NANO · MICRO small
www.small-journal.com

Nanozyme-Enabled Treatment of Cardio- and Cerebrovascular Diseases

Yihong Zhang, Wanling Liu, Xiaoyu Wang, Yufeng Liu,* and Hui Wei**

Cardio- and cerebrovascular diseases are two major vascular-related diseases that lead to death worldwide. Reactive oxygen species (ROS) play a vital role in the occurrence and exacerbation of diseases. Excessive ROS induce cellular context damage and lead to tissue dysfunction. Nanozymes, as emerging enzyme mimics, offer a unique perspective for therapy through multifunctional activities, achieving essential results in the treatment of ROS-related cardio- and cerebrovascular diseases by directly scavenging excess ROS or regulating pathologically related molecules. This review first introduces nanozyme-enabled therapeutic mechanisms at the cellular level. Then, the therapies for several typical cardio- and cerebrovascular diseases with nanozymes are discussed, mainly including cardiovascular diseases, ischemia reperfusion injury, and neurological disorders. Finally, the challenges and outlooks for the application of nanozymes are also presented. This review will provide some instructive perspectives on nanozymes and promote the development of enzyme-mimicking strategies in cardio- and cerebrovascular disease therapy.

1. Introduction

Cardio- and cerebrovascular diseases account for an enormous and increasing health burden worldwide, leading to the most disability and death every year.[1,2] These diseases share common risk characteristics, such as obesity, high blood pressure, high lipid/glucose metabolism, and oxidative stress, thereby interfering with many biological processes in our bodies.[3,4] Among them, oxidative stress plays a critical role in the occurrence and development of cardio- and cerebrovascular diseases.[5,6] Excess free radicals attack proteins, lipids, and DNA in cells and tissues, inactivating their functions, therefore hindering normal signaling pathways and causing damage to the body.[7–9]

Maintaining the balance of redox levels in living organisms is one of the vital functions of natural enzymes.[10] However, with the onset of diseases, the loss of natural enzyme activity severely affects their function of regulating reactive oxygen species (ROS).[11] Meanwhile, an evoked immune reaction increases the activities of some related enzymes that cause more ROS production.[12,13] Natural enzymes have been used as therapeutics to solve these problems but with limited success. The failure of enzymatic therapeutics could be attributed to their weaknesses, such as high cost, low stability, and potential immunogenicity. Therefore, developing enzyme-like mimics offers a promising strategy to address this dilemma.[14,15] In particular, functional nanomaterials with enzyme-like activities (called nanozymes) have been considered as emerging artificial enzymes. Nanozymes have unique advantages over natural enzymes and conventional enzyme mimics, including lower cost, more facile preparation, and superior robustness.[16–18] In addition, nanozymes have multiple enzyme-like activities and multi-functionality. The primary effects of nanozymes are essential for related therapies. Taking SOD-like activity as an example, researchers have applied different probes to capture the superoxide radicals to evaluate the scavenging abilities of nanozymes. For instance, they used hydroethidine (HE), nitro blue tetrazolium (NBT), iodonitrotetrazolium chloride (INT), water-soluble tetrazolium salt (WST)-8, cytochrome *c*, and 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) as probes.[19] Through a comparative study, the pros and cons of these probes as well as several matters needing attention have been addressed. These developed efforts help to select a more suitable SOD-like activity detection method for nanozymes in the future. Likewise, a convincing method for measuring CAT-like activities was established.[20] Notably, a comprehensive comparison among the dopamine (DA)-enabled assay and other methods was made, including the dissolved oxygen sensor, spectrophotometric assay (240 nm), $Ti(SO_4)_2$ method, ammonium molybdate method, $KMnO_4$ method, and ferrous oxidation in xylenol

Y. Zhang, W. Liu, X. Wang, Y. Liu, H. Wei
College of Engineering and Applied Sciences
Nanjing National Laboratory of Microstructures
Jiangsu Key Laboratory of Artificial Functional Materials
Nanjing University
Nanjing, Jiangsu 210023, China
E-mail: wangxiaoyu@njfu.edu.cn; liuyufengno1@nju.edu.cn; weihui@nju.edu.cn

X. Wang
Department of Chemistry and Material Science
College of Science
Nanjing Forestry University
Nanjing, Jiangsu 210037, China

H. Wei
State Key Laboratory of Analytical Chemistry for Life Science
School of Chemistry and Chemical Engineering
Chemistry and Biomedicine Innovation Center (ChemBIC)
Nanjing University
Nanjing, Jiangsu 210023, China

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/smll.202204809.

DOI: 10.1002/smll.202204809

orange (FOX) assay. This helps to select an appropriate detection method according to the users' needs. The methods for evaluating other scavenging activities are summarized in this review.[21] Similarly, at cellular levels, numerous probes are available to evaluate the ROS elimination abilities of nanozymes. 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) is widely used as a fluorescent probe to detect ROS elimination abilities at cellular levels. In addition, dihydroethidium (DHE), ROS-Green and hydroxyphenyl fluorescein (HPF) are probes specific for superoxide radicals, hydrogen peroxide, and hydroxyl radicals, respectively.[22] Based on these convincing methods of research, researchers can easily confirm the primary effects of nanozymes, so that nanozymes are widely studied. Nowadays, nanozymes have been used to treat many chronic inflammatory diseases, especially cardio- and cerebrovascular diseases. Generally, nanozymes use two mechanisms to treat these diseases. On the one hand, nanozymes can scavenge excess ROS directly and regulate the inflammatory microenvironment. On the other hand, nanozymes can regulate the pathologically related signaling molecules and coordinate cell communications for therapy.

In this review, we select some representative works to elaborate on how nanozymes make differences in disease treatment. We first discuss the mechanisms of nanozyme-enabled therapies for cardio- and cerebrovascular diseases at the cellular level. Then, with the aid of nanozymes, in vivo applications and curative effects for cardiovascular diseases, ischemia reperfusion injury, and neurological disorders will be discussed. Furthermore, we discuss the challenges to achieving the clinical application of nanozymes in the future.

2. Therapeutic Mechanisms of Nanozyme-Enabled Therapies for Cardio- and Cerebrovascular Diseases

One of the challenges for nanozyme application is to incarnate their authentic competencies in life systems. In this section, we introduce several therapeutic mechanisms of nanozymes in treating several representative cardio- and cerebrovascular diseases at the cellular levels.

3. Antioxidative and Anti-Inflammatory Strategies

The mitochondrial respiratory chain is key site of ROS production. A suitable level of ROS can be metabolically beneficial. However, an increased level of intracellular free radicals will not only affect the mitochondrial electron transport chain but also alter mitochondrial function and impair cell regenerative capacity.[23,24] For example, cardio- and cerebrovascular diseases are usually accompanied by the production of excessive ROS, which further induces oxidative stress and leads to DNA damage, an inflammatory response, cellular senescence, and programmed cell death. In normal cells, many antioxidative enzymes are deployed to scavenge excessive ROS and maintain mitochondrial functions. In diseased cells, however, these enzymes are either insufficient to scavenge excess ROS, or may even be dysfunctional. Nanozymes with superoxide dismutase (SOD)-, catalase (CAT)-, and glutathione peroxidase (GPx)-like activities can function like their natural counterparts to scavenge excessive ROS in living systems. Alternatively, nanozymes with cytochrome *c* oxidase-like (C*c*O) activity can convert oxygen to water without the release of ROS. In this regard, Mugesh and coworkers synthesized a cerium vanadate ($CeVO_4$) nanozyme with C*c*O-like activity, which was utilized to protect mitochondrial damage from a lack of C*c*O (**Figure 1**a). In addition, they showed that the $CeVO_4$ exhibited intrinsic SOD-like activity, which was able to eliminate partially reduced oxygen species (PROS) generated during simulated C*c*O catalysis and protect mitochondria from damage.[25] In a subsequent study, they explored the SOD-like activity of $CeVO_4$ nanozyme in an attempt to replace the function of native SOD in cells. They demonstrated that the $CeVO_4$ nanozyme showed potential substitution functions of three isoforms of SOD (i.e., SOD1, SOD2, and SOD3) in mammalian cells. Specifically, the $CeVO_4$ nanozyme could almost entirely substitute for the function of natural SOD1 and SOD2 in neuronal cells when the natural SOD enzymes were downregulated by specific gene silencing (Figure 1b,d). In the SOD1- and SOD2-depleted cells, due to the nanozyme-enabled regulation of ROS levels, the physiological levels of the anti-apoptotic Bcl-2 family proteins were restored, which helped to prevent mitochondrial damage and rebuild mitochondrial integrity (Figure 1f–h). In addition, the $CeVO_4$ nanozyme could regulate the ATP levels in neuronal cells for mitochondrial melioration (Figure 1c,e).[26]

Excessive ROS can induce oxidative stress and lead to DNA damage, cellular senescence, and programmed cell death. In most cases, these phenomena do not occur in isolation.[27,28] For example, DNA damage-induced senescence and stress-induced senescence are two subtypes of damage-induced senescence.[29] Next, we will use DNA damage and cell senescence as examples to demonstrate that nanozymes can achieve therapeutic purposes by scavenging ROS. DNA damage evokes a series of cellular responses, such as DNA lesions, cell cycle arrest, DNA repair, cellular senescence, and apoptosis.[30] Moreover, DNA damage triggers many dangerous results in all organ systems, including the heart and vasculature, resulting in cardiovascular and cerebrovascular diseases.[31] ROS is the main factor that causes oxidative DNA damage. Therefore, antioxidant nanozymes can be used to protect cells from DNA damage. Mn_3O_4 nanoflowers with SOD-, CAT-, and GPx-like activities could efficiently scavenge excessive ROS under physiological conditions. Because of the excellent antioxidant activity of Mn_3O_4 nanozymes, DNA, lipids, and proteins in cells were protected from oxidative damage, showing a significant reduction in the accumulation of DNA double-strand breaks and no accumulation of lipid peroxides and protein carbonyls. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is the main protein that enhances the expression of antioxidants in cells. Notably, the Nrf2 protein response did not change after Mn_3O_4 nanozyme treatment under oxidative stress conditions, indicating that the nanozyme could protect cells from ROS-induced DNA damage but did not interrupt the sensing mechanism of oxidative stress.[32] Similarly, Nobuaki et al. found that Ce-doped titanate nanosheets with SOD-like activity inhibited UV-induced DNA damage since they catalyzed the conversion of $O_2^{\bullet-}$ to O_2 and H_2O_2.[33]

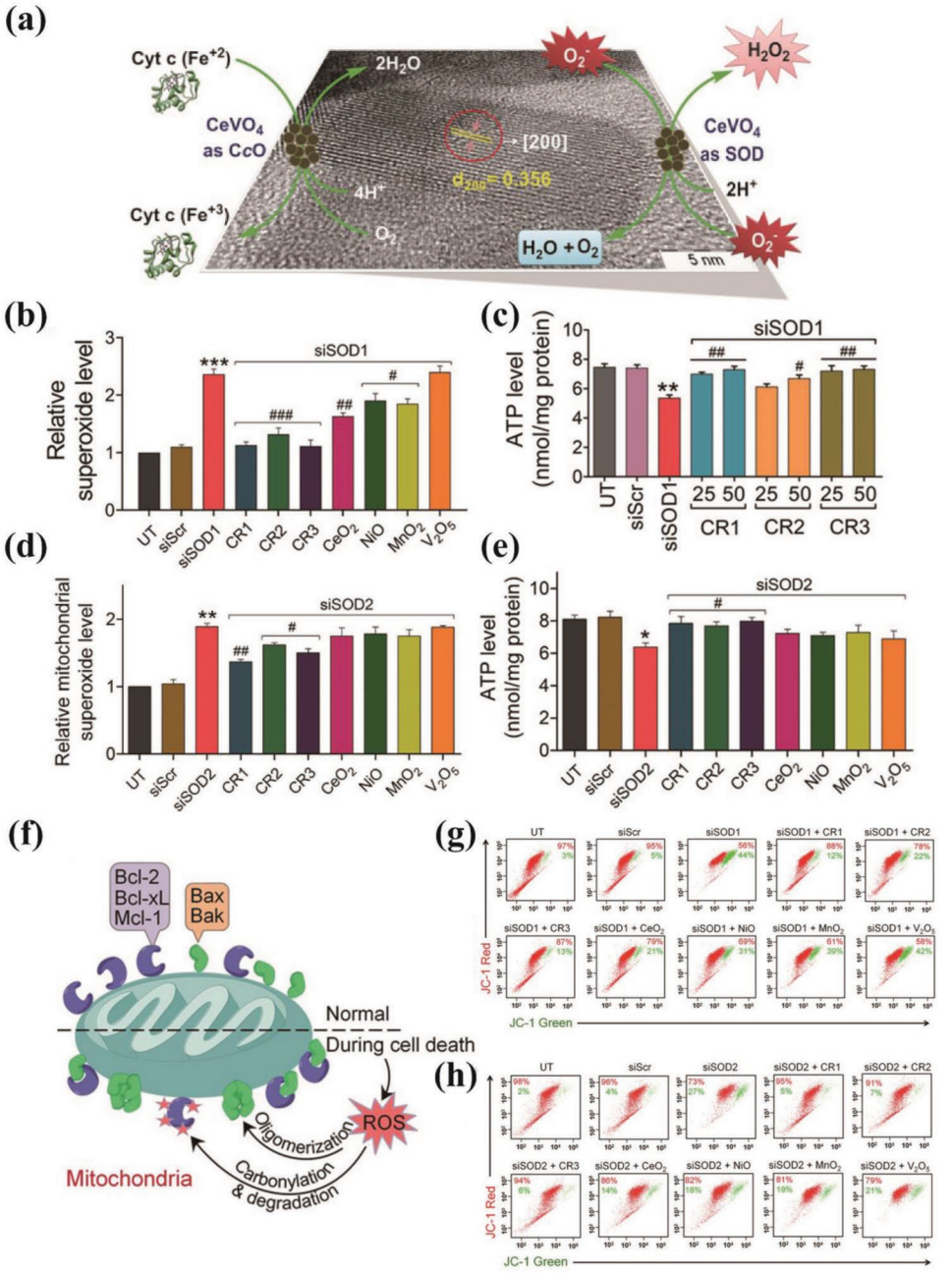


Figure 1. a) $CeVO_4$ nanozymes catalyze the reduction of dioxygen to water without releasing partially reduced oxygen species. Reproduced with permission.[25] Copyright 2019, Wiley-VCH. SH-SY5Y cells were transfected with SOD1-siRNA or with Scr-siRNA for up to 24 h, and incubated with 50 ng μL^{-1} nanomaterials ($CeVO_4$ nanorods, NiO, MnO_2, CeO_2, and V_2O_5) for another 24 h, followed by treating the cells with DHE (5 μM) and JC-1 (5 μM) for b) superoxide levels and g) mitochondrial membrane potential, respectively. Estimation of cellular ATP level after 48 h of transfection with c) siSOD1 and e) siSOD2 in the presence or absence of $CeVO_4$ nanorods using bioluminescence detection kit. SH-SY5Y cells were transfected with SOD2-siRNA or Scr-siRNA for up to 24 h, and 50 ng μL^{-1} nanomaterials ($CeVO_4$ nanorods, NiO, MnO_2, CeO_2, and V_2O_5) were incubated for another 24 h, followed by treating the cells with MitoSOX (10 μM) and JC-1 (5 μM) for d) mitochondrial superoxide levels and h) mitochondrial membrane potential, respectively. f) Schematic representation of pro-survival and pro-apoptotic Bcl-2 family proteins alignment on the mitochondrial membrane. Adapted with permission.[26] Copyright 2021, Wiley-VCH.

In addition, nanozymes also attenuate cellular senescence, which is closely related to the development of vascular pathologies. Ultraviolet A (UVA) irradiation can produce ROS, which then in turn induces cellular senescence. Luo and coworkers synthesized ultrasmall Prussian blue nanoparticles (USPBNPs) with excellent antioxidant activity, which could significantly scavenge ROS for cellular senescence therapy. Benefiting from the ultrasmall size and superior activity of PB, as low as 1 μg mL^{-1} USPBNPs significantly decreased the SA-β-gal activity. After that, the authors elucidated the molecular pathway by which PB

protected cellular senescence from UVA. After adding USPBNPs, the G1/S phase cell cycle arrest of UVA-irradiated human fibroblasts was attenuated, and senescence-associated proteins such as p16, p21, p53, and γ-H_2AX were all reduced, suggesting that USPBNPs could inhibit ERK/AP by eliminating excess ROS to achieve the treatment of senescent cells.[34] The presence of nanozymes has positive impacts on regulating these ROS-associated pathways, making sense to attenuate senescence.

After discussing the protective mechanism of nanozymes by ROS scavenging, we introduce several in vitro studies that used antioxidant nanozymes for cardio- and cerebrovascular diseases. In Parkinson's disease (PD), a high level of ROS leads to cell damage and prevails condition exacerbated. To this end, Kuang et al. prepared a series of chiral molecule-mediated Cu_xO nanozymes with ROS scavenging capacity (**Figure 2**). Such Cu_xO synthesized with L-phenylalanine (Cu_xO-Phe NCs)

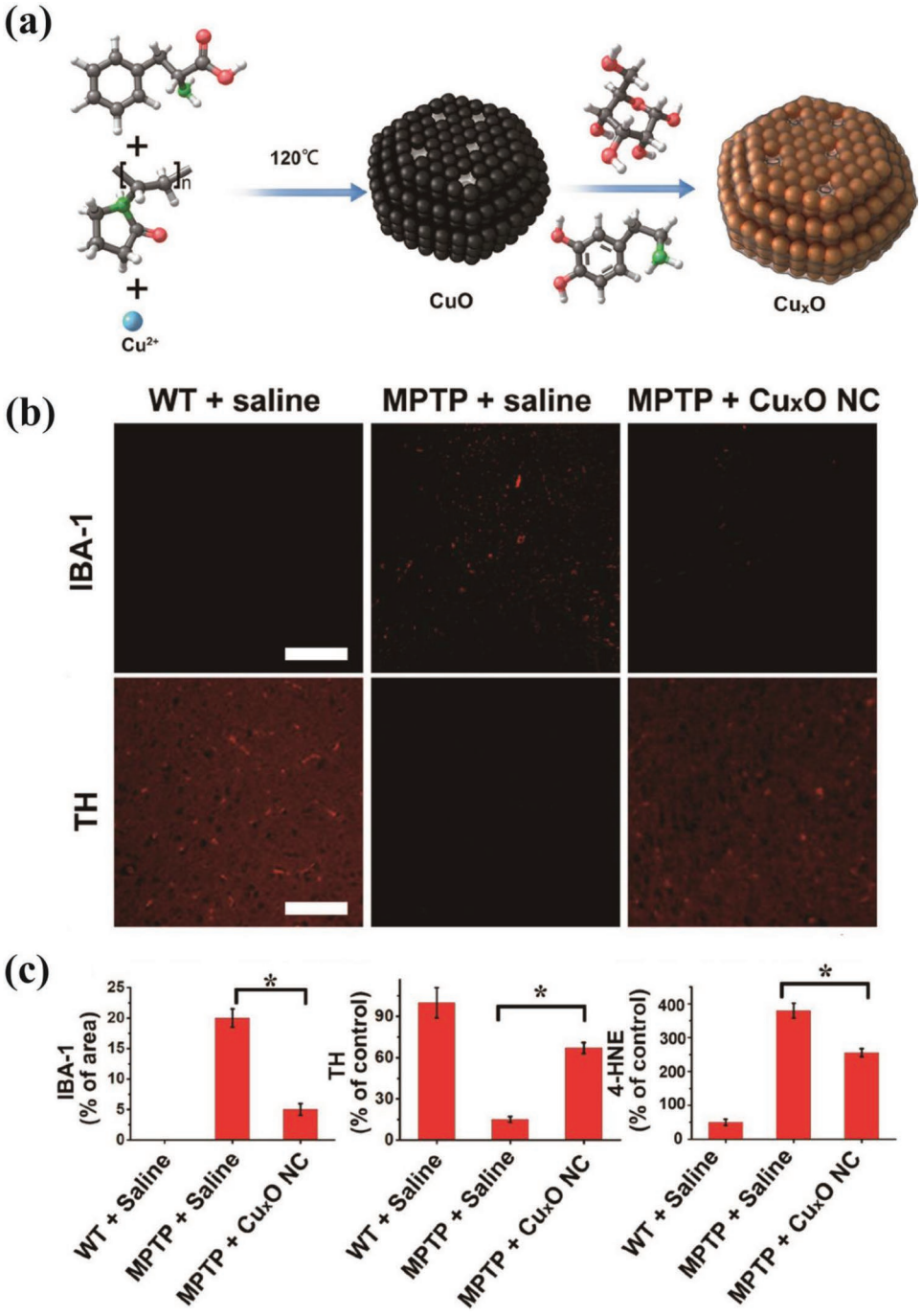


Figure 2. Chiral molecule-mediated porous Cu_xO nanoparticle clusters (NCs) with antioxidation activity for ameliorating Parkinson's disease. a) Schematic illustration of the preparation of Cu_xO NCs. b) Confocal images of wild-type mice striata, MPTP-induced PD mice striata, and Cu_xO NCs-treated PD mice striata: expression of IBA-1 and TH. c) Average expression levels of: IBA-1, TH, and 4-HNE in each treatment group ($n = 6$). Adapted with permission.[35] Copyright 2019, American Chemical Society.

had triple enzyme-like activities, which could synergistically eliminate ROS, endowing them with outstanding cytoprotecting ability. The representative apoptotic pathway, caspase 3, was downregulated by nanozyme treatment, while the expression of the related ionic calcium-binding adaptor 1 (IBA-1) was also decreased. IBA-1 is an indicator of neuroinflammation, and a reduced level of IBA-1 indicates amelioration of unbalanced oxidative states. Meanwhile, Kuang demonstrated that Cu_xO nanozymes could improve the striatal tyrosine hydroxylase (TH) level, which was necessary for dopamine biosynthesis. In the Cu_xO treatment group, the content of TH was upregulated, suggesting that possible blocking of dopamine-depletion pathway induced PD.[35] These results showed that nanozymes possessed superior cytoprotecting capacity via ROS scavenging.

Besides, ceria-based nanomaterials were designed for to treat the neurotoxicity of amyloid-β peptide (Aβ). By coating CeONPs with polyoxometalates (POMs), CeONP@POMs nanozymes with SOD- and proteolytic enzyme-like activity were synthesized (**Figure 3**). The CeONP@POMs nanozymes could penetrate the blood brain barrier (BBB) by the endocytic pathway and then effectively reduce Aβ-mediated toxicity by clearing Aβ and decreasing cellular ROS.[36] This work was based on the ROS-scavenging abilities of nanozymes and, more importantly, demonstrated the use of hydrolase-like nanozymes for therapies.

The signals and mass transfer among the cells are also vital biological processes. For example, the finding of pathologic α-synuclein transmission among brain cells is a breakthrough to help understand the possible causes of PD.[37] In this case, the excessive ROS significantly affects this spreading process (**Figure 4**a). Mao and coworkers reported that bimetal nanozymes (PtCu nanoalloys) with excellent

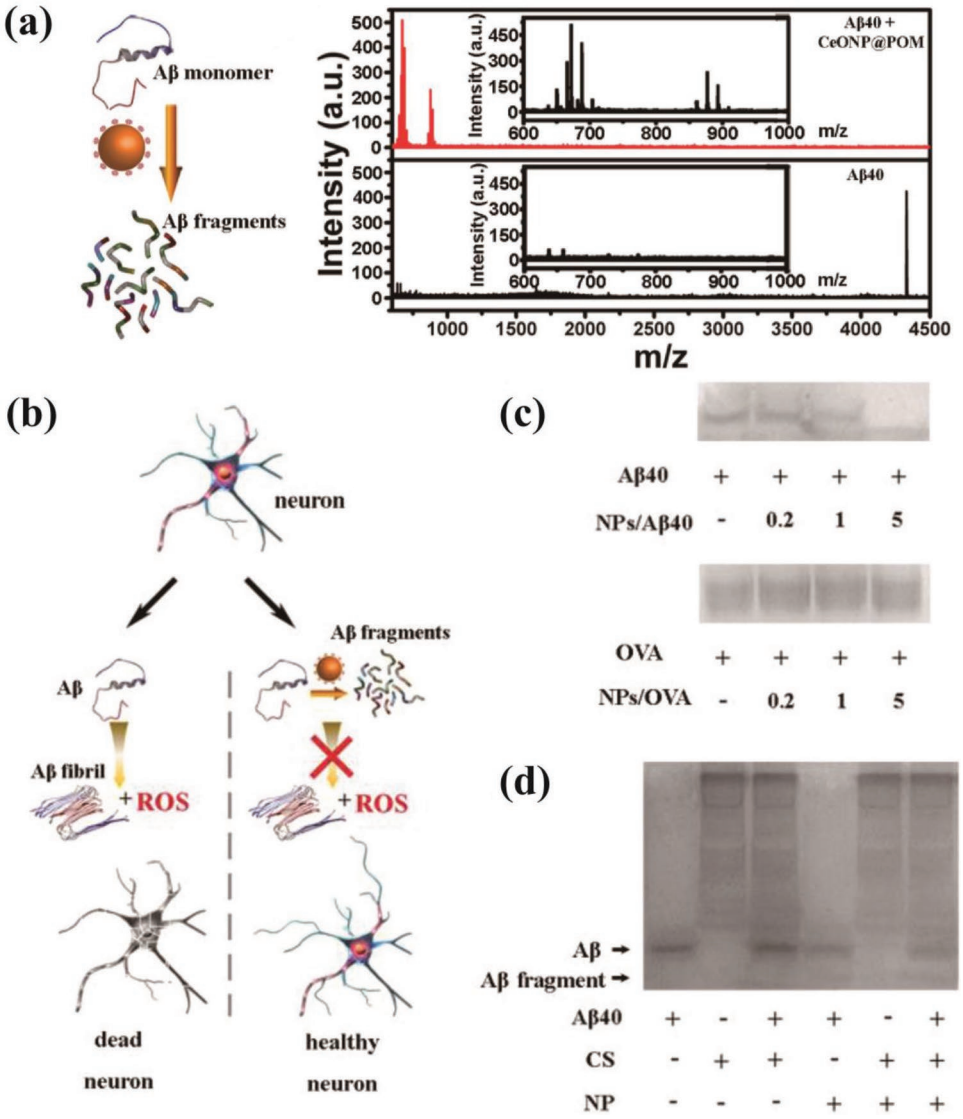


Figure 3. Ceria/POMs hybrid nanoparticles mimicking metallopeptidase for treatment of neurotoxicity of amyloid-β peptide. a) Scheme of CeONP@POMs as a hydrolytic enzyme to degrade Aβ40 monomers and MALDI-TOF MS of Aβ40 monomers untreated or treated with CeONP@POMs. b) Schematic representation of the cytotoxicity of Aβ40 and the effect of CeONP@POM on improving the process. SDS-PAGE analysis of c) Aβ40 and OVA treated or untreated with CeONP@POMs, d) Aβ40 monomers treated or untreated with CeONP@POMs. Adapted with permission.[36] Copyright 2016, Elsevier.

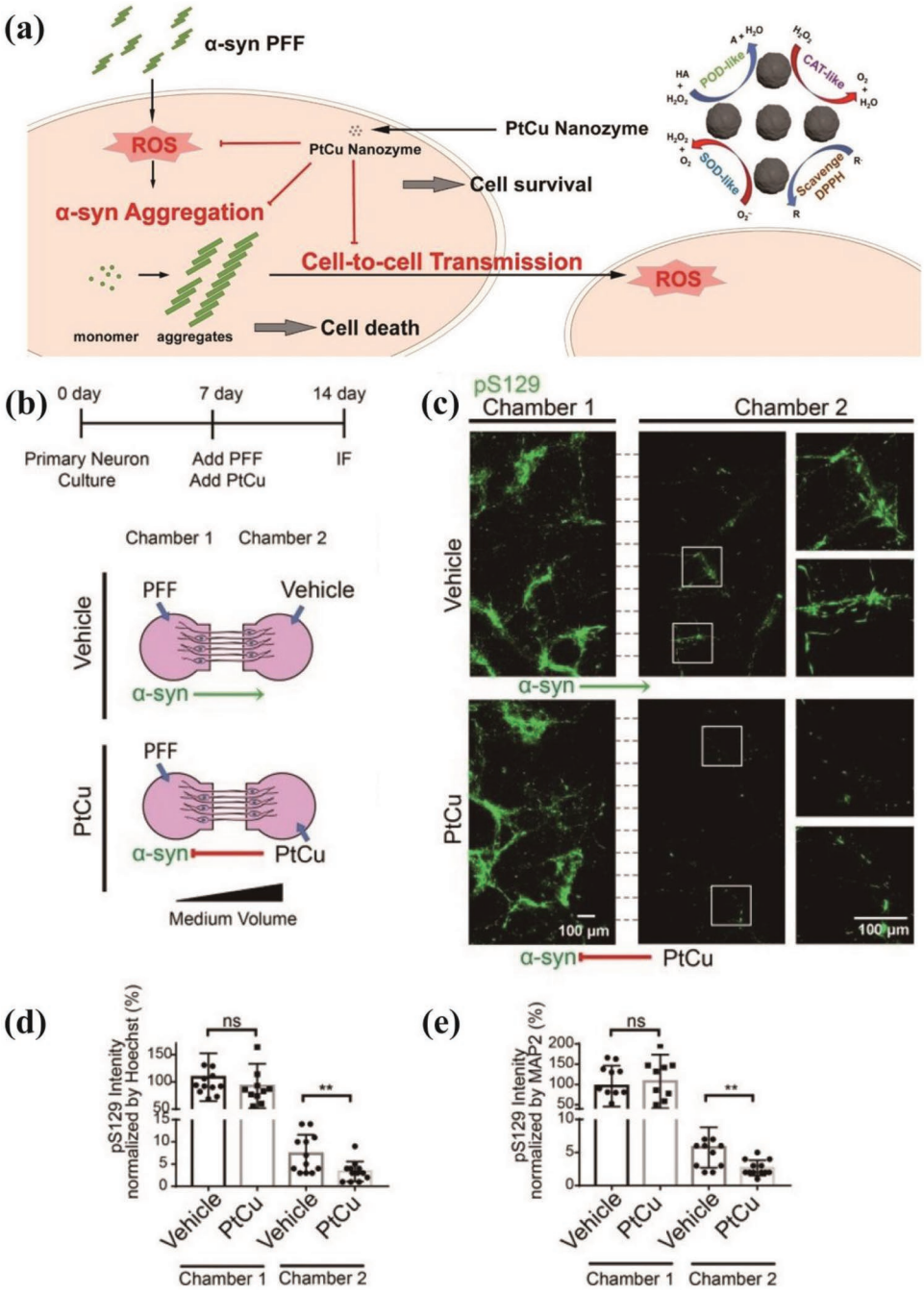


Figure 4. Nanozyme scavenging ROS for prevention of pathologic α-synuclein transmission in Parkinson's disease. a) PtCu nanozyme scavenging ROS and preventing pathologic α-synuclein-induced pathology, neurotoxicity and cell-to-cell transmission in vitro and in vivo. b) Timeline of α-syn transmission in the in vitro experiment (top) and the experimental design with PtCu NA treatment in the microfluidic chamber (bottom). c) Neurons were cultured in chamber 1 and chamber 2. Preformed fibrils were added to neuron cultures at 7 days in vitro in chamber 1. PtCu NAs (1 μM) were treated simultaneously into neuron cultures in chamber 2. d,e) pS129 immunostaining for α-syn transmission. Adapted with permission.[38] Copyright 2021, Elsevier.

ROS scavenging abilities prevented the aggregation of ROS-induced α-synuclein and the transmission of related cell-to-cell prion-like proteins. PtCu alloys possessed adjustable activities of ROS scavenging by changing the content of Pt, which benefited nanozymes to protect cells from oxidative stress. PtCu nanozymes significantly decreased the amount of pS129 in preformed fibril-treated neurons (≈50% less), which was a crucial marker for indicating the degree of α-synuclein pathology and spreading (Figure 4c–e). Moreover, they used a two-chamber microfluidic neuronal culture device as an in vitro model to demonstrate the blocking effect of PtCu nanozymes on α-synuclein transmission (Figure 4b). Similarly, the pS129 immunoreactivity was reduced by nanozyme treatments.[38]

4. Oxygen Regulation

Obstructed blood flow is a direct cause of some disorders,[39] resulting in hypoxia in cells in the ischemic area, which in turn leads to cell loss or dysfunction.[40] Regulation of angiogenesis by hypoxia is an essential component of homeostatic mechanisms linking vascular oxygen supply to metabolic demands.[41] Stenosis or occlusion of the vasculature would induce the cellular apoptosis or necrosis and further deteriorate into tissue damage in cardiovascular and cerebrovascular diseases.[42] Pro-angiogenesis is an effective strategy to improve the cellular apoptosis and necrosis. Therefore, oxygen regulation is a critical strategy to alleviate cardio- and cerebrovascular disorders.

Recently, with the help of pro-angiogenic cytokines, it has become easier to transfer blood flow to chronic inflammation-damaged areas.[43] However, many side effects have been reported during clinical trials, such as thrombosis and fibrosis. Due to these challenges, various nanozymes have been exploited. Among them, nanoceria, one of the most studied nanozymes, could act as oxygen buffers due to its adjustable valence of cerium. Thus, nanoceria has been employed to improve hypoxic microenvironments. For example, Seal and coworkers employed nanoceria as an oxygen sponge (i.e., an oxygen transfer station) to promote angiogenesis. The oxygen level in cells can affect the stability of hypoxia-inducible factor 1α (HIF-1α), which directly regulates gene expression of angiogenesis. Nanoceria could dynamically mediate oxygen in cells like a buffer solution, resulting in different activation of HIF-1α. Therefore, through this approach, pro-angiogenesis was realized.[44]

As mentioned above, based on its pro-angiogenesis ability, nanoceria was also adapted to build a tissue engineering scaffold in chicken chorioallantoic membranes and Sprague–Dawley rats. A biocompatible polymer polycaprolactone (PCL) was chosen as the scaffold, which was decorated with different contents of nanoceria as therapeutics for angiogenesis (**Figure 5**a). The PCL/nCeO_2 scaffolds played a role in cell adhesion, subsequent migration, and proliferation, which were necessary for the functions of in vivo implants (Figure 5b). A further molecular mechanism study revealed that the nanozyme upregulated the expression of HIF, VEGF (vascular endothelial growth factor), and EGFR (endothelial growth factor) signals by its oxygen buffer ability (Figure 5c–e). These results demonstrated the feasibility of nanozymes for clinical usage.[45]

5. NO Generation

Most vascular lesions originate from the dysfunction of endothelial cells (ECs) induced by physical damage, unhealthy habits, and excessive ROS.[46,47] In this case, the level of nitric oxide (NO), an important signaling molecule, decreases, which affects the behaviors of smooth muscle cells (SMCs), platelets, and even the ECs themselves. Endothelin nitric oxide synthase (eNOS) is a critical enzyme that produces NO and plays a vital role in endothelial vascular protection. Moreover, persistent oxidative stress renders eNOS uncoupled, causing severe dysfunction.[48] A number of studies have focused on fixing or replacing the damaged ECs to rebuild normal microenvironments. However, eNOS is very large and complicated, making it impossible to use as a therapeutic. Therefore, much attention is paid to finding alternative therapeutics to generate additional NO.[49,50]

In the presence of L-arginine (L-Arg) and β-nicotinamide adenine dinucleotide phosphate (NADPH), NOS can catalyze NO generation. Inspired by the natural NOS enzymes, Wu, Chen and co-workers built an NOS-like nanoplatform. The mesoporous silica-decorated noble metal nanostructures called Au@SiO_2-NH_2 (NanoNOS) had NOS-, SOD-, and oxidase-mimicking functions. NO was produced via a three-step cascade reaction: first, superoxide anions were produced by oxidase-like activity; second, H_2O_2 was produced from the superoxide anions via SOD-like activity; and finally, NO was generated from the oxidation of arginine by H_2O_2 (**Figure 6**a). NanoNOS-catalyzed NO release inhibited the injury-induced monocyte-endothelial cell adhesion by reducing the expression of adhesion molecules on the membrane of endothelial cells, such as intercellular cell adhesion molecule-1 (ICAM-1). With the precise modulation of the catalytic performance, undesirable cell adhesion was prevented by NanoNOS to a great extent, protecting endothelial cells from damage (Figure 6b).[51] In addition, researchers have also synthesized many nanozymes with GPx-like activities, which can convert endogenous prodrugs (e.g., S-nitrosoglutathione, GSNO) to NO.[52–55] Weng et al. made a polydopamine coating containing HKUST-1 MOF on stainless steel to mimic the function of ECs. They found that the HKUST-1 MOF coating could catalyze GSNO decomposition to generate NO, similar to natural enzymes. The immobilization of HKUST-1 MOF could inhibit SMC proliferation and migration at the EC location and promote EC formation by the generated NO molecules. In addition, the activation and aggregation of platelets were suppressed through the NO-cGMP signaling pathway. Based on the intercellular modulating effects of nanozymes, thrombosis was effectively prevented and reendothelization was obviously accelerated.[56]

Moreover, NO exerts its cellular effects via different mechanisms, including cGMP-dependent and cGMP-independent pathways. NO can modify proteins through nitrosation to affect the signaling pathways.[57] More examples showing the efficiency of NO in vivo will be discussed in the following sections.

6. Nanozymes for the Treatment of Cardio- and Cerebrovascular Diseases In Vivo

After discussing the therapeutic mechanisms of nanozymes in vitro, in this section, we selected representative examples to demonstrate the great promise of nanozymes for treating cardio- and cerebrovascular diseases in vivo.

7. Nanozymes for Cardiovascular Diseases

Cardiovascular diseases are the primary cause of death globally. The multifaceted etiology of cardiovascular diseases often involves atherosclerosis (AS). The current medications for treating AS include anti-cholesterol, anti-inflammatory, and anti-thrombus drugs. In severe cases, interventional treatment

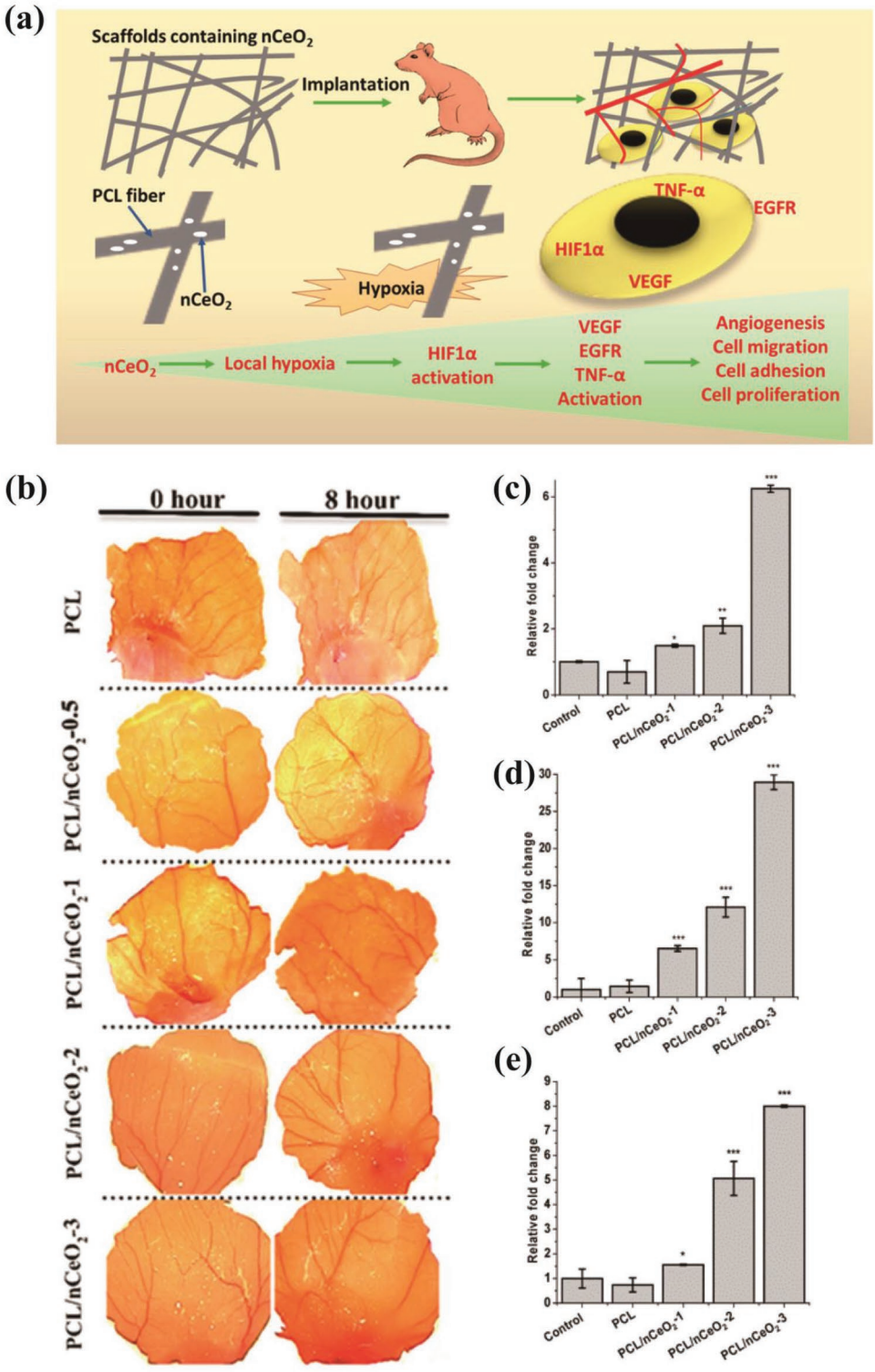


Figure 5. a) CeO_2-containing scaffolds supported cell adhesion and angiogenesis in tissue engineering scaffolds. b) CAM incubated with PCL, PCL/nCeO_2-0.5, PCL/nCeO_2-1, PCL/nCeO_2-2, and PCL/nCeO_2-3 scaffolds and analyzed for the growth of blood vessels for a period of 0–8 h. Reverse-transcriptase PCR analysis of c) HIF1α, d) VEGF, and e) EGFR mRNA in tissues isolated from implanted scaffolds. Adapted with permission.[45] Copyright 2018, American Chemical Society.

is needed. Implanting a drug-eluting stent (DES) provides the most effective treatment by enlarging the lumen of an artery narrowed by an atherosclerotic lesion.[58] However, neither the medicine for AS nor the drugs on the DES can avoid side effects. Therefore, new treatments have been exploited. Among them, nanomedicine has made considerable advancements in

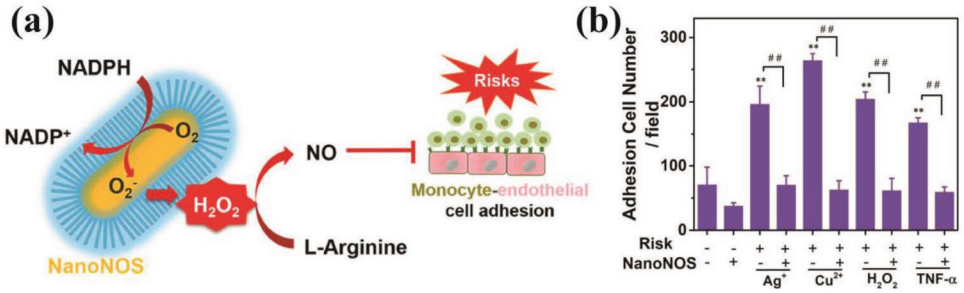


Figure 6. a) A nitric oxide synthase (NOS)-like nanoplatform (NanoNOS) that consists of a noble metal nanoparticle core and a mesoporous silica shell. NanoNOS can catalyze constant NO generation and protect from cardiovascular injury. b) Image-based quantitative results of HUVEC and THP-1 cells stained with calcein: cell–cell adhesion increased due to endothelial cell injury resulting from external stimuli, while adhesion decreased after NanoNOS treatment. Adapted with permission.[51] Copyright 2020, American Chemical Society.

cardiovascular disease treatment.[48] Various nanomaterials have been designed to deliver drugs at the arterial injury sites.[59,60] Nanozymes can act as antioxidants for tissue recovery and disease treatment. Meanwhile, many nanozymes with porous structures can serve as carriers for drug delivery.

In an early study, Kolattukudy and coworkers found that CeO_2 could inhibit progressive left ventricular dysfunction by decreasing the expression of monocyte chemoattractant protein (MCP-1), whose expression could cause ischemic reperfusion.[61] In the MCP-1 transgenic mice, the expression of MCP-1 in serum levels was downregulated owing to the auto-regenerative antioxidant properties of CeO_2, while the proinflammatory and endoplasmic reticulum (ER) stress-associated genes were also suppressed. As a consequence, the cardioprotective effects of CeO_2 resulted in significant preservation of the left ventricular dimension with less ventricular dilatation and a slight decrease in cardiac fractional shortening. Apart from being antioxidants, nanozymes could also be used as drug carriers without affecting their catalytic activity. The porous manganese-substituted PB (PMPB) nanocube (NC) with rich porosity was used to load a clinical antioxidant drug (i.e., simvastatin). In the case of AS treatment, Xu et al. found that Simvastatin@PMPB NC outweighed either simvastatin alone or PMPB NC alone.[62] As the PMPB NC decreased the secretion of pro-inflammatory cytokines, the most significant decrease in oxidative stress was observed. Then, the oxidized LDL internalization and foam cell formation were also suppressed to a large extent. Accordingly, Simvastatin@PMPB NC was expected to have an antiatherosclerotic effect owing to the decreased thickness of the fibrous cap in the AS plaques. In another strategy of AS treatment, Zhao and coworkers used platinum (Pt) and cerium (Ce) bimetallic nano-raspberry (PtCe NRs) with ticagrelor to inhibit foam cells and platelet aggregation (**Figure 7**a).[63] The ROS scavenging activity from PtCe NRs and ticagrelor acted on the P2Y12 receptor (preventing AS plaque expansion). Consequently, the PtCe NRs controlled the area of atherosclerotic lesions in high-fat diet-fed $ApoE^{-/-}$ mice. The ticagrelor- and DSPE-PEG2000-Ticagrelor-PtCe NRs-treated groups had fewer oil red O (ORO)-positive areas than the saline treatment group, indicating good therapeutic effects (Figure 7b–f).

Endovascular interventional treatment, one of the primary methods for cardiovascular diseases, is needed in severe conditions. However, vascular restenosis is a significant drawback of endovascular interventional treatment.[64] Zhang et al. reported that PB nanozyme (PBzyme) could modulate macrophage polarization to prevent vascular restenosis. PBzyme infiltration inhibited the expression of p-STAT1 by reducing ROS levels, thereby suppressing the inflammatory response and initiating the macrophages polarization toward the M1 phenotype. Since the PBzyme accumulated in the damaged vascular intima, it impeded the M1 responses and promoted the protective M2 responses in macrophages, regulating the migration and proliferation of ECs and SMCs indirectly. In this context, endovascular intervention induced endothelial cell shedding through vascular balloon injury, which was a favorable condition for the passive infiltration of nanozymes into the vascular intima and accumulation in macrophages to alleviate long-term vascular restenosis.[65]

Due to trauma, disease, and congenital abnormalities, tissue disorders or organ loss inevitably occur, especially in the vessels. Autografting and allografting are utilized for damaged area replacement. Because of the induced immunoreaction or complication of the current biomaterials, a new generation of biomedical materials is needed. As mentioned above, NO is a signaling molecule that modulates the steady state of the blood. A long-term in situ NO generation platform was recently established by Wang and coworkers.[66] They obtained electrospun scaffolds incorporating MOF-199, a copper-based framework, as active catalytic materials to catalyze endogenous RSNO decomposition (**Figure 8**a). Compared with PCL alone, the functional vascular grafts (PCL-0.125% MOF) achieved a higher degree of endothelial cell coverage and a lower percentage of platelet adhesion (Figure 8b). After 4 weeks of treatment, the endothelialization rate was evaluated by immunofluorescence staining, and the rate of nanozyme-loaded scaffolds was 25.74% higher than that of the PCL alone group (Figure 8c,d). Moreover, the newly generated ECs were oriented in the direction of blood flow, which was the same as that of the native endothelium. These results demonstrated that NO produced by nanozymes-loaded artificial vessels could effectively promote normal vessel reconstruction. And the repaired tissue displayed normal biological behaviors without any inappropriate sites. Another treatment for vessel damage is stent implantation. As mentioned earlier, NO produced by nanozymes could mediate the behaviors of ECs, SMCs, platelets, and even macrophages. On this account, researchers have paid more attention to the decoration of stents. Weng and coworkers used a layer-by-layer method to prepare a MOF coating on the surface of stents (Figure 8e).[67]

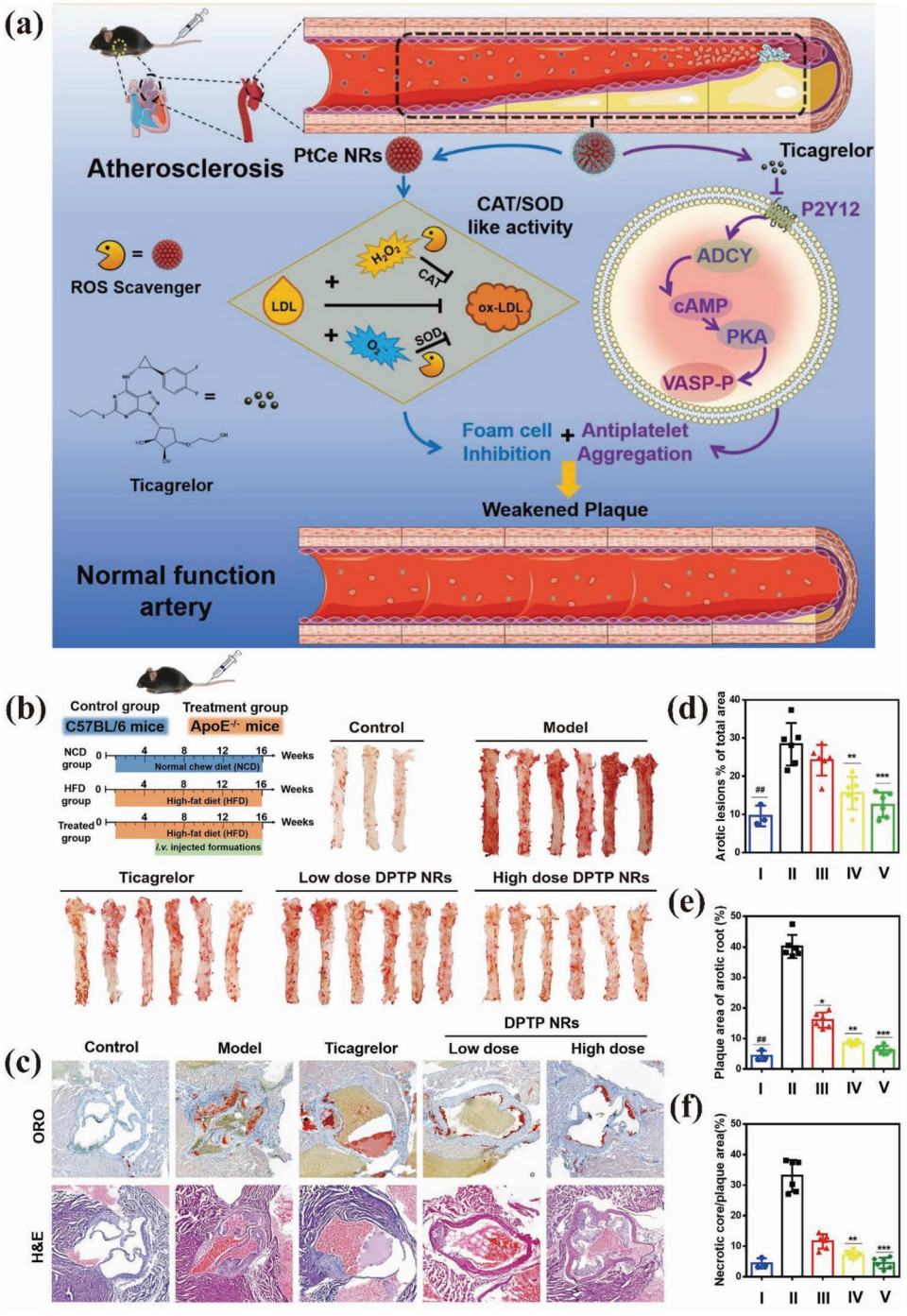


Figure 7. a) Platinum–cerium bimetallic nano-raspberry for atherosclerosis treatment via synergistic foam cell inhibition and P2Y12 targeted antiplatelet aggregation. b) Representative photographs of ORO-stained enface aortas from mice treated with different formulations. c) Representative images of aortic root sections stained with ORO and HE. d) Quantitative analysis of the lesion area in aortas. e,f) Quantitative analysis of the lesion area in aortas. Adapted with permission.[63] Copyright 2022, Elsevier.

The Cu-MOFs could catalyze the generation of NO, which successfully suppressed neointimal hyperplasia in vessels and reduced the inflammatory response.

While NO is an indispensable substance in vessel systems, it also causes some diseases.[68] Pulmonary arterial hypertension (PAH) is a dangerous disease that can lead to heart failure and even death. It is established that the significant increase in NO, at least in part, raises oxidative stress in diseased areas and triggers worse conditions. In addition, long-term hypertension would initiate right ventricular (RV) hypertrophy, a representative symptom. To address these problems, nanozymes have been employed to avoid the abnormal proliferation of the

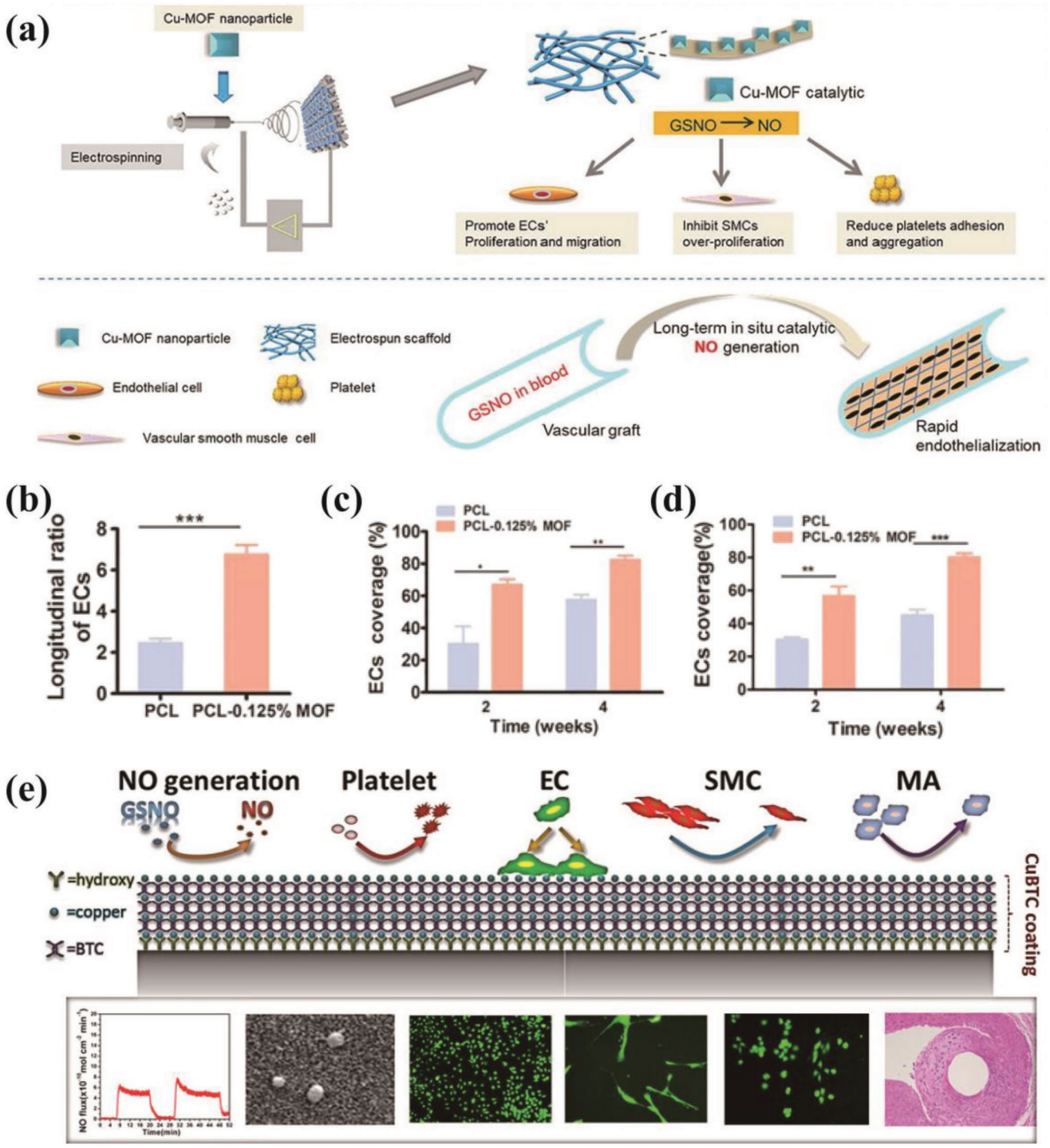


Figure 8. a) A metal–organic-framework incorporated vascular graft for sustained nitric oxide generation and long-term vascular patency. b) The ratio of endothelial cell long axis to short axis was calculated by En-face staining. c) The endothelial coverage at 2 and 4 weeks was calculated by SEM images. d) Endothelial coverage at 2 and 4 weeks was acquired based on longitudinal sections with CD31 staining. Adapted with permission.[66] Copyright 2021, Elsevier. e) Copper-based SURMOFs for NO generation could be a promising strategy for the surface modification of cardiovascular stents. Reproduced with permission.[67] Copyright 2019, American Chemical Society.

right ventricle.[69] In a monocrotaline-induced (MCT) rat model, ceria nanoparticles showed a splendid ability to inhibit undesired tissue proliferation by decreasing oxidative stress and cardiomyocyte apoptosis. In the measurement of pulmonary arterial pressure (PA Pr), mean pulmonary arterial diameter (MPA diameter), mean pulmonary arterial area (MPA area), and right ventricular outflow tract diameter (RVOT), the related results of the nanozyme treatment group had no significant changes

at day 28 when compared with the beginning, while the control group showed 18%, 27%, 46%, and 14% higher parameters, respectively. Moreover, at the whole tissue level, RV anterior free wall thickness as well as inter-ventricular septum diameter was obviously attenuated by nanozymes.

8. Nanozymes for Ischemia Reperfusion Injury

The ischemia reperfusion injury (IRI) occurs because the restoration of blood flow results in ROS accumulation, calcium overload, and inflammation. Cardiac ischemia/acute myocardial infarction causes cardiac ischemia–reperfusion (I/R) injury, while ischemic stroke causes cerebral ischemic reperfusion injury (CIRI). IRI is a pathological process involving multiple factors, and a common manifestation is the production of a large amount of ROS. Considering such pathological features, it is reasonable to use antioxidative nanozymes to treat ischemia reperfusion.[70–76]

Bursting of $O_2^{\bullet-}$, a kind of ROS from the mitochondrial respiratory chain upon reperfusion, has been recognized as the initiating reason for IRI. Targeting mitochondria and mitigating mitochondrial oxidative damage are suitable methods to treat IRI. Huang, Kong, and coworkers made a hybrid nanozyme with mitochondria-targeting ability for IRI therapy. By using the ferritin-heavy-chain-based protein (FTn) as an enzyme scaffold, the hybrid Mn-based nanozyme overcame the intracellular lysosomal barrier to escape into the cytoplasm and accumulate in mitochondria (**Figure 9**a,b). The nanozymes had both SOD-like and CAT-like activities, preventing secondary damage from the process of $O_2^{\bullet-}$ elimination. As a result, there was gradual improvement in cardiac-functionality recovery after the mice were administered the nanozymes, as evidenced by increased parameters of left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) (Figure 9c). And, the areas of healthy myocardium (red) tissue were improved (Figure 9d). Similar results were also seen in the cardiac patch model (Figure 9e,f).[76]

Stroke is the second leading cause of death worldwide after cardiovascular diseases. Ischemic stroke is the primary type of stroke, mainly due to the sudden blockage of blood supply to the brain, accompanied by an explosively increasing amount of ROS. Cerebral ischemic reperfusion injury also occurs with neural apoptosis. Very recently, Liu et al. made a multi-enzyme cascade antioxidant system to eliminate intracellular ROS and inhibit neural apoptosis during CIRI. They successfully synthesized Fe_2NC@Se nanozyme with three types of antioxidant activities, which provided excellent cytoprotecting abilities. In the middle cerebral artery occlusion (MCAO) model of SD rats, Fe_2NC@Se nanozyme inhibited the ASK1/JNK signaling pathway and protected MCAO rats. The antioxidant effects of Fe_2NC@Se nanozyme suppressed oxidative stress-triggered neural apoptosis, markedly decreased infarct volume, and improved neurological deficits (**Figure 10**).[75]

9. Nanozymes for Neurological Disorders

Growing evidence shows a strong association between the dysfunction of brain vessels and neurodegenerative disorders.[77–80] Neurodegenerative disorders share a pathological basis with cerebrovascular diseases. They are all influenced by oxidative stress and then cause damage to proteins and other biomolecules. It is of significance to discuss the application of nanozymes in neurodegeneration in this review. Alzheimer's, Parkinson's, and Huntington's diseases are the most common neurodegenerative disorders.[81,82] Oxidative stress is involved in these diseases, as oxidative molecules have been observed in the brain tissues of patients with neurodegenerative diseases.[83] The oxidized molecules of proteins, like Aβ, interfere with the use of metals by brains, leading to neurodegenerative diseases.[3] Consequently, the redox modulatory nanozymes, such as Mn_3O_4 nanoflowers,[84] ultrasmall lactoferrin-modified Au-Bi_2Se_3,[85] CeO_2,[86] hemin with g-C_3N_4 nanosheets,[87] PB,[88] etc., have been applied to neurological disorder therapy.

Alzheimer's disease (AD) is a common form of irreversible dementia whose therapeutic demand is unmet.[89] Similar with other neurodegenerative diseases, AD exhibits severe neuroinflammation but is accompanied by the accumulation of Aβ. To avoid biomolecule interference and prevent immune response activation, Qu et al. designed a Cu_xO nanozyme coated with erythrocyte membrane with Aβ-targeting pentapeptide (Cu_xO@EM-K). With the help of targeting molecules, nanozymes could capture the Aβ in blood and brain. They, meanwhile, scavenged excessive ROS. In vivo experiments confirmed that Cu_xO@EM-K adsorbed the Aβ present in the blood and brain and improved memory deficits in a rat model. The immunoassay and ELISA analyses supported the efficiencies and biosafety of nanozymes. Due to the removal of Aβ, the memory function was maintained.[90] This work provides a novel method to ease AD conditions. Indeed, there are also many reliable works for the treatment of AD.[91–94]

PD is an intractable neurodegenerative disorder associated with neuroinflammation and loss of nigrostriatal dopaminergic neurons. Importantly, pyroptosis may contribute to neuronal loss, further causing PD. Very recently, Zheng and Cai et al. reported that PB nanozyme (PBzyme) inhibited pyroptosis and alleviated neurodegeneration through the NLRP3 pathway. When loaded around the lateral ventricles, the PBzyme rescued the loss of dopaminergic neurons and striatal dopaminergic fibers. In the MPTP-induced PD mouse model, PBzyme attenuated motor deficits by intra-cerebroventricular (ICV) injection (**Figure 11**a–d). The distance traveled, central area traveled, and duration of mobility of PD were significantly improved after PBzyme treatment (Figure 11e–h). Further study showed that the PBzyme reduced the activation of microglial NLRP3 inflammasomes and caspase-1, leading to the inhibition of microglial pyroptosis.[88]

Regarding neurological functional recovery after ischemic stroke, nanozymes also play essential roles. In another study, PBzyme was used to cure ischemic stroke after microglial phagocytosis. In the stroke mice, from day 3 to day 28 post-stroke, the volume of brain lesions of MPBzyme@NCM-treated mice was significantly smaller than that of the control group. Due to the anti-inflammatory ability, MPBzyme@NCM made microglia polarization toward the M2 phenotype and decreased the apoptosis of neurons. By targeting inflamed brain microvascular endothelial cells, the recruitment of

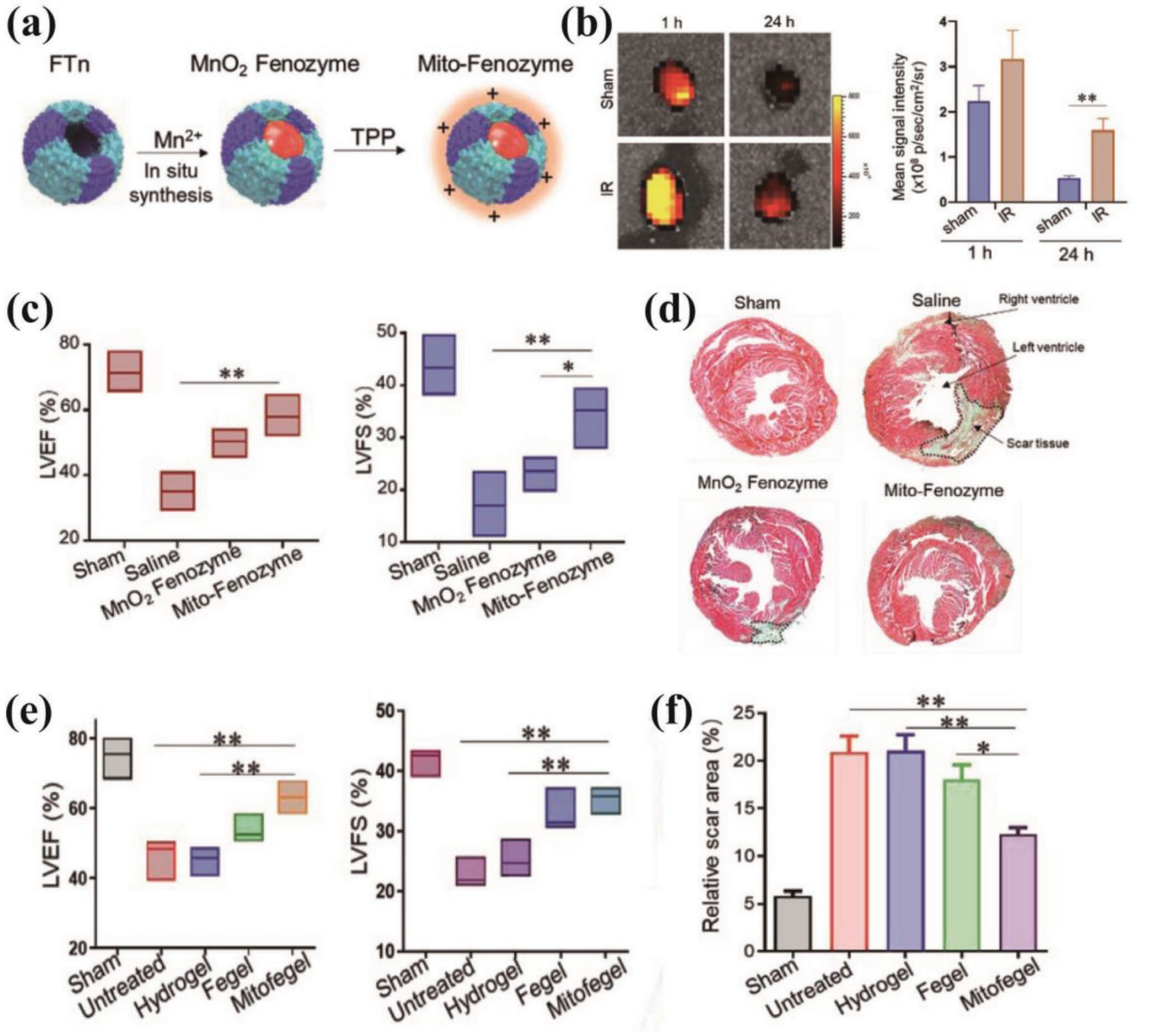


Figure 9. a) Mito-Fenozyme was fabricated by in situ synthesis of MnO_2 into FTn core via Mn^{2+} oxidation in the presence of H_2O_2, followed by TPP-NHS ester conjugation with free -NH_2 of protein. b) Representative ex vivo fluorescence imaging of mouse hearts and quantification analysis of fluorescence intensities at different time points after tail vein injection of Mito-Fenozyme into sham and IR mice ($n = 3$ per group). c) Quantification analysis of cardiac function by determining the parameters of LVEF and LVFS. d) Representative images of midpapillary regions of the hearts, 14 days after IR using Masson's trichrome staining (blue, collagen-rich scar tissue; red, viable myocardium). e) Quantification analysis of the cardiac function of the left ventricular wall motion of mice after hydrogel adhesion at 14 days by determining the parameters of LVEF and LVFS. f) Quantification analysis of scar area of midpapillary regions of the hearts isolated. Adapted with permission.[76] Copyright 2021, Wiley-VCH.

neutrophils and proliferation of neural stem cells were reduced.[95] This work demonstrated the superiority of nanozymes in neurological functional recovery, indicating that the strategies based on nanozymes are feasible for brain diseases. Another representative disorder is Huntington's disease, a complex, multifactorial disease incorporating epigenetic factors and oxidative stress. Chen and coworkers synthesized selenium nanoparticles to protect the brain from oxidative damage and repair neural functions. They used *Caenorhabditis elegans* (*C. elegans*) as an animal model to induce a Huntington's disease, performing behavioral dysfunction. After treatment of nanozymes, the level of ROS decreased and the condition of *C. elegans* improved.[96]

10. Summary and Outlook

Nanozymes have received growing attention since ferromagnetic nanoparticles as HRP mimics were discovered in 2007.[97] Because of their high stability, high activity, and

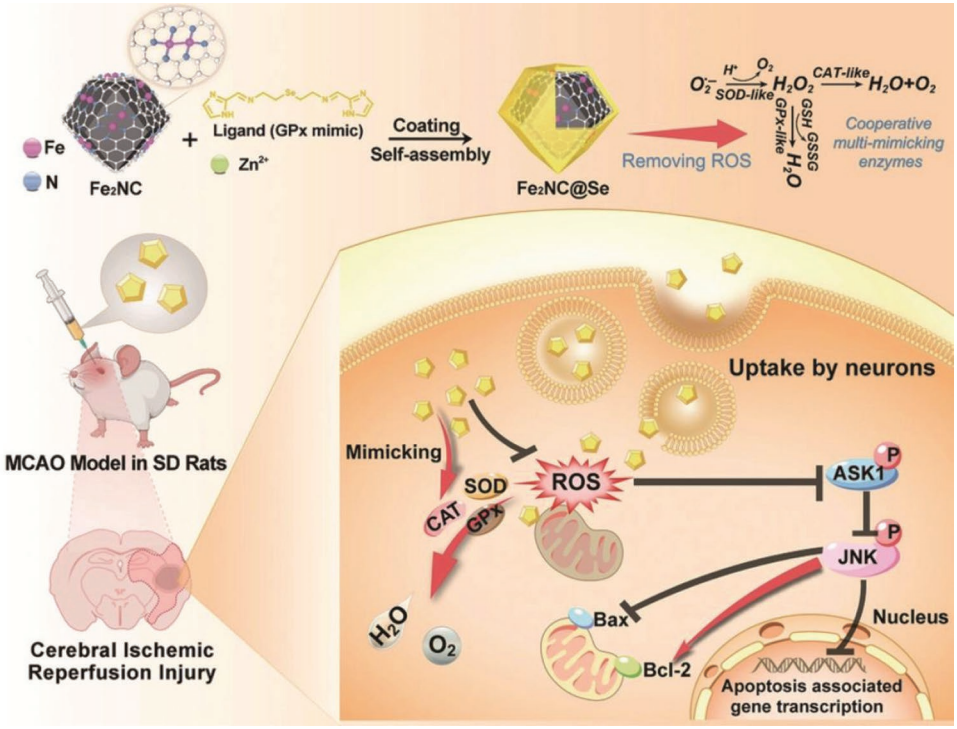


Figure 10. Fe_2NC@Se with multi-enzyme mimicking activities and its therapeutic use for reperfusion injury in ischemic stroke. Reproduced with permission.[75] Copyright 2022, Wiley-VCH.

low cost, nanozymes have been studied for various applications including disease therapy. The intrinsic physiochemical properties of nanozymes give them the capacity to solve many questions in some diseases. In this review, we focus on the treatment of cardio- and cerebrovascular diseases with nanozymes that can directly or indirectly modulate inflammation through ROS scavenging, oxygen regulation, and NO generation (as shown in **Table 1**). Despite numerous achievements that have been demonstrated, there are still many challenges in developing better therapeutic nanozymes.

11. For Nanozymes Themselves

There is plenty of complex enzymes in the evolution of human species. Although nanozymes effectively solve some limitations of natural enzymes, the characteristic structure and abundant co-enzymes make them challenging to mimic, especially in blood systems. Hence, in some situations, it is an alternative strategy to simulate natural enzyme functions first. However, the ultimate aim of nanozymes is to mimic or even surpass natural enzymes. Therefore, it is necessary to introducing the structural features of natural enzymes when design a nanozyme. This could be achieved via various approaches, including a high-throughput screening and natural enzyme-inspired rational design. Meanwhile, the following questions should be considered. Although many nanozymes were designed for disease treatment, nearly all of them are still in the animal research stage. Before nanozymes can be translated to clinical applications, there is still a long way to go. The main barriers and challenges for a clinical translation involve these issues (i.e., side effects, the route of administration, catalytic mechanism, immunogenicity, and tolerance).

First, the biosafety of nanozymes is an unavoidable problem before they are translated to the clinic. Unlike natural enzymes, the metabolism of nanozymes is a critical issue that should be addressed. In some cases, some of the metal ions used to synthesize nanozymes are not essential to bodies and organisms, and some components in nanozymes have potential toxicity, which might compromise the therapeutic effect of the nanozymes. Few articles have studied the potential toxicity of nanozymes, such as reproductive toxicity. A promising kind of nanozymes may be a biodegradable one, like decomposable inorganic composite-based nanozymes. For example, Mn_3O_4 could be a superior nanozyme that exhibits many antioxidant activities. Moreover, it could be converted to manganese ions under some acidic conditions, invoking related immune responses, which opens up new horizons for combination therapy. Meanwhile, a series of organic biodegradable nanozymes, such as polydopamine nanoparticles,[98,99] and melanin nanoparticles,[100] have attracted worldwide attention due to their biodegradable and biocompatible properties. After effective removal of ROS, they can be degraded into harmless substances and excreted out of bodies.

On the other hand, it is necessary to explore the route of metabolism of nanozymes in the blood system. The in vivo behavior of nanozymes is an important issue to explore more deeply. In future studies, the transport, transformation, and bioavailability of nanozymes need to be investigated. Inspiringly, a recent study found that the biodistribution of MoS_2 nanomaterials is mediated by protein coronas that spontaneously form in the blood.[101] This study also demonstrated that nanomaterials

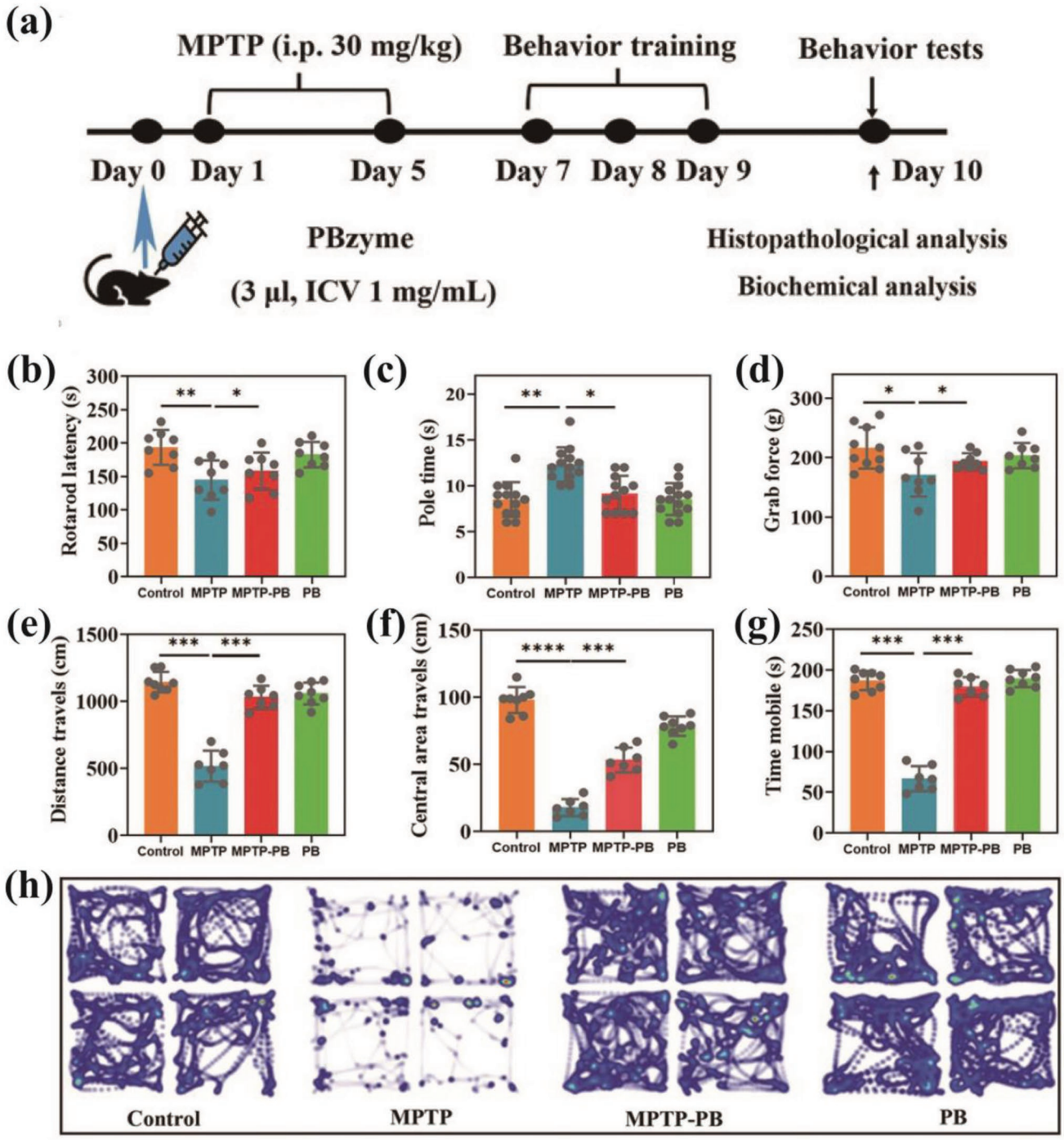


Figure 11. PBzyme as a pyroptosis inhibitor alleviates neurodegeneration. a) Treatment schedule of MPTP-induced mouse model of PD in the presence or absence of PBzyme. b) Latency to fall during the rotarod test ($n = 8$). c) Pole test time ($n = 12$–13). d) Forelimb grip strength ($n = 8$–10). e–g) Open-field parameters: e) distance travels, f) central area travels, and g) duration of mobility. h) Motion heat map of mice, which was tracked by Ethovision Tracking software ($n = 8$). Adapted with permission.[88] Copyright 2022, Wiley-VCH.

consisting of essential trace elements might be converted into active biological molecules that organisms could exploit. And a long-term study is required to understand chronic influences. In short, to make nanozymes reach the clinical trial stage, the metabolism and biosafety of nanozymes should be explored clearly.

Additionally, some strategies have been developed to make the platforms more biocompatible to reduce potential toxicity. For example, nanozyme surface functionalization with PEG,[102–104] cell membranes,[95,105,106] and liposomes[107,108] is an excellent way to improve biosafety and therapeutic efficacy. These modifications endow nanozymes with superior stealth ability, enhanced

Table 1. Nanozyme-enabled treatment of cardio- and cerebrovascular diseases.

Type of diseases	Therapeutic mechanisms	Symptom or model	Nanozymes	Activities	Strategies of nanozyme-enabled therapies	Ref.
Cardiovascular diseases	Antioxidative and anti-inflammatory strategies	Ischemic reperfusion	CeO_2	Autoregenerative anti-oxidant property	Attenuation of myocardial oxidative stress, ER stress	[61]
		Hydrogel-based cardiac patch	Mito-Fenozyme	CAT, SOD	Protection of mitochondrial functions	[76]
		Right ventricular hypertrophy	CeO_2	Antioxidant activity	Decreasing oxidative stress and cardiomyocyte apoptosis	[69]
		Atherosclerosis	PtCe NRs	Antioxidant activity	Synergistic foam cell inhibition and antiplatelet aggregation	[63]
			Sim@PMPB	H_2O_2 scavenging ability	ROS scavenging	[62]
		Vascular restenosis	PBzyme	SOD, CAT	Macrophages polarization toward M2	[65]
	NO generation	In-stent restenosis	Cu-SURMOFs	GPx	Promoting EC proliferation, inhibiting platelet adhesion	[67]
			Nano Cu-MOFs	GPx	Promoting EC proliferation, suppressing SMCs, and macrophage proliferation	[56]
		Thrombogenicity model	Cu NPs	GPx	NO generation, attenuating activated fibrinogen, and preventing platelet aggregation	[54]
		Small diameter vascular grafts	Cu-MOFs	GPx	NO generation, promoting EC migration and increasing Ac-LDL uptake	[66]
		Cardiovascular injury	Au@SiO_2-NH_2	OXD, SOD	Diminishing injury-induced monocyte–endothelial cell adhesion	[51]
	Oxygen regulation	Angiogenesis model	$nCeO_2$	Autoregenerative property	Stabilizing hypoxia HIF-1α by regulating the intracellular oxygen environment	[45]
Cerebrovascular diseases	Antioxidative and anti-inflammatory strategies	Parkinson's disease	Mn_3O_4	SOD, CAT, GPx	Antioxidative and anti-inflammatory	[84]
			Cu_xO NCs	SOD, CAT, GPx	ROS scavenging, inhibiting neurotoxicity	[35]
			PBzyme	SOD, CAT	Inhibiting the activation NLRP3 inflammasome and attenuating mitochondrial dysfunction	[88]
			Lf-Au-Bi_2Se_3 NDs	CAT, SOD, GPx, and POD	ROS scavenging and ameliorating the mitochondrial state	[85]
			Ceria NPs	SOD, CAT	Scavenging mitochondrial, intracellular, and extracellular ROS selectively	[86]
			PtCu NAs	POD, CAT, SOD	Inhibition of α-syn spreading and ROS scavenging	[38]
		Cerebral ischemic reperfusion injury	Fe_2NC@Se NPs	SOD, CAT, GPx	ROS scavenging and inhibiting the ASK1/JNK apoptotic signaling pathway	[75]
		Autosomal recessive spastic ataxia of Charlevoix–Saguenay	PDNPs	ROS scavenging capacity	Antioxidative and anti-inflammatory	[99]
		Huntington's disease	Nano-Se NPs	Antioxidant activity	ROS scavenging, inhibiting the aggregation of huntingtin proteins	[96]
		Alzheimer's disease	AuNPs@ POMD-8pep	Proteolytic activity, SOD	Antioxidative and anti-inflammatory strategies	[92]
			CeONP@POMD	Proteolytic activity, SOD	Degrading Aβ aggregates, promoting PC12 cell proliferation	[36]
			Nb_2C MXenzyme	SOD, CAT, POD	ROS scavenging, preventing the formation of Aβ deposition and neuroinflammation	[94]
			Cu_xO@EM-K	SOD, CAT, GPx	Relieving Aβ-induced membrane oxidative injury, decreasing brain Aβ burden	[90]
			Se@PDA@Bor	Antioxidant property	Scavenging RONS, restoring mitochondrial homeostasis, formation of M2 phenotypes	[93]

Table 1. Continued.

Type of diseases	Therapeutic mechanisms	Symptom or model	Nanozymes	Activities	Strategies of nanozyme-enabled therapies	Ref.
			Pd NPs	SOD, CAT	Reducing ROS and Ca^{2+} contents, protecting the mitochondria	[91]
		Ischemic stroke	MPBzyme@NCM	SOD, CAT	ROS scavenging, promoting microglia polarization toward M2 and neurogenesis	[95]
			MeNPs	RONS scavenging ability	Broad antioxidative activities against toxic RONS	[100]
			2D V_2C MXene	SOD, CAT, POD, GPx	Alleviating oxidative stress, inhibiting cell apoptosis and counteracting inflammation	[71]
			HSA-Mn_3O_4	SOD, CAT, GPx	Restraining cell apoptosis and endoplasmic reticulum stress	[72]

circulation time, and improved accumulation in the target sites. Besides, they offer a platform to easily fabricate or encapsulate disease-related molecules to achieve combination therapy.

12. For Cardiovascular and Cerebrovascular Diseases

ROS in multiple physiological and pathological processes are growingly appreciated for these vascular-related diseases. The design and application of anti-ROS nanozymes for cardiovascular diseases shall be the focus of future studies. However, some cruxes of matter remain. First, passing through the blood-brain barrier in neurological disorders and accumulating to diseased sites are inevitable problems that are still challenging to solve. And it depends on the mode of administration. In addition, nanozymes participate in tissue remodeling processes upon damage, but their final effects in diseases depend on the types of pathology attributed to complex pathological environments.

Acknowledgements

Y.Z. and W.L. contributed equally to this work. This work was supported by the National Natural Science Foundation of China (22104055, 21874067, and 21722503), the National Key R&D Program of China (2021YFF1200700 and 2019YFA0709200), Jiangsu Provincial Key R&D Program (BE2022836), the CAS Interdisciplinary Innovation Team (JCTD-2020-08), the PAPD Program, the Innovation Foundation of Nanjing University, and Fundamental Research Funds for the Central Universities (202200325 and 021314380195).

Conflict of Interest

The authors declare no conflict of interest.

Keywords

cardio- and cerebrovascular diseases, nanomedicine, nanozymes, reactive oxygen species

Received: August 5, 2022
Revised: September 18, 2022
Published online:

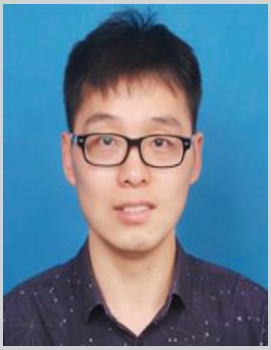
[1] M. A. B. Khan, M. J. Hashim, H. Mustafa, M. Y. Baniyas, S. K. B. M. Al Suwaidi, R. AlKatheeri, F. M. K. Alblooshi, M. E. A. H. Almatrooshi, M. E. H. Alzaabi, R. S. Al Darmaki, S. N. A. Lootah, *Cureus* **2020**, *12*, e9349.
[2] G. Deuschl, E. Beghi, F. Fazekas, T. Varga, K. A. Christoforidi, E. Sipido, C. L. Bassetti, T. Vos, V. L. Feigin, *Lancet Public Health* **2020**, *5*, e551.
[3] M. Sharifi-Rad, N. V. A. Kumar, P. Zucca, E. M. Varoni, L. Dini, E. Panzarini, J. Rajkovic, P. V. T. Fokou, E. Azzini, I. Peluso, A. P. Mishra, M. Nigam, Y. El Rayess, M. El Beyrouthy, L. Polito, M. Iriti, N. Martins, M. Martorell, A. O. Docea, W. N. Setzer, D. Calina, W. C. Cho, J. Sharifi-Rad, *Front. Physiol.* **2020**, *11*, 694.
[4] A. M. Tolppanen, A. Solomon, H. Soininen, M. Kivipelto, *J. Alzheimers Dis.* **2012**, *32*, 531.
[5] A. Ayala, M. F. Munoz, S. Arguelles, *Oxid. Med. Cell. Longevity* **2014**, *2014*, 31.
[6] E. B. Kurutas, *Nutr. J.* **2016**, *15*, 71.
[7] R. Padureanu, C. V. Albu, R. R. Mititelu, M. V. Bacanoiu, A. O. Docea, D. Calina, V. Padureanu, G. Olaru, R. E. Sandu, R. D. Malin, A. M. Buga, *J. Clin. Med.* **2019**, *8*, 1815.
[8] S. Reuter, S. C. Gupta, M. M. Chaturvedi, B. B. Aggarwal, *Free Radicals Biol. Med.* **2010**, *49*, 1603.
[9] A. Tsatsakis, A. O. Docea, D. Calina, K. Tsarouhas, L. M. Zamfira, R. Mitrut, J. Sharifi-Rad, L. Kovatsi, V. Siokas, E. Dardiotis, N. Drakoulis, G. Lazopoulos, C. Tsitsimpikou, P. Mitsias, M. Neagu, *J. Clin. Med.* **2019**, *8*, 1295.
[10] D. Trachootham, W. Q. Lu, M. A. Ogasawara, N. R. D. Valle, P. Huang, *Antioxid. Redox Signal* **2008**, *10*, 1343.
[11] W. T. Roubal, A. L. Tappel, *Arch. Biochem. Biophys.* **1966**, *113*, 5.
[12] Y. Xia, J. L. Zweier, *Proc. Natl. Acad. Sci. U. S. A.* **1997**, *94*, 6954.
[13] V. Bronte, P. Zanovello, *Nat. Rev. Immunol.* **2005**, *5*, 641.
[14] D. W. Jiang, D. L. Ni, Z. T. Rosenkrans, P. Huang, X. Y. Yan, W. B. Cai, *Chem. Soc. Rev.* **2019**, *48*, 3683.
[15] H. Wei, L. Z. Gao, K. L. Fan, J. W. Liu, J. Y. He, X. G. Qu, S. J. Dong, E. K. Wang, X. Y. Yan, *Nano Today* **2021**, *40*, 101269.
[16] M. M. Liang, X. Y. Yan, *Acc. Chem. Res.* **2019**, *52*, 2190.
[17] H. Wei, E. K. Wang, *Chem. Soc. Rev.* **2013**, *42*, 6060.
[18] J. J. X. Wu, X. Y. Wang, Q. Wang, Z. P. Lou, S. R. Li, Y. Y. Zhu, L. Qin, H. Wei, *Chem. Soc. Rev.* **2019**, *48*, 1004.
[19] Y. F. Liu, Y. H. Zhang, Q. Y. Liu, Q. Wang, A. Q. Lin, J. Luo, Y. Du, Y. W. Lin, H. Wei, *Analyst* **2021**, *146*, 1872.
[20] A. Q. Lin, Q. Y. Liu, Y. H. Zhang, Q. Wang, S. R. Li, B. J. Zhu, L. Y. Miao, Y. Du, S. Zhao, H. Wei, *Anal. Chem.* **2022**, *94*, 10636.
[21] R. Apak, A. Calokerinos, S. Gorinstein, M. A. Segundo, D. B. Hibbert, I. Gulcin, S. D. Cekic, K. Guclu, M. Ozyurek, S. E. Celik, L. M. Magalhaes, P. Arancibia-Avila, *Pure Appl. Chem.* **2022**, *94*, 87.

[22] Q. Wang, C. Q. Cheng, S. Zhao, Q. Y. Liu, Y. H. Zhang, W. L. Liu, X. Z. Zhao, H. Zhang, J. Pu, S. Zhang, H. G. Zhang, Y. Du, H. Wei, *Angew. Chem., Int. Ed.* **2022**, *61*, e202201101.
[23] R. Rodriguez, R. Redman, *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 3175.
[24] S. Papa, P. L. Martino, G. Capitanio, A. Gaballo, D. De Rasmo, A. Signorile, V. Petruzzella, *Adv. Exp. Med. Biol.* **2012**, *942*, 3.
[25] N. Singh, G. Mugesh, *Angew. Chem., Int. Ed.* **2019**, *58*, 7797.
[26] N. Singh, S. K. NaveenKumar, M. Geethika, G. Mugesh, *Angew. Chem., Int. Ed.* **2021**, *60*, 3121.
[27] M. Valko, C. J. Rhodes, J. Moncol, M. Izakovic, M. Mazur, *Chem. Biol. Interact.* **2006**, *160*, 1.
[28] I. Ben-Porath, R. A. Weinberg, *Int. J. Biochem. Cell Biol.* **2005**, *37*, 961.
[29] D. Munoz-Espin, M. Serrano, *Nat. Rev. Mol. Cell Biol.* **2014**, *15*, 482.
[30] B. B. S. Zhou, S. J. Elledge, *Nature* **2000**, *408*, 433.
[31] L. Wu, J. R. Sowers, Y. M. Zhang, J. Ren, *Cardiovasc. Res.* **2022**, *00*, 1.
[32] N. Singh, M. A. Savanur, S. Srivastava, P. D'Silva, G. Mugesh, *Nanoscale* **2019**, *11*, 3855.
[33] K. Kamada, N. Soh, *J. Phys. Chem. B* **2015**, *119*, 5309.
[34] Y. Y. Li, N. Zeng, Z. G. Qin, Y. H. Chen, Q. Lu, Y. X. Cheng, Q. Y. Xia, Z. Y. Lu, N. Gu, D. Luo, *Nanoscale* **2021**, *13*, 16104.
[35] C. L. Hao, A. H. Qu, L. G. Xu, M. Z. Sun, H. Y. Zhang, C. L. Xu, H. Kuang, *J. Am. Chem. Soc.* **2019**, *141*, 1091.
[36] Y. J. Guan, M. Li, K. Dong, N. Gao, J. S. Ren, Y. C. Zheng, X. G. Qu, *Biomaterials* **2016**, *98*, 92.
[37] K. C. Luk, V. Kehm, J. Carroll, B. Zhang, P. O'Brien, J. Q. Trojanowski, V. M. Y. Lee, *Science* **2012**, *338*, 949.
[38] Y. Q. Liu, Y. Y. Mao, E. Q. Xu, H. M. Jia, S. Zhang, V. L. Dawson, T. M. Dawson, Y. M. Li, Z. Zheng, W. W. He, X. B. Mao, *Nano Today* **2021**, *36*, 101027.
[39] N. Korin, M. Kanapathipillai, B. D. Matthews, M. Crescente, A. Brill, T. Mammoto, K. Ghosh, S. Jurek, S. A. Bencherif, D. Bhatta, A. U. Coskun, C. L. Feldman, D. D. Wagner, D. E. Ingber, *Science* **2012**, *337*, 738.
[40] C. T. Taylor, J. Pouyssegur, *Ann. N. Y. Acad. Sci.* **2007**, *1113*, 87.
[41] C. W. Pugh, P. J. Ratcliffe, *Nat. Med.* **2003**, *9*, 677.
[42] P. Deb, S. Sharma, K. M. Hassan, *Pathophysiology* **2010**, *17*, 197.
[43] M. Milkiewicz, E. Ispanovic, J. L. Doyle, T. L. Haas, *Int. J. Biochem. Cell Biol.* **2006**, *38*, 333.
[44] S. Das, S. Singh, J. M. Dowding, S. Oommen, A. Kumar, T. X. T. Sayle, S. Saraf, C. R. Patra, N. E. Vlahakis, D. C. Sayle, W. T. Self, S. Seal, *Biomaterials* **2012**, *33*, 7746.
[45] R. Augustine, Y. B. Dalvi, P. Dan, N. George, D. Helle, R. Varghese, S. Thomas, P. Menu, N. Sandhyarani, *ACS Biomater. Sci. Eng.* **2018**, *4*, 4338.
[46] J. O. Lundberg, M. T. Gladwin, E. Weitzberg, *Nat. Rev. Drug Discov.* **2015**, *14*, 623.
[47] H. Haybar, S. Shahrabi, H. Rezaeeyan, R. Shirzad, N. Saki, *Cardiovasc. Toxicol.* **2019**, *19*, 13.
[48] J. Chen, X. X. Zhang, R. Millican, J. Sherwood, S. Martin, H. Jo, Y. S. Yoon, B. C. Brott, H. W. Jun, *Adv. Drug Delivery Rev.* **2021**, *170*, 142.
[49] M. C. Jen, M. C. Serrano, R. van Lith, G. A. Ameer, *Adv. Funct. Mater.* **2012**, *22*, 239.
[50] T. Yang, A. N. Zelikin, R. Chandrawati, *Small* **2020**, *16*, 1907635.
[51] H. Y. Li, J. Yan, D. J. Meng, R. Cai, X. S. Gao, Y. L. Ji, L. M. Wang, C. Y. Chen, X. C. Wu, *ACS Nano* **2020**, *14*, 12854.
[52] S. Ghosh, P. Roy, S. Prasad, G. Mugesh, *Chem. Sci.* **2019**, *10*, 5308.
[53] S. Ghosh, P. Roy, S. Prasad, G. Mugesh, *Faraday Discuss.* **2022**, *234*, 284.
[54] T. C. Major, D. O. Brant, C. P. Burney, K. A. Amoako, G. M. Annich, M. E. Meyerhoff, H. Handa, R. H. Bartlett, *Biomaterials* **2011**, *32*, 5957.
[55] T. Yang, A. S. Fruergaard, A. K. Winther, A. N. Zelikin, R. Chandrawati, *Small* **2020**, *16*, 1906744.
[56] Y. H. Fan, Y. Zhang, Q. Zhao, Y. H. Xie, R. F. Luo, P. Yang, Y. J. Weng, *Biomaterials* **2019**, *204*, 36.
[57] U. Forstermann, N. Xia, H. G. Li, *Circ. Res.* **2017**, *120*, 713.
[58] S. Cook, P. Wenaweser, M. Togni, M. Billinger, C. Morger, C. Seiler, R. Vogel, O. Hess, B. Meier, S. Windecker, *Circulation* **2007**, *115*, 2426.
[59] T. J. Beldman, M. L. Senders, A. Alaarg, C. Perez-Medina, J. Tang, Y. M. Zhao, F. Fay, J. Deichmoller, B. Born, E. Desclos, N. N. van der Wel, R. A. Hoebe, F. Kohen, E. Kartvelishvily, M. Neeman, T. Reiner, C. Calcagno, Z. A. Fayad, M. P. J. de Winther, E. Lutgens, W. J. M. Mulder, E. Kluza, *ACS Nano* **2017**, *11*, 5785.
[60] G. Fredman, N. Kamaly, S. Spolitu, J. Milton, D. Ghorpade, R. Chiasson, G. Kuriakose, M. Perretti, O. Farokzhad, I. Tabas, *Sci. Transl. Med.* **2015**, *7*, 275ra20.
[61] J. L. Niu, A. Azfer, L. M. Rogers, X. H. Wang, P. E. Kolattukudy, *Cardiovasc. Res.* **2007**, *73*, 549.
[62] Y. Zhang, Y. Yin, W. Zhang, H. Li, T. Wang, H. Yin, L. Sun, C. Su, K. Zhang, H. Xu, *J. Nanobiotechnol.* **2021**, *19*, 161.
[63] S. Y. Wang, Y. Zhou, X. Y. Liang, M. Xu, N. Li, K. Zhao, *Chem. Eng. J.* **2022**, *430*, 132859.
[64] L. H. Bonati, J. Gregson, J. Dobson, D. J. H. McCabe, P. J. Nederkoorn, H. B. van der Worp, G. J. de Borst, T. Richards, T. Cleveland, M. D. Muller, T. Wolff, S. T. Engelter, P. A. Lyrer, M. M. Brown, I. C. S. S. Investi, *Lancet Neurol.* **2018**, *17*, 587.
[65] L. S. Feng, C. R. Dou, Y. G. Xia, B. H. Li, M. Y. Zhao, A. M. El-Toni, N. F. Atta, Y. Y. Zheng, X. J. Cai, Y. Wang, Y. S. Cheng, F. Zhang, *Adv. Funct. Mater.* **2020**, *30*, 2006581.
[66] X. Y. Zhang, Y. B. Wang, J. Liu, J. Shi, D. Mao, A. C. Midgley, X. G. Leng, D. L. Kong, Z. H. Wang, B. Liu, S. F. Wang, *Chem. Eng. J.* **2021**, *421*, 129577.
[67] Q. Zhao, Y. Fan, Y. Zhang, J. Liu, W. Li, Y. Weng, *ACS Appl. Mater. Interfaces* **2019**, *11*, 7872.
[68] S. S. Gross, M. S. Wolin, *Annu. Rev. Physiol.* **1995**, *57*, 737.
[69] M. B. Kolli, N. D. P. K. Manne, R. Para, S. K. Nalabotu, G. Nandyala, T. Shokuhfar, K. He, A. Hamlekhan, J. Y. Ma, P. S. Wehner, L. Dornon, R. Arvapalli, K. M. Rice, E. R. Blough, *Biomaterials* **2014**, *35*, 9951.
[70] R. Hou, T. Lu, W. Gao, J. Shen, Z. Yu, D. Li, R. Zhang, Y. Zheng, X. Cai, *ACS Nano* **2022**, *16*, 9559.
[71] H. Hu, H. Huang, L. L. Xia, X. Q. Qian, W. Feng, Y. Chen, Y. H. Li, *Chem. Eng. J.* **2022**, *440*, 135810.
[72] G. Huang, J. Zang, L. He, H. Zhu, J. Huang, Z. Yuan, T. Chen, A. Xu, *ACS Nano* **2021**, *16*, 431.
[73] J. Mu, C. Li, Y. Shi, G. Liu, J. Zou, D. Y. Zhang, C. Jiang, X. Wang, L. He, P. Huang, Y. Yin, X. Chen, *Nat. Commun.* **2022**, *13*, 2513.
[74] A. Sahu, J. Jeon, M. S. Lee, H. S. Yang, G. Tae, *ACS Appl. Mater. Interfaces* **2021**, *13*, 25649.
[75] R. Z. Tian, H. Y. Ma, W. Ye, Y. J. Li, S. P. Wang, Z. R. Zhang, S. D. Liu, M. S. Zang, J. X. Hou, J. Y. Xu, Q. Luo, H. C. Sun, F. Q. Bai, Y. Yang, J. Q. Liu, *Adv. Funct. Mater.* **2022**, *32*, 2204025.
[76] Y. Zhang, A. Khalique, X. C. Du, Z. X. Gao, J. Wu, X. Y. Zhang, R. Zhang, Z. Y. Sun, Q. Q. Liu, Z. L. Xu, A. C. Midgley, L. Y. Wang, X. Y. Yan, J. Zhuang, D. L. Kong, X. L. Huang, *Adv. Mater.* **2021**, *33*, 2006570.
[77] J. C. de la Torre, *Stroke* **2002**, *33*, 1152.
[78] C. K. Firoz, N. R. Jabir, M. S. Khan, M. Mahmoud, S. Shakil, G. A. Damanhouri, S. K. Zaidi, S. Tabrez, M. A. Kamal, *Saudi J. Biol. Sci.* **2015**, *22*, 19.
[79] J. Drouin-Ouellet, S. J. Sawiak, G. Cisbani, M. Lagace, W. L. Kuan, M. Saint-Pierre, R. J. Dury, W. Alata, I. St-Amour, S. L. Mason, F. Calon, S. Lacroix, P. A. Gowland, S. T. Francis, R. A. Barker, F. Cicchetti, *Ann. Neurol.* **2015**, *78*, 160.
[80] N. Malek, M. A. Lawton, D. M. A. Swallow, K. A. Grosset, S. L. Marrinan, N. Bajaj, R. A. Barker, D. J. Burn, J. Hardy, H. R. Morris, N. M. Williams, N. Wood, Y. Ben-Shlomo, D. G. Grosset, P. C. Consortium, *Mov. Disord.* **2016**, *31*, 1518.

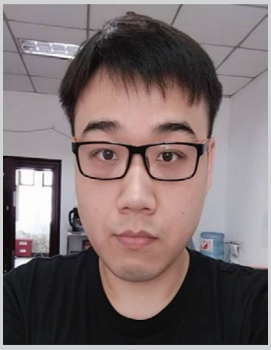
[81] P. H. Reddy, *CNS Spectrums* **2009**, *14*, 8.
[82] B. Salehi, D. Calina, A. O. Docea, N. Koirala, S. Aryal, D. Lombardo, L. Pasqua, Y. Taheri, C. M. S. Castillo, M. Martorell, N. Martins, M. Iriti, H. A. R. Suleria, J. Sharifi-Rad, *J. Clin. Med.* **2020**, *9*, 430.
[83] M. Sharifi-Rad, C. Lankatillake, D. A. Dias, A. O. Docea, M. F. Mahomoodally, D. Lobine, P. L. Chazot, B. Kurt, T. B. Tumer, A. C. Moreira, F. Sharopov, M. Martorell, N. Martins, W. C. Cho, D. Calina, J. Sharifi-Rad, *J. Clin. Med.* **2020**, *9*, 1061.
[84] N. Singh, M. A. Savanur, S. Srivastava, D. P. Silva, G. Mugesh, *Angew. Chem., Int. Ed.* **2017**, *56*, 14267.
[85] L. H. Li, Y. Lu, X. Y. Xu, X. F. Yang, L. L. Chen, C. M. Jiang, Y. Wang, W. Y. Hu, X. M. Wei, Z. M. Yang, *Adv. Healthcare Mater.* **2021**, *10*, 2100316.
[86] H. J. Kwon, D. Kim, K. Seo, Y. G. Kim, S. I. Han, T. Kang, M. Soh, T. Hyeon, *Angew. Chem., Int. Ed.* **2018**, *57*, 9408.
[87] L. Lei, Q. X. Tu, L. Jiao, S. Xiang, L. Wang, X. Ran, B. Xiao, G. W. Feng, J. Feng, C. L. Zhang, *Chem. Eng. J.* **2022**, *432*, 134356.
[88] X. X. Ma, J. N. Hao, J. R. Wu, Y. H. Li, X. J. Cai, Y. Y. Zheng, *Adv. Mater.* **2022**, *34*, 2106723.
[89] M. Citron, *Nat. Rev. Drug Discov.* **2010**, *9*, 387.
[90] M. M. Ma, Z. Q. Liu, N. Gao, Z. F. Pi, X. B. Du, J. S. Ren, X. G. Qu, *J. Am. Chem. Soc.* **2020**, *142*, 21702.
[91] Z. Jia, X. Y. Yuan, J. A. Wei, X. Guo, Y. C. Gong, J. Li, H. Zhou, L. Zhang, J. Liu, *ACS Appl. Mater. Interfaces* **2021**, *13*, 49602.
[92] N. Gao, K. Dong, A. D. Zhao, H. J. Sun, Y. Wang, J. S. Ren, X. G. Qu, *Nano Res.* **2016**, *9*, 1079.
[93] Y. C. Gong, A. L. Huang, X. Guo, Z. Jia, X. Chen, X. F. Zhu, Y. Xia, J. Liu, Y. Xu, X. Y. Qin, *Chem. Eng. J.* **2021**, *418*, 129345.
[94] C. J. Du, W. Feng, X. Y. Dai, J. H. Wang, D. Y. Geng, X. D. Li, Y. Chen, J. Zhang, *Small* **2022**, *18*, 2203031.
[95] L. S. Feng, C. R. Dou, Y. G. Xia, B. H. Li, M. Y. Zhao, P. Yu, Y. Y. Zheng, A. M. El-Toni, N. F. Atta, A. Galal, Y. S. Cheng, X. J. Cai, Y. Wang, F. Zhang, *ACS Nano* **2021**, *15*, 2263.
[96] W. S. Cong, R. Bai, Y. F. Li, L. M. Wang, C. Y. Chen, *ACS Appl. Mater. Interfaces* **2019**, *11*, 34725.
[97] L. Z. Gao, J. Zhuang, L. Nie, J. B. Zhang, Y. Zhang, N. Gu, T. H. Wang, J. Feng, D. L. Yang, S. Perrett, X. Yan, *Nat. Nanotechnol.* **2007**, *2*, 577.
[98] M. Battaglini, A. Marino, A. Carmignani, C. Tapeinos, V. Cauda, A. Ancona, N. Garino, V. Vighetto, G. La Rosa, E. Sinibaldi, G. Ciofani, *ACS Appl. Mater. Interfaces* **2020**, *12*, 35782.
[99] M. Battaglini, A. Carmignani, C. Martinelli, J. Colica, A. Marino, S. Doccini, V. Mollo, F. Santoro, M. Bartolucci, A. Petretto, F. M. Santorelli, G. Ciofani, *Biomater. Sci.* **2022**, *10*, 3770.
[100] Y. L. Liu, K. L. Ai, X. Y. Ji, D. Askhatova, R. Du, L. H. Lu, J. J. Shi, *J. Am. Chem. Soc.* **2017**, *139*, 856.
[101] M. J. Cao, R. Cai, L. N. Zhao, M. Y. Guo, L. M. Wang, Y. C. Wang, L. L. Zhang, X. F. Wang, H. D. Yao, C. Y. Xie, Y. L. Cong, Y. Guan, X. Y. Tao, Y. L. Wang, S. X. Xu, Y. Liu, Y. L. Zhao, C. Y. Chen, *Nat. Nanotechnol.* **2021**, *16*, 708.
[102] P. J. Derry, L. G. Nilewski, W. K. A. Sikkema, K. Mendoza, A. Jalilov, V. Berka, E. A. McHugh, A. L. Tsai, J. M. Tour, T. A. Kent, *Nanoscale* **2019**, *11*, 10791.
[103] V. Baldim, N. Yadav, N. Bia, A. Graillot, C. Loubat, S. Singh, A. S. Karakoti, J. F. Berret, *ACS Appl. Mater. Interfaces* **2020**, *12*, 42056.
[104] X. W. Wang, X. Y. Zhong, L. X. Bai, J. Xu, F. Gong, Z. L. Dong, Z. J. Yang, Z. J. Zeng, Z. Liu, L. Cheng, *J. Am. Chem. Soc.* **2020**, *142*, 6527.
[105] H. Ding, Y. J. Cai, L. Z. Gao, M. M. Liang, B. P. Miao, H. W. Wu, Y. Liu, N. Xie, A. F. Tang, K. L. Fan, X. Y. Yan, G. H. Nie, *Nano Lett.* **2019**, *19*, 203.
[106] Z. Y. Sun, Q. Q. Liu, X. Y. Wang, J. Wu, X. Y. Hu, M. M. Liu, X. Y. Zhang, Y. H. Wei, Z. J. Liu, H. J. Liu, R. Chen, F. Wang, A. C. Midgley, A. T. Li, X. Y. Yan, Y. M. Wang, J. Zhuang, X. L. Huang, *Theranostics* **2022**, *12*, 1132.
[107] Y. Q. Xu, J. B. Fei, G. L. Li, T. T. Yuan, X. Xu, J. B. Li, *Angew. Chem., Int. Ed.* **2019**, *58*, 5572.
[108] L. Z. Feng, Z. L. Dong, C. Liang, M. C. Chen, D. L. Tao, L. Cheng, K. Yang, Z. Liu, *Biomaterials* **2018**, *181*, 81.

Yihong Zhang is a Ph.D. candidate at the College of Engineering and Applied Sciences at Nanjing University. After he received his B.S. degree from Lanzhou University in 2018, he joined Professor Hui Wei's group to start his research journey. Currently, his research interest is focused on synthesis and application of nanozymes.

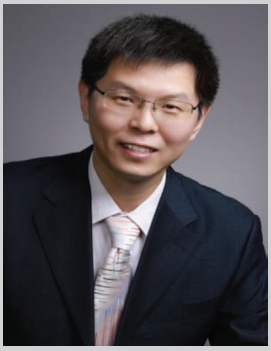
Wanling Liu is a Ph.D. candidate at the College of Engineering and Applied Sciences at Nanjing University. After she received her M.S. degree from Chongqing University in 2020, she joined Professor Hui Wei's group to start her research journey. Currently, her research interests focus on the biomedical application of nanozymes.



Xiaoyu Wang is now an Associate Professor at Nanjing Forestry University. He received his B.S. degree from Nanjing Institute of Technology in 2014 and his Ph.D. degree from Nanjing University (advisor: Professor Hui Wei) in 2019. He then worked with Professor Hui Wei at Nanjing University as a Postdoctoral fellow before he moved to Nanjing Forestry University. His research interests focus on the rational design and synthesis of functional nanomaterials (such as nanozymes) and exploiting their wide applications in bioanalysis and biomedicine.



Yufeng Liu now works with Professor Hui Wei at Nanjing University as a Postdoctoral fellow after receiving his Ph.D. degree from Nanjing University (advisor: Professor Hui Wei) in 2020. His research interests focus on the rational design of nanozymes and their biomedical applications.



Hui Wei is a Professor at Nanjing University and a Fellow of the Royal Society of Chemistry. He received his B.S. degree from Nanjing University (advisor: Professor Xinghua Xia) and Ph.D. degree from Changchun Institute of Applied Chemistry, Chinese Academy of Sciences (advisor: Professor Erkang Wang). He then joined Professors Yi Lu's and Shuming Nie's groups for two Postdoctoral trainings before he started his independent career at Nanjing University. His research interests are focused on the design and synthesis of functional nanomaterials (such as nanozymes) and the development of new methodologies for analytical and biomedical applications.