

# A New Era of Nanozyme Research: Rational Design, Mechanistic Insights, and Emerging Applications

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Nanozymes—nanomaterials with intrinsic enzyme-like catalytic activity—have emerged as powerful platforms bridging materials chemistry, catalysis, and biomedicine. Since their taking off in the field in 2007, they have evolved from serendipitous catalytic materials to intelligent catalytic systems capable of precise regulation of biological reactions and environmental adaptation. Recent advances in single-atom nanozymes (SAzymes), oxygen–vacancy engineering, and biointerface adaptation have greatly accelerated the understanding and applications of nanozyme catalysis.

This joint special issue by *ACS Applied Materials & Interfaces* and *ACS Applied Nano Materials*, “Nanozymes: Design, Mechanisms, and Applications”, presents a comprehensive collection of more than 50 cutting-edge papers by authors from numerous countries (regions), spanning rational design, mechanistic insights, and emerging applications of nanozymes.

Recent progress in nanozyme engineering has gradually shifted the field from empirical observations toward systematic and mechanism-informed design. Karyakin and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c07510>) performed a comparative analysis of redox pathways across different peroxidase-like nanozymes, establishing a quantitative relationship between nanozyme redox potential and catalytic rate constants while highlighting the significant roles of particle size and electron-transfer characteristics in dictating activity. To extend beyond single-step catalysis, Jiang and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c09544>) systematically outlined the principles for constructing cascade catalytic nanozymes, emphasizing the integration of multiple active sites and spatial optimization to emulate natural multienzyme networks, along with their expanding biomedical applications.

Research on the influence of surface modification on the catalytic activity of nanozymes is making continuous progress. Willner and Chen (<https://pubs.acs.org/doi/10.1021/acsami.5c07647>) showed that introducing aptamers, chiral receptors, peptide ligands, or molecularly imprinted shells can concentrate substrates around catalytic sites through affinity interactions, thereby increasing reactivity and enabling selective or chiroselective transformations. Wang and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c03591>) highlighted how both biomolecular coronas formed *in vivo* and artificially engineered surface chemistry shape nanozyme activity, biodistribution, and therapeutic efficacy, emphasizing

the interface as a decisive factor for clinical translation. Together, these reviews demonstrate that surface modification plays a vital role in enhancing substrate recognition, interfacial electron transfer, nanozyme–bio interactions, and the biocompatibility of nanozymes, paving the way for more precise, rational and application-oriented nanozyme design.

Recent advances in modulating nanozyme activity have increasingly emphasized the importance of crystal engineering, atomic coordination, multimetal synergy, and local reaction microenvironments. Zhang and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.4c22599>) demonstrated that the crystal phase of MnO<sub>2</sub> critically governs oxygen–vacancy formation, which in turn regulates laccase-like activity and aerobic catalytic oxidation through enhanced oxygen mobility. Lin and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c00043>) developed a graphdiyne-supported Cu-cluster (Cu-GDY) nanozyme in which intersite communication between adjacent Cu atoms lowers the reaction energy barriers, thereby increasing both superoxide dismutase-like and catalase-like activities and enabling practical reactive oxygen species (ROS)-scavenging applications. In parallel, Yeh and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c02135>) showed that exposed Bi<sup>3+</sup> sites in SU-101 Bi-MOF precisely control electron-transfer pathways and substrate binding, achieving highly selective Cr<sup>6+</sup> reduction under mild conditions. Collectively, these studies illustrate diverse strategies for rationally tuning nanozyme reactivity, providing insights for both environmental and biomedical applications.

Significant progress has also been made in the research of SAzymes, which emphasize precise atomic coordination and electronic structure engineering to increase catalytic efficiency and selectivity. Zhang and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c07454>) showed that single-atom doping of WSe<sub>2</sub> with Cu, Ru, or Zn enables tunable peroxidase- and catalase-like activities, where electron transfer modulation around single atoms governs catalytic selectivity. Guo and co-

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workers (<https://pubs.acs.org/doi/10.1021/acsanm.4c06508>) highlighted asymmetrically coordinated SAzymes, which distort the electron cloud distribution to achieve superior catalytic performance compared with that of conventional metal–N<sub>4</sub> active sites. Moreover, Ren and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c02321>) introduced bioinspired Fe<sub>1</sub>@SAzymes with mesoporous supports that mimic enzymatic substrate channels, enhancing substrate transport and peroxidase-like activity. Furthermore, Lu and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c00847>) revealed that graphitic nitrogen in Fe–N<sub>4</sub> single-atom nanozymes regulates the charge distribution at the active site, accelerating O<sub>2</sub> activation and oxidase-like activity, which was validated in an ultrasensitive colorimetric assay. Finally, Shi and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.4c20487>) demonstrated that Cu single-atom nanozymes can generate ROS and heat under laser irradiation, inducing immunogenic cell death and significantly boosting tumor vaccine efficacy when used with cold-exposure therapy. In summary, these studies demonstrate that single-atom design, asymmetric coordination, and local environment engineering are critical for precise modulation of nanozyme activity across biomedical and sensing applications.

Recent advances in nanozyme-based *in vitro* detection have demonstrated remarkable versatility and sensitivity across a wide range of analytes. For small molecule and metabolite detection, Du and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c02147>) developed a mesoporous Pd@Pt nanoparticle-mediated lateral flow immunoassay (LFIA) integrated with a 3D-printed smartphone reader for rapid S-PMA detection, achieving ng/mL sensitivity in urine samples. Qu and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c04606>) and Xiao and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.4c06683>) used Au–TiO<sub>2</sub>/C and HE-LDH nanozymes, respectively, to convert H<sub>2</sub>O<sub>2</sub> to radicals, enabling sensitive colorimetric detection of cholesterol and tetracycline, with broad linear ranges and low limits of detection. Shang and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.4c06311>) and Cui and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.4c06510>) employed Ru<sub>0.13</sub>/HSA<sub>0.06</sub>/ZIF-67 and Fe-MOG/GO-COOH composites for rapid colorimetric or electrochemical sensing of glucose and H<sub>2</sub>O<sub>2</sub> relevant to cancer monitoring. Kamruzzaman and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c00013>) designed sustainable organic elastic polymer/acrylamide nanozymes for sensitive toxic mycotoxin detection in food and agriculture. Chandra and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c10664>) constructed a tetrametallic dendritic nonenzymatic sensor for glutathione, achieving ultralow detection limits and rapid smartphone-integrated analysis. Kan and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c01031>) utilized Fe/NC nanozymes to detect the ROS scavenging abilities of Chinese herbal polysaccharides, thereby evaluating their antioxidant capacities. To improve the selectivity of detection, He and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c02309>) highlighted the role of ligand engineering in optimizing catalytic interfaces and designed pyrimidine-derived ligand-coordinated Pt nanozymes, thereby detecting glucose with minimal cross-reactivity toward common interferents.

For biomarker and pathogen detection, Zhang and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c05405>) applied Ce/Uio-67 nanozymes to detect CD20 (a lymphoma

biomarker) on extracellular vesicles with superior sensitivity and simplicity. Li and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c01030>) developed oxidase-like surface-enhanced Raman scattering sandwich sensors to detect *Staphylococcus aureus* with ultrahigh sensitivity. Su and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c02313>) reviewed the biomimetic design of tunable nanozymes for microbial detection, with a particular focus on innovative signal amplification strategies that optimize performance. Many studies have focused on enhancing nanozyme performance for point-of-care testing (POCT). Xia and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c10567>) introduced Pt–Co magnetic nanozymes for ELISA-based cancer biomarker detection, while Liu and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c03789>) systematically evaluated 67 core@shell nanoparticles comprising Au cores and Ag, Pd, Pt, or Ir shells with varying thicknesses for lateral flow assays, showing that peroxidase-like activity strongly correlates with improved detection limits. Fan and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c02319>) reviewed MOF-enzyme-based POCT platforms, emphasizing their modularity, stability, and multifunctional capabilities for flexible sensor design. In summary, these studies illustrate that nanozyme-based detection systems combine high catalytic efficiency, signal amplification, and integration with portable devices, offering powerful solutions for clinical, environmental, and agricultural applications.

Nanozymes have become as powerful tools in catalytic tumor therapy because of their enzyme-like activities and multifunctionality. Zhang and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c08400>) emphasized the importance of rational design, systematically addressing catalytic mechanisms and structure–activity relationships to optimize nanozyme performance and safety in tumor treatment. Ding and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c11596>) advanced this field by developing a multifunctional biomimetic nanozyme bioreactor combining Fe<sub>3</sub>S<sub>4</sub> nanozymes, macrophage-derived exosomes, and a hemoglobin allosteric effector. This system enables tumor-targeting capability, efficient conversion of H<sub>2</sub>O<sub>2</sub> into cytotoxic ·OH, alleviates tumor hypoxia, and modulates immune responses by repolarizing tumor-associated macrophages, resulting in effective tumor ablation *in vitro* and *in vivo*. Feng and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.4c06635>) designed PEG-modified CeO<sub>2</sub>/graphene nanoribbon nanocomposites with multiple enzymatic activities, realizing O<sub>2</sub> production and ROS generation. The addition of photothermal effects further amplifies oxidative stress in the tumor microenvironment, enhancing tumor ablation. Overall, these studies demonstrate innovations in multifunctional nanozyme design, multimodal catalytic activity, tumor-targeted delivery, and microenvironment modulation for precise and effective cancer therapy. Finally, Yu and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c02585>) constructed Pd@CaO<sub>2</sub> nanozymes that self-supply H<sub>2</sub>O<sub>2</sub> and O<sub>2</sub> in acidic tumor environments, enhancing peroxidase- and oxidase-like reactions while simultaneously coupling ferroptosis and apoptosis through ROS–Ca<sup>2+</sup> positive feedback loops.

Nanozymes have shown remarkable potential in accelerating wound repair by regulating ROS homeostasis. Gu and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c07229>) utilized Prussian blue nanozymes integrated into hydrogel dressings to enhance enzyme-like activity during long-term

wound healing, resulting in stable ROS scavenging and self-enhanced catalytic effects. When the fundus sustains damage, excessive ROS are often produced. In light of this, Zhang and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c07979>) reviewed the emerging use of nanozymes in ocular diseases with fundus damage, highlighting their ROS scavenging, immunomodulatory, and antiangiogenic effects. Zhou and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.4c06859>) fabricated CuEr nanoalloys with dual enzyme-mimicking activities that generate ROS and deplete glutathione, effectively eliminating *Escherichia coli* and promoting tissue remodeling and collagen deposition. To improve ROS generation, Liu and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.4c07284>) employed near-infrared light irradiation to increase the peroxidase-like activity of RuO<sub>2</sub> nanozymes, providing broad-spectrum antibacterial efficacy and promoting wound healing in drug-resistant infections. To address the problem of low peroxidase-like activity at neutral pH, which impedes ROS generation, Li and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c01974>) developed amino acid-coordinated Cu-His nanozymes that are effective at catalyzing endogenous H<sub>2</sub>O<sub>2</sub> to generate ·OH in the infection microenvironment (neutral pH), achieving efficient antibacterial therapy *in vivo*. Yu and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c03513>) designed DMOS@CP nanozymes with pH and GSH dual-responsive sequential release of ·OH and H<sub>2</sub>S for combined chemodynamic and gas therapy, eradicating biofilms, modulating the inflammatory microenvironment, and enhancing angiogenesis and wound closure. Notably, Xu and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c02743>) developed Fe-DHB nanozymes with regenerated Fe(II) active centers enabling cyclic oxidoreductase reactions under neutral pH, achieving simultaneous ROS production/scavenging and oxygen release, accelerating infected wound healing and bacterial clearance. Similarly, Pang and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c05025>) engineered magnesium-doped carbon dot nanozymes with photoswitchable antioxidant/prooxidant activities, achieving rapid ROS-mediated antibacterial action and anti-inflammatory effects for wound treatment. These studies highlight innovations of nanozymes in controllable ROS regulation, multifunctional catalytic cascades, and integration with microenvironment-responsive therapeutic strategies for wound healing.

In addition to eliminating pathogens *in vivo*, nanozymes can also be incorporated into various materials *in vitro* to prevent pathogen infections. Rotello and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c02074>) developed visible-light-responsive alginate hydrogel beads embedded with bioorthogonal polyzymes, enabling spatiotemporal activation of prodrugs such as linezolid for precise eradication of resistant *S. aureus* biofilms. Liang and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c07302>) designed Ni–Co nanozyme-based composite coatings that exhibit mechanocatalytic antibacterial activity and flame-retardant properties, meeting the urgent need for advanced protection materials in safe-critical environments. He and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c01936>) synthesized silver-based nanozymes (AgNZs-g) to combat *Fusarium* crown rot in wheat; these nanozymes exhibited peroxidase-like activity, induced intracellular ROS accumulation in fungal cells, impaired membrane integrity, and significantly controlled disease progression both alone and synergistically with tebuconazole, suggesting a

sustainable antifungal strategy. Palomo and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c01377>) introduced a Cu–Ag nanobiohybrid featuring cooperative metal centers that exhibit strong catalytic efficiency and broad-spectrum virucidal activity at low metal contents. These works highlight the potential of nanozymes as excellent candidates for coating application materials against pathogen infections.

Recent studies have demonstrated innovative strategies for employing nanozymes in therapies for diseases associated with bones and bone joints. Wang and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.4c23069>) developed a ZnO–CuS/F127 nanozyme hydrogel that integrates catalase- and superoxide dismutase-like activities to scavenge ROS, modulates macrophage polarization toward the M2 phenotype, and promotes osteogenesis and angiogenesis, thereby facilitating bone defect repair in rodent models with high biocompatibility. Cheng and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c07574>) designed metal–polyphenol coordination nanozymes (termed Zn–LB NPs) that combine ROS scavenging with immunomodulation, restoring mitochondrial function, reducing apoptosis in IL-1 $\beta$ -stimulated chondrocytes, and polarizing macrophages from M1 to M2; intra-articular injection in osteoarthritic mice reduced cartilage degradation, suppressed MMP13 and TNF- $\alpha$  expression, and improved locomotor performance without systemic toxicity. Shen and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c09234>) comprehensively reviewed nanozyme applications in orthopedic conditions, highlighting their roles in regulating the osteoblast–osteoclast balance, promoting vascular and neural regeneration, controlling infections, and modulating immune responses, thus facilitating bone repair and regeneration. Zhang and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c07644>) conducted a review on nanozyme-based strategies for gout management, noting constructs based on monometallic species, metal oxides, and hybrid nanocomposites that modulate urate crystallization, inflammatory cascades, and tissue regeneration. These findings indicate that multifunctional nanozymes can synergistically target oxidative stress, immune dysregulation, and tissue regeneration pathways, suggesting promising strategies for bone regenerative medicine.

Recent studies have highlighted the innovative use of nanozymes to modulate pathological microenvironments across diverse diseases. Zhang and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c08068>) developed *Atractylodes macrocephala*-derived carbon dots (AM-CDs) to treat ulcerative colitis by integrating ROS scavenging, anti-inflammatory signaling, and intestinal barrier restoration; these nanozymes effectively downregulated the key proinflammatory cytokines TNF- $\alpha$ , IL-6, and IL-1 $\beta$ ; restored tight junction proteins; and reduced M1 macrophage infiltration, acting through coordinated PI3K–Akt, Jak–STAT, TGF- $\beta$ , and MAPK pathway regulation, surpassing conventional 5-ASA therapy with excellent biosafety. Zheng and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c10593>) employed Prussian blue nanozymes for hepatic fibrosis, leveraging peroxidase-, superoxide dismutase-, and catalase-like activities to suppress oxidative stress, inflammation, and hepatic stellate cell activation; *in vivo*, these nanozymes attenuated liver enzyme elevations, reduced collagen deposition, and restored histopathology via a synergistic triad mechanism of ROS scavenging, immunomodulation, and hepatic stellate cell quiescence, with selective hepatic accumulation and favorable

pharmacokinetics. Kong and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c01140>) designed a dissolvable microneedle system that codelivered nickel–copper nanozymes and minoxidil to remodel the hair follicle microenvironment in androgenetic alopecia; the system achieved efficient ROS clearance, mechanically enhanced angiogenesis, and improved hair regeneration coverage, cell proliferation, and vascular density, providing a minimally invasive combination therapy. Gao and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c03046>) developed fibroblast activation protein  $\alpha$ /ultrasound dual-targeted nanoparticle for myocardial infarction treatment, integrating sonodynamic therapy with fibroblast modulation, thereby remodeling the cardiac microenvironment. Gu and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.5c02305>) summarized the biomedical applications of iron-based nanozymes, which have advantages in remodeling the disease microenvironment. Considering that mesenchymal stem cells possess excellent microenvironment-modulating ability, Zeng and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c10441>) applied a sodium hyaluronate-platinum nanoparticle composite (SHA-PtNPs) to increase the survival, migration, and chondrogenic differentiation of adipose-derived mesenchymal stem cells in tracheal fistula repair, achieving complete tissue regeneration while attenuating oxidative stress and inhibiting NF- $\kappa$ B/I $\kappa$ B $\alpha$ /IL-1 $\beta$  signaling. Taken together, these studies exemplify how nanozyme-based interventions can precisely control oxidative stress, inflammation, and cellular behavior, offering transformative approaches for treating microenvironment-associated pathologies.

In addition to their applications in the biomedical field, nanozymes have also been found utility in industrial production. Hou and co-workers (<https://pubs.acs.org/doi/10.1021/acsanm.4c06967>) developed carbon dot nanozymes (CD-NZ) to enhance ethanol fermentation, demonstrating catalase- and superoxide dismutase-like activities that lower ROS in yeast, accelerate electron transfer, and increase ethanol and ester production while modifying microbial communities, suggesting the potential for enhancing product quality. On the other hand, to ensure that nanozymes can successfully transition to industrial applications in the future, a crucial issue is how to realize their large-scale synthesis at an economical cost. In view of this, Peng and co-workers (<https://pubs.acs.org/doi/10.1021/acsami.5c05766>) introduced a simplified and scalable strategy in which Cu/Cu<sub>2</sub>O core–shell nanoparticles self-assemble within a porous carbon framework during nitrogen calcination, offering a cost-effective route to high-activity peroxidase-like nanozyme production.


In conclusion, this special issue highlights the remarkable evolution and versatility of nanozymes as a transformative platforms at the interface of materials chemistry, catalysis, and biomedicine. By bridging mechanistic insights with functional design, these contributions underscore the potential of nanozymes to enable next-generation catalytic systems for diverse biomedical, environmental, and industrial applications.

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## Notes

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