetallic nanozymes. By introducing a second or multiple metal elements, these nanozymes fully leverage the synergistic effects between metals, achieving significant surpassing of single-metal nanozymes in terms of catalytic activity, stability, and functionality. The versatility of these nanozymes allows them to address health challenges across a continuum of care, spanning from direct clinical intervention to proactive environmental health protection. At the therapeutic front, Fe-based, Mn-based, and Cu-based nanozymes demonstrate great potential in direct interventions such as antibacterial and anti-tumor therapy. Concurrently, in the domain of diagnostics and preventive health, Pt-based, Au-based, and Pd-based nanozymes exhibit unique advantages in ultra-sensitive biosensing for precision medical diagnosis, while their application in monitoring and degrading environmental pollutants provides a crucial safeguard against exogenous health threats. Furthermore, Ga-based, Mo-based, Ni-based, and multi-metal ($\geq$3 metals) nanozymes are pushing the boundaries in advanced areas like tumor catalytic-metabolic therapy and self-powered sensing, thereby exemplifying the trend towards integrating diagnostic, therapeutic, and environmental health monitoring functions into unified platforms. These materials not only provide new models for exploring enzymological mechanisms in basic scientific research but also offer innovative platform technologies for addressing major challenges in clinical medicine, environmental monitoring, and governance.

Despite the rapid development, the field still faces several key challenges in translating basic research into practical applications. First, the depth of mechanistic understanding is insufficient. Currently, the understanding of enhanced catalytic activity in many bimetallic/multimetallic nanozymes remains at the level of experimental observation and relevant analysis. The precise electronic interactions between metal sites, the kinetics of valence state changes during reactions, and the detailed interaction mechanisms between active centers and substrates

still need to be thoroughly revealed using more advanced *in situ* characterization techniques and theoretical calculations. Second, concerns about biocompatibility and long-term toxicity persist. Although many studies have reported favorable *in vitro* and short-term *in vivo* biosafety, the long-term *in vivo* fate, metabolic pathways, potential accumulation, and possible immunogenicity and systemic toxicity of nanozymes still require systematic and rigorous evaluation, especially for those containing noble metals or multiple metal components. Third, challenges persist in the catalytic selectivity and specificity of nanozymes. Compared with natural enzymes, nanozymes generally have lower catalytic selectivity and are susceptible to interference from various substances in complex systems (*e.g.*, *in vivo* microenvironments or actual wastewater), which may lead to off-target effects or side reactions and affect therapeutic efficacy or detection accuracy. Fourth, large-scale preparation and batch-to-batch consistency are problematic. Many high-performance nanozymes rely on complex and sophisticated synthesis processes (*e.g.*, atomic-level doping, exposure of specific crystal planes). Achieving large-scale, low-cost, and highly reproducible green preparation is an indispensable step toward practical applications.

To address the above challenges and promote the development of the field, future research can focus on the following directions. First, precise design and atomic-level synthesis. With the aid of rational design guided by machine learning and theoretical simulations, combined with advanced synthesis methods (*e.g.*, atomic layer deposition, template synthesis, photochemical synthesis), precise control over the type, coordination environment, and spatial distribution of metals in active sites can be achieved to customize nanozymes with specific functions. Second, in-depth mechanistic research. Vigorously develop and apply *in situ*/*operando* characterization techniques (*e.g.*, *in situ* XAS, *in situ* SEM/TEM, cryo-electron microscopy) and multi-scale theoretical simulations to track catalytic processes in real time at the atomic and molecular levels, and thoroughly understand the structure–activity relationship and synergistic mechanisms. Third, intelligent responsive nanozyme systems. Design and develop "smart" nanozymes that can respond to specific biological or environmental signals (*e.g.*, pH, GSH, H_2O_2, specific enzymes, light, heat) to achieve on-demand activation, regulation, and spatiotemporal precise control of catalytic activity, thereby improving therapeutic efficiency and reducing side effects. Fourth, advancing clinical translation and practical applications. Strengthen interdisciplinary cooperation and conduct standardized long-term toxicological studies and large-animal model experiments. Meanwhile, actively explore large-scale application demonstrations of nanozymes in fields such as POCT, embedded sensors, green chemical catalysis, and on-site environmental pollution remediation to ultimately realize their social and economic value.

Through continuous efforts, bimetallic and multimetallic nanozymes are expected to become an important bridge connecting nanotechnology, catalytic science, and life science/environmental science, providing innovative solutions for improving human health and quality of life.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Acknowledgements

The authors acknowledge the financial support by Shanxi Province Central Government Guidance Fund for Local Science and Technology Development (YDZJSX2024B011), Research and Innovation Team Project for Scientific Breakthroughs at Shanxi Bethune Hospital (2024AOXIANG02), National Natural Science Foundation of China (82502195), Talent Introduction Research Initiation Fund of Shanxi Bethune Hospital (2022RC04), Shanxi Province Clinical Theranostics Technology Innovation Center for Immunologic and Rheumatic Diseases (CXZX-202302), and Research Project Plan of Shanxi Provincial Administration of Traditional Chinese Medicine (2023ZYYB2021). All authors are grateful for assistance from the following research platforms: Shanxi Province Clinical Research Center for Dermatologic and Immunologic Diseases (Rheumatic diseases), Shanxi Province Clinical Theranostics Technology Innovation Center for Immunologic and Rheumatic Diseases, Shanxi Province Engineering Research Center of Translational Drugs for Immune Diseases.

References

1 M. Liang and X. Yan, Nanozymes: From New Concepts, Mechanisms, and Standards to Applications, *Acc. Chem. Res.*, 2019, **52**(8), 2190–2200.
2 L. Gao, J. Zhuang, L. Nie, J. Zhang, Y. Zhang, N. Gu, T. Wang, J. Feng, D. Yang, S. Perrett and X. Yan, Intrinsic peroxidase-like activity of ferromagnetic nanoparticles, *Nat. Nanotechnol.*, 2007, **2**(9), 577–583.
3 Q. Tian, S. Li, Z. Tang, Z. Zhang, D. Du, X. Zhang, X. Niu and Y. Lin, Nanozyme-Enabled Biomedical Diagnosis: Advances, Trends, and Challenges, *Adv. Healthcare Mater.*, 2025, **14**(8), 2401630.
4 K. Zheng, R. Song, R. Li, M. Liu, Y. Ba, W. Jiang and K. Fan, Nanomaterials for refining tumor microenvironment and enhancing therapy in head and neck squamous cell carcinoma: a review, *Oncol. Transl. Med.*, 2024, **10**(4), 151–161.
5 R. Zhang, X. Yan, L. Gao and K. Fan, Nanozymes expanding the boundaries of biocatalysis, *Nat. Commun.*, 2025, **16**(1), 6817.
6 V. G. Panferov, X. Zhang, K.-Y. Wong, J. H. Lee and J. Liu, Biomedical Applications of Nanozymes: An Enzymology Perspective, *Angew. Chem., Int. Ed.*, 2025, **64**(46), e202512409.

7 L. Gao, L. Chen, R. Zhang and X. Yan, Nanozymes: next-generation artificial enzymes, *Sci. Sin.: Chim.*, 2022, **52**(9), 1649–1663.
8 Y. Ai, Z.-N. Hu, X. Liang, H.-b. Sun, H. Xin and Q. Liang, Recent Advances in Nanozymes: From Matters to Bioapplications, *Adv. Funct. Mater.*, 2022, **32**(14), 2110432.
9 L.-J. Yang, Y.-Y. Cai, N. Nurtay, M.-M. Pan, C. Zhang, X. Hu, X.-T. Peng, Y. Wei, M. Jiang, X.-W. Wu, L. Xu and X. Yu, Three-in-One: Biomimetic Trimetallic Ionic-Site Nanozyme Composite as a Redox Homeostasis Disruptor for Ferroptosis/Cuproptosis/Pyroptosis Co-Activated Nanocatalytic Therapy, *Small*, 2025, e09285.
10 J. Feng, X. Yang, T. Du, L. Zhang, P. Zhang, J. Zhuo, L. Luo, H. Sun, Y. Han, L. Liu, Y. Shen, J. Wang and W. Zhang, Transition Metal High-Entropy Nanozyme: Multi-Site Orbital Coupling Modulated High-Efficiency Peroxidase Mimics, *Adv. Sci.*, 2023, **10**(33), 2303078.
11 M. Cui, B. Xu and L. Wang, Recent advances in multi-metallic-based nanozymes for enhanced catalytic cancer therapy, *BioMed. Eng. Mater.*, 2024, **2**(1), e12043.
12 L. Huang, Y. Feng, H. Chen, L. Lai, H. Li, A. Li, J. Du, Z. Wang, T. Xin, L. Tian, S. Li, P. Zheng, C. Nie, W. Zhu and Q. Pan, Metal valence transition strategy-engineered bimetallic nanozyme thermosensitive hydrogel for deep-tissue therapy of subcutaneous abscess wounds and bacterial corneal ulcers, *J. Colloid Interface Sci.*, 2025, **700**, 138613.
13 S. Sun, X. Liu, X. Meng, Z. Yang, X. Zhang and H. Dong, Bimetallic Metal–Organic Framework Microneedle Array for Wound Healing through Targeted Reactive Oxygen Species Generation and Electron Transfer Disruption, *ACS Nano*, 2025, **19**(15), 15109–15119.
14 H. Zhang, J. Lv, H. Wu, Y. He, M. Li, C. Wu, D. Lv, Y. Liu and H. Yang, Endogenous/exogenous dual-responsive nanozyme for photothermally enhanced ferroptosis-immune reciprocal synergistic tumor therapy, *Sci. Adv.*, 2025, **11**(20), eadq3870.
15 L.-J. Yang, M.-M. Pan, H. Hu, F. Liu, M. Jiang, S. Ning, X. Chen, Z. Zhang, X. Yu and L. Xu, Bioinspired Dual-Ionic-Site Single-Atom Nanozymes for Synergistic Ferroptosis/Cuproptosis and Enhanced Immune Checkpoint Blockade Therapy, *Small*, 2025, **21**(35), 2501076.
16 X.-X. Lv, X. Chen, Y. Liu, H.-L. Liu and L.-Z. Gao, Synergistic optimization of electron layout at spatially adjacent dual-atom sites promotes regeneration of nanozymes and deep removal of paracetamol, *Appl. Catal., B*, 2025, **371**, 125256.
17 L. Chen, K. Yang, C. Wang, D. Han and J. Wen, Next-generation of a Fe-Ce double variable-valence metals modulated high-efficiency nanozyme, *Chem. Eng. J.*, 2024, **495**, 153314.
18 B. Yu, Y. Bai, W. Gao, J. Wei, C. Gao, X. Ma and P. Zhu, Colorimetric sensor array constructed based on bimetallic porphyrin-based metal organic framework nanozyme for the detection and recognition of tannic acid, *Food Chem.*, 2025, **486**, 144592.
19 H. Zhang, Z. Wu, H. Lu, Z. Hao, W. Liu, F. Zhang, R. Zhang, X. Li and L. Zhang, Efficient bimetallic nanozyme precisely tuned by DNA for high-throughput foldable paper biosensing, *Chem. Eng. J.*, 2025, **503**, 158504.
20 J. He, T. Li, X. Pan, Z. Deng, J. Huang, X. Mo, X. Shen, X. Qin, X. Yang, M. Gao and J. Yang, CD44 and αV-integrins dual-targeting bimetallic nanozymes for lung adenocarcinoma therapy *via* NIR-enhanced ferroptosis/apoptosis, *Biomaterials*, 2025, **323**, 123407.
21 Y. Zhu, R. Zhao, L. Feng, C. Wang, S. Dong, M. V. Zyuzin, A. Timin, N. Hu, B. Liu and P. Yang, Dual Nanozyme-Driven PtSn Bimetallic Nanoclusters for Metal-Enhanced Tumor Photothermal and Catalytic Therapy, *ACS Nano*, 2023, **17**(7), 6833–6848.
22 K. Xiang, H. Wu, Y. Liu, S. Wang, X. Li, B. Yang, Y. Zhang, L. Ma, G. Lu, L. He, Q. Ni and L. Zhang, MOF-derived bimetallic nanozyme to catalyze ROS scavenging for protection of myocardial injury, *Theranostics*, 2023, **13**(8), 2721–2733.
23 J. Ye, C. Li, J. Xu, S. Liu, J. Qu, Q. Wang, J. Cao, Y. Zhao, C. Li and P. Yang, Engineered Nanozymes with Asymmetric Mn–O–Ce Sites for Intratumorally Leveraged Multimode Therapy, *Adv. Mater.*, 2025, **37**(30), 2419673.
24 O. Heidary, H. Ashrafi, M. Akhond and B. Hemmateenejad, Array of Manganese-Based Bimetallic Metal–Organic-Framework Nanozymes with Enhanced Oxidase-like Catalytic Activity Can Simultaneously Identify and Measure Antioxidants, *Anal. Chem.*, 2025, **97**(9), 4860–4870.
25 H. Gu, P. Li, J. Wang, N. Niu and L. Chen, Bioinspired bimetallic metal–organic framework nanozyme with laccase-mimicking activity for detection and removal of phenolic contaminants, *Microchem. J.*, 2024, **201**, 110568.
26 C. Zhang, X. Zhang, F. Li, B. Li, M. Zhang, W. Li, P. Zhuge, J. Yao, Y. Zhang, S. Chen, Y. Fang and C. Cai, Thermosensitive Hydrogel Integrated with Bimetallic Nano-Enzymes for Modulating the Microenvironment in Diabetic Wound Beds, *Adv. Sci.*, 2025, **12**(6), 2411575.
27 M. Ou, K. Zhang, G. Liao, Z. Wei, L. Yang, S. Chen, X. Fan, Y. Xie and C. Zhao, Polyphenol-Regulated Bimetallic Artificial Metalloproteinases with Broad-Spectrum RONS Scavenging Activities for Diabetic Wound Repair, *Adv. Funct. Mater.*, 2025, **35**(35), 2501438.
28 S. Lu, A. Li, H. Huang, C. Ni, X. Cao, X. Shi and R. Guo, Dendrimer-Entrapped CuPt Bimetallic Nanozymes for Tumor Microenvironment-Regulated Photothermal/Catalytic Therapy, *ACS Appl. Mater. Interfaces*, 2025, **17**(21), 30716–30730.
29 J. Xu, N. Ji, M. Guo, Y. Wang and X. Xu, $CuCoO_2$ Nanoparticles as a Nanoprotease for Selective Proteolysis with High Efficiency at Room Temperature, *Angew. Chem., Int. Ed.*, 2023, **62**(31), e202304554.
30 S. M. Shaban, S. Kim, N. M. E. Basiony, J. Kappen, M. H. Mostafa, A. Y. Elbalaawy, M. R. Elmasry, J. Shin, I. Jeon and D.-H. Kim, Ecofriendly Sunlight-Mediated Nontoxic Bimetallic Nanoparticles: Synthesis, Reusable Catalytic Membrane, and Biosensor Applications, *Adv. Sci.*, 2025, **12**(27), 2503120.
31 M. Jiang, C. Chu, J. Wei, Y. Zhang, Q. Zhang, C. Hua, W. Zhu, L. Wu, X.-F. Yu, L. Ji, Z. Zhao, S. Geng and W. Zhou, A

bimetallic core-shell Cu@MnO nanozyme with enhanced oxygen activation for efficient oxidase-like activity, *Talanta*, 2025, **293**, 128059.

32 Q. Wu, G. Zheng, L. Li and L. Wang, Enhancing Peroxidase-Like Activity and Photothermal Property of Copper Single-Atom Nanozyme *via* A Cascade Competition Strategy, *Adv. Funct. Mater.*, 2025, **35**(22), 2422588.

33 Y. Gong, Y. Xiao, C. Zhao, H. Deng, H. Liu, S. Ke, H. Zhou, G. Chen and H. Wang, Ultrasmall PtIr Bimetallic Nanozyme Treats Myocardial Infarction *via* Ischemic/Inflammatory Cardiac Microenvironment Remodeling, *ACS Nano*, 2025, **19**(14), 13723–13739.

34 S.-M. Dang, D. Yang, Z.-Y. Wang, X.-M. Ding, X.-L. Li, D.-Y. Li and D.-X. Li, Vasculogenic mimicry: a pivotal mechanism contributing to drug resistance in antiangiogenic therapy, *Oncol. Transl. Med.*, 2024, **10**(3), 119–125.

35 Y. Wu, Y. Zhang, J. Han, Y. Jiang, M. Chen, X. Gu, W. Jiang, K. Fan and B. Liu, Nanozyme-Based Biomimetic Intelligent Immune Organelles for the Treatment of Bladder-Metastasized Tumors, *Adv. Mater.*, 2025, e11181.

36 M. M. Pan, P. Li, Y. P. Yu, M. Jiang, X. Yang, P. Zhang, J. Nie, J. Hu, X. Yu and L. Xu, Bimetallic Ions Functionalized Metal-Organic-Framework Nanozyme for Tumor Microenvironment Regulating and Enhanced Photodynamic Therapy for Hypoxic Tumor, *Adv. Healthcare Mater.*, 2023, **12**(26), e2300821.

37 Y. Ren, L. Cao, H. Li, R. Jiao, Y. Zhan, X. Zhang, X. Yu, M. Li, W. Wu, Z. Liang, G. Li, X. Xia, D. Zhang, N. Ling and Y. Ye, Trimetal–Organic Framework-Derived Diatomic Nanozymes-Driven Cascaded Signal Sensitization Intelligent Flexible Sensors for *In Situ* Detection of the Pesticide Residue, *ACS Nano*, 2025, **19**(26), 23703–23718.

38 Y. Hui, J. Mao, M. Rui, Y. Huang, X. Jiang, Y. Xu, W. Wang, J. Wu, L. Zhou, K. Xi, L. Huang and L. Chen, Hydrogel Microsphere-Encapsulated Bimetallic Nanozyme for Promoting Diabetic Bone Regeneration *via* Glucose Consumption and ROS Scavenging, *Adv. Healthcare Mater.*, 2024, **13**(32), 2402596.

39 J. Xing, X. Ma, Y. Yu, Y. Xiao, L. Chen, W. Yuan, Y. Wang, K. Liu, Z. Guo, H. Tang, K. Fan and W. Jiang, A Cardiac-Targeting and Anchoring Bimetallic Cluster Nanozyme Alleviates Chemotherapy-Induced Cardiac Ferroptosis and PANoptosis, *Adv. Sci.*, 2025, **12**(1), e2405597.

40 R. Xu, Y. Yang, M. Xu, Y. Tao, C. Deng, M. Li, D. Wei, Y. Deng, J. Lv, C. Wu and Z. Zhang, Screening and discrimination of phenolic acids using bimetallic nanozymes based colorimetric sensor array, *Sens. Actuators, B*, 2024, **420**, 136484.

41 J. Xiao, X. Yang, X. Zhang, X. Niu, Y. Guo, N. Zhu, K. Zeng and Z. Zhang, Investigation for Regulation of a DNA-Programmed Bimetallic Nanozyme and Its Biosensing Applications, *Anal. Chem.*, 2024, **96**(49), 19796–19802.

42 X. Zhang, Y. Lyu, J. Li, X. Yang, Z. Lan and Z. Chen, Bimetallic Nanozymes-Integrated Parachute-Like Au_2Pt@PMO@ICG Janus Nanomotor with Dual Propulsion for Enhanced Tumor Penetration and Synergistic PTT/PDT/CDT Cancer Therapy, *Adv. Funct. Mater.*, 2024, **34**(44), 2406059.

43 C. Wang, L. Wang, V. Nallathambi, Y. Liu, J. Kresse, R. Hübner, S. Reichenberger, B. Gault, J. Zhan, A. Eychmüller and B. Cai, Structural Regulation of Au-Pt Bimetallic Aerogels for Catalyzing the Glucose Cascade Reaction, *Adv. Mater.*, 2024, **36**(41), 2405200.

44 M. Cai, Y. Zhang, Z. Cao, W. Lin and N. Lu, DNA-Programmed Tuning of the Growth and Enzyme-Like Activity of a Bimetallic Nanozyme and Its Biosensing Applications, *ACS Appl. Mater. Interfaces*, 2023, **15**(15), 18620–18629.

45 X. Meng, W. Zuo, P. Wu, Y. Song, G.-J. Yang, S. Zhang, J. Yang, X. Zou, W. Wei, D. Zhang, J. Dai and Y. Ju, Bimetallic Nanozyme: A Credible Tag for In Situ-Catalyzed Reporter Deposition in the Lateral Flow Immunoassay for Ultrasensitive Cancer Diagnosis, *Nano Lett.*, 2024, **24**(1), 51–60.

46 T. Qu, H. Liu, X. Tong, H. Zhao, J. Ma and Q. Zhang, Homologous phospholipid bilayer-modified Pd-based bimetallic nanozymes provide parallel therapy through efficient triple enzyme activity under NIR light excitation, *Colloids Surf., A*, 2025, **708**, 135959.

47 S. Zhong, Z. Zhang, Z. Wang, Q. Zhao, W. Chen, G. Chen, Z. Jiang, Q. Cai, L. Gong, Y. Lai, D. Wang and L. Li, Synergizing Catalysis with Post-catalysis Pseudo-Iron Release by Building Dynamic Catalytic Active Sites in Diatomic Nanozymes for Boosting Cancer Therapy, *J. Am. Chem. Soc.*, 2025, **147**(18), 15814–15826.

48 G. Song, X. Zheng, Z. Zhang, M.-L. Fauconnier, C. Li, L. Chen and D. Zhang, Streamlined Synthesis of Ga-Cu Dual Single-Atom Nanozymes for Advanced Electrochemical Sensing Applications, *Adv. Funct. Mater.*, 2025, 10909.

49 C. Xu, J. Li, C. Ou, J. Yang, S. Fu, W. Hu, L. Wang, Z. Wang, L. Hai, L. Deng and D. He, Natural enzyme cascade bimetallic sulfide $MoCuS_x$ nanozyme for synergistic photothermal/photodynamic enhanced chemodynamic antimicrobial therapy of wound infection, *Chem. Eng. J.*, 2024, **499**, 156170.

50 Z. Li, B. Ding, J. Li, H. Chen, J. Zhang, J. Tan, X. Ma, D. Han, P. a. Ma and J. Lin, Multi-Enzyme Mimetic MoCu Dual-Atom Nanozyme Triggering Oxidative Stress Cascade Amplification for High-Efficiency Synergistic Cancer Therapy, *Angew. Chem., Int. Ed.*, 2025, **64**(1), e202413661.

51 S. He, X. Guo, Q. Zheng, H. Shen, Y. Xu, F. Lin, J. Chen, H. Deng, Y. Zeng and W. Chen, Engineering nickel-supported osmium bimetallic nanozymes with specifically improved peroxidase-like activity for immunoassay, *Chin. Chem. Lett.*, 2025, **36**(4), 110096.

52 D. Wu, Z. Yu, J. Qin, M. Li and D. Tang, A Bimetallic Nanozyme Synergistic Effect-Driven Enzyme Cascade Nanoreactor for Instant Immunoassay, *Anal. Chem.*, 2025, **97**(20), 10947–10954.

53 S. Mu, Y. Yang, T. Han, J. Liu, Z. Zhu, H. Zheng and H. Zhang, Synergistic surface ligand modification of Ni-Pt bimetallic nanozymes: Enhanced catalytic activity and

versatile detection of penicillin, *Sens. Actuators, B*, 2025, **423**, 136724.

54 X.-J. Wang, Y. Long, C.-W. Wei, S.-Q. Gao and Y.-W. Lin, Ni-Fe bimetallic hydrogel with bifunctional enzyme activity for colorimetric detection of phenolic pollutants, *Microchem. J.*, 2025, **209**, 112851.

55 Z. Mu, S. Wu, J. Guo, M. Zhao and Y. Wang, Dual Mechanism Enhanced Peroxidase-like Activity of Iron–Nickel Bimetal–Organic Framework Nanozyme and Its Application for Biosensing, *ACS Sustain. Chem. Eng.*, 2022, **10**(9), 2984–2993.

56 Z. Xing, C. Wang, Z. Fan, S. Qi, Q. Sun, R. B. Song and Z. Li, Substrate-Switched Dual-Signal Self-Powered Sensing System Based on Dual-Nanozyme Activity of Bimetal-Doped CeO(2) Nanospheres for Electrochemical Assay of Aflatoxin B1, *Anal. Chem.*, 2024, **96**(37), 14944–14952.

57 Q. Chen, H. Zhang, H. Sun, Y. Yang, D. Zhang, X. Li, L. Han, G. Wang and Y. Zhang, Sensitive dual-signal detection and effective removal of tetracycline antibiotics in honey based on a hollow triple-metal organic framework nanozymes, *Food Chem.*, 2024, **442**, 138383.

58 G. Song, X. Shao, C. Qu, D. Shi, R. Jia, Y. Chen, J. Wang and H. An, A large-pore mesoporous Au@Pt@Rh trimetallic nanostructure with hyperthermia-enhanced enzyme-mimic activities for immunomodulation-improved tumor catalytic therapy, *Chem. Eng. J.*, 2023, **477**, 147161.

59 K. Luo, S. You, J. Chen, W. Ye, J. Tian, X. Feng, Y. Wang, L. Li and X. Yu, Construction of multifunctional nanozymes with amplified immunogenic death effect as a long-term anti-tumor nanoplatform, *Biomater. Adv.*, 2025, **175**, 214336.

60 Y. Wang, X. Dai, L. Wu, H. Xiang, Y. Chen and R. Zhang, Atomic vacancies-engineered ultrathin trimetallic nanozyme with anti-inflammation and antitumor performances for intestinal disease treatment, *Biomaterials*, 2023, **299**, 122178.

61 F. Jiang, N. Jin, L. Wang, S. Wang, Y. Li and J. Lin, A multimetallic nanozyme enhanced colorimetric biosensor for *Salmonella* detection on finger-actuated microfluidic chip, *Food Chem.*, 2024, **460**, 140488.

62 Y. Guan, Y. Lu, J. Zhao, W. Huang and Y. Liu, Cobalt-based zeolitic imidazole framework incorporated with well-dispersed bimetallic nanoparticles/ions as a multifunctional nanozyme for the degradation of environmental pollutants and discrimination of various phenolic substances, *Chem. Eng. J.*, 2023, **465**, 142703.