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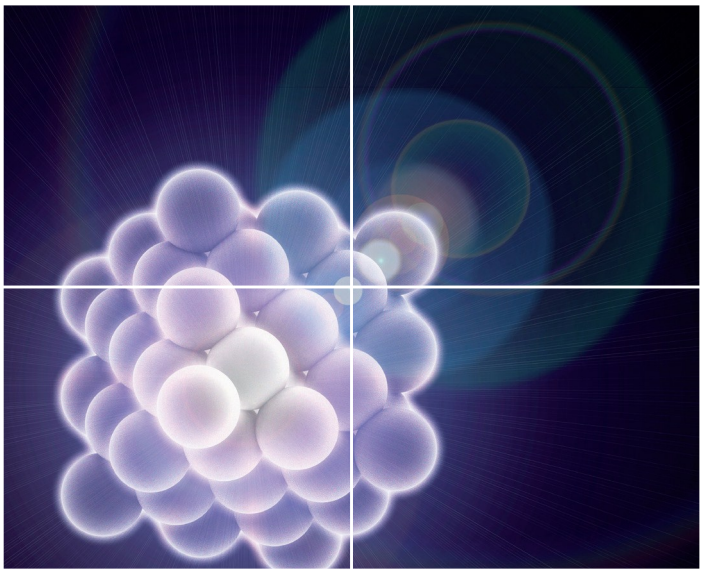

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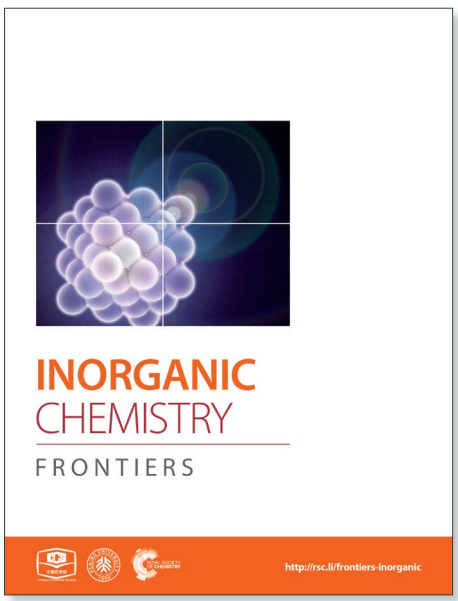

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Nanozymes in bionanotechnology: from sensing to therapeutics and beyond

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In the past few decades, researchers have developed lots of artificial enzymes with various materials to mimic the structures and functions of natural enzymes. Recently, nanozymes, nanomaterials with enzyme-like characteristics, are emerging as novel artificial enzymes, and attracting researchers' enormous interests. Remarkable advances have been made in the area of nanozymes due to their unique properties compared with natural enzymes and classic artificial enzymes. Till now, lots of nanomaterials have been studied to mimic various natural enzymes for wide applications. To highlight the recent progress of nanozymes (especially in bionanotechnology), here we discuss the diverse applications of nanozymes, which cover from sensing, imaging, and therapeutics, to logic gates, pollutant removal, and water treatment, etc. Finally, we address the current challenges facing nanozyme research as well as possible directions to fulfill their great potentials in future.

1. Introduction

Nanozymes are the nanomaterials with enzyme-like characteristics.[1] As an emerging research area in the field of artificial enzymes, nanozymes have attracted researchers' enormous interests due to their unique properties compared with natural enzymes and classic artificial enzymes.[1-4] Compared with natural enzymes, nanozymes are advantageous in several aspects, such as low cost, easy for mass production, robustness to harsh environments, high stability, long-term storage, and size/composition dependent activity.[1] Besides, nanozymes have also showed unique properties compared with other artificial enzymes in terms of their size- (shape-, structure-, composition-) dependent catalytic activities, integrated (multi-)functions besides catalysis, large surface area for further modification and bioconjugation, smart response to external stimuli, self-assembly capability, etc.[1] Till now, lots of nanomaterials have been explored to mimic various natural enzymes, such as catalase, oxidase, peroxidase, superoxide dismutase (SOD), esterase, nuclease, phosphatase, protease and ferroxidase (Figure 1).[5-26] These nanozymes have been extensively investigated for diverse applications in bionanotechnology, ranging from biosensing and bioimaging to tissue engineering, therapeutics and beyond. In 2013, we have made a comprehensive review on nanozymes.[1] Since then, substantial progress has been achieved in the field. To highlight the recent exciting progress, the present review discusses the key reports of nanozymes, especially their applications in bionanotechnology. A few early studies are also included to provide a historic view of nanozyme research. Several well established mechanisms about nanozyme catalytic reactions are also covered. The current challenges facing nanozyme research as well as possible directions to fulfill their great potentials are discussed in the final section.

We do not attempt to cover all the related publications on nanozymes due to the space limit. Readers are referred to numerous critical reviews and references therein for more information.[1-4, 27-36]

2. Nanozymes for sensing and imaging

Since the seminal reports by Yan's and Wang's groups,[11, 12] nanozymes have been widely used for detecting a variety of important targets, such as bioactive small molecules, metal ions, nucleic acids, cancer cells and even bacteria.

2.1 Nanozymes for H_2O_2 sensing

H_2O_2 detection is of great interest owing to its important roles in biology, medicine, food industry and environmental protection.[37, 38] H_2O_2 detection is usually achieved by using nanomaterials' peroxidase mimicking activities, in which the H_2O_2-mediated oxidation of a substrate is catalyzed by a peroxidase mimic (Scheme 1 and Figure 2). By monitoring the production of oxidized substrate (i.e., A in Scheme 1), H_2O_2 can be determined.

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$$AH_2 + ROOH \xrightarrow{\text{Peroxidase}} A + ROH + H_2O \quad (1)$$

Scheme 1. The reaction catalyzed by peroxidase.

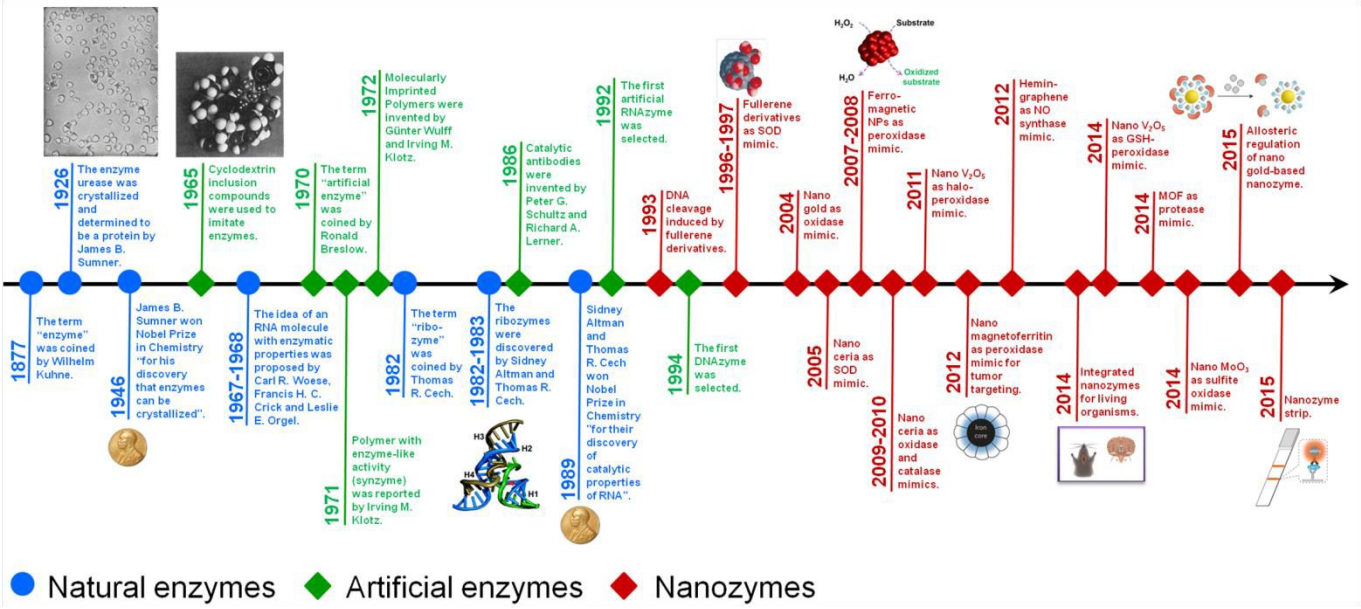

Figure 1. A brief timeline for the development of artificial enzymes (natural enzymes are also listed for comparison) (see Table S1, ESI† for related references). Adapted with permission from reference 1. Copyright (2013) Royal Society of Chemistry.

Wei and Wang have developed a colorimetric method for H_2O_2 detection.[12] They used Fe_3O_4 magnetic nanoparticles (MNPs) as the peroxidase mimic and ABTS as the substrate for signalling (Figure 2a). The presence of H_2O_2 generated green coloured $ABTS^{\cdot+}$, which could be quantified by absorption spectra or even visualized by naked eyes. Since then, considerable amount of studies have been devoted to H_2O_2 detection by exploring various nanomaterials' peroxidase mimicking activities (also see Table S2, ESI†).[39-86] Besides colorimetric detection with peroxidase substrates (such as ABTS, 4-AAP, DPD, OPD, and TMB), H_2O_2 has also been determined via fluorescent, electrochemical and surface enhanced Raman scattering (SERS) methods.[42, 52, 56, 58, 64, 68, 72, 73, 77, 79, 82, 84]

Recently, Zhang and co-workers developed 3D Fe- and N-doped carbon nanostructures to mimic peroxidase.[52] Due to the presence of highly active Fe-N and doped-N species as well as the large surface area, the nanostructures exhibited good peroxidase mimicking activity. They further constructed a fluorescent sensor for H_2O_2 detection with the developed nanozyme, which had a linear range from 100 nM to 100 μM and a detection limit of 68 nM. In another study, Fe_7S_8 nanowires with intrinsic peroxidase-like activity have been studied for fluorescent detection of H_2O_2.[59]

Fang et al. used Fe_3O_4/reduced graphene oxide (rGO) nanocomposites as peroxidase mimic to prepare modified glassy carbon electrode for electrochemical sensing of H_2O_2 (Figure 3).[67] The developed electrochemical sensor showed good selectivity toward H_2O_2 detection over several metal ions (Na^+, K^+, Ag^+, Mg^{2+}, and Cu^{2+}) and bioactive small molecules (glutathione (GSH), glucose, ascorbic acid, L-cysteine, and uric acid). Interestingly, with the developed electrochemical biosensor, they were able to monitor CdTe quantum dots-stimulated extracellular H_2O_2 release from living Hela cells. This study may be useful for understanding biological effects of nanomaterials.

When a target of interest is used as the substrate for peroxidase, it can be measured with nanozymes as peroxidase mimics. 5-hydroxyindole-3-acetic acid (5-HIAA), an indoleamine metabolite, is an important diagnostic biomarker for carcinoid tumours. To selectively oxidize 5-HIAA with hemin as a peroxidase mimic, magnetic molecularly imprinted catalytic polymers were fabricated.[87] The products of 5-HIAA oxidation were then separated and detected with HPLC to quantitatively measure 5-HIAA.

2.2 Nanozymes for glucose (and other oxidase substrates) sensing

As shown in Figure 2, when an oxidase is combined with a peroxidase mimic, the corresponding oxidase substrate can be determined. By combining glucose oxidase with Fe_3O_4 MNPs as the peroxidase mimic, a sensitive and selective colorimetric approach to glucose detection was reported by Wei et al. (Figure 4).[12]

Till now, varieties of nanozymes with peroxidase activities have been developed and used for glucose detection when they were combined with glucose oxidase (also see Table S3, ESI†).[39-44, 46-52, 59-65, 69-71, 78, 88-121] For example, NiTe thorny nanostructures have been synthesized and used for sensitive and selective glucose detection by Wan et al.[105] Some of the nanozymes have already been successfully used for

determining glucose in drinks and biological samples (such as blood and urine).[89, 94, 104, 106, 108, 112]

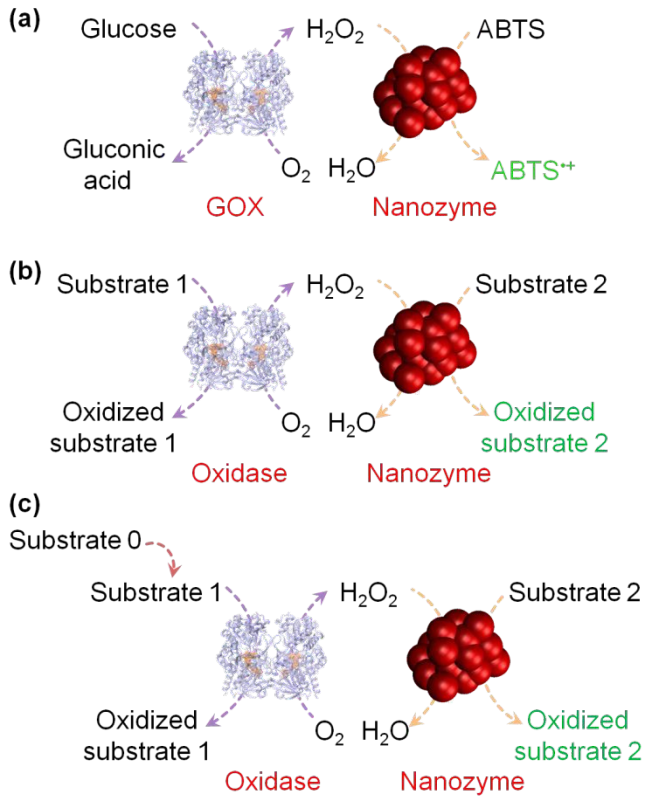

Figure 2. (a) Nanozyme as peroxidase mimic for colorimetric sensing of H_2O_2, and glucose when combined with glucose oxidase. (b) The sensing format in (a) could be extended to other targets (substrate 1 here) when combined with a proper oxidase. (c) Target of interest as substrate 0 could be determined if it could be converted into an oxidase substrate. Numerous transduction signals can be adopted for sensing (such as colorimetric, fluorometric, chemiluminescent, and SERS signals when the corresponding substrates are used; and electrochemical signals when a nanozyme is immobilized on an electrode). Adapted with permission from reference 1. Copyright (2013) Royal Society of Chemistry.

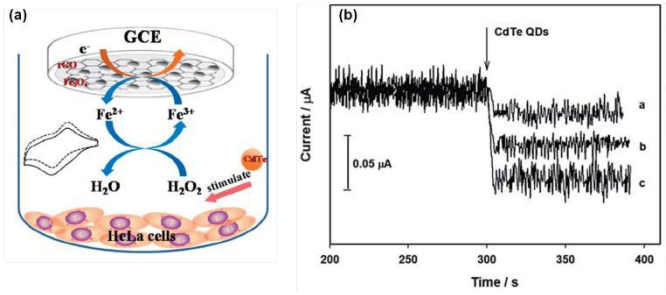

Figure 3. Electrochemical monitoring of H_2O_2 release from living cells stimulated by CdTe quantum dots with a nanozyme-modified electrode. Reprinted with permission from reference 67. Copyright (2014) Royal Society of Chemistry.

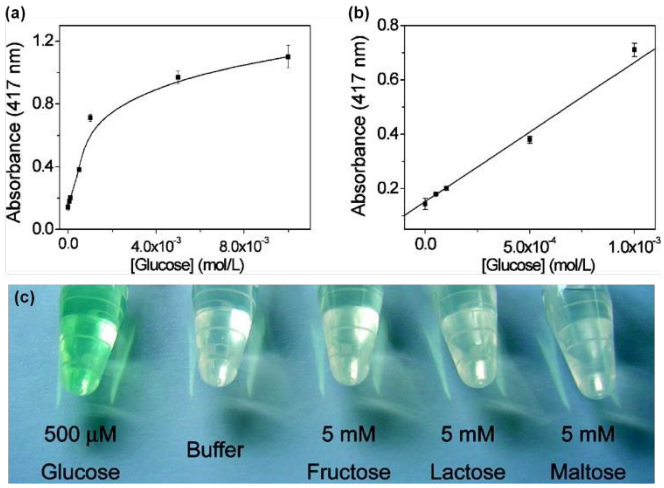

Figure 4. Colorimetric detection of glucose by combining glucose oxidase with Fe_3O_4 MNPs as peroxidase mimic. Reprinted with permission from reference 12. Copyright (2008) American Chemical Society.

To further promote the cascade reactions, glucose oxidase and a nanozyme could be assembled together as integrated nanocomposites.[118, 119] Qu et al. recently reported an inspiringly method for glucose detection.[104] They replaced both glucose oxidase and peroxidase with the nanomaterial mimics (i.e., gold nanoparticles (AuNPs) as glucose oxidase mimic and V_2O_5 nanowires as peroxidase mimic) (Figure 5). The two nanozymes were assembled together via polymerized dopamine for the cascade reactions. By eliminating the use of both natural enzymes, the current system displayed higher robustness but much lower cost.

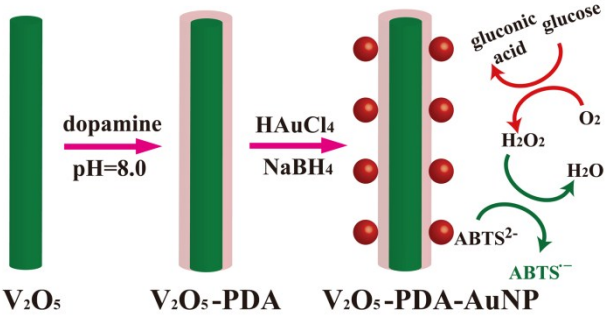

Figure 5. Colorimetric detection of glucose by assembled AuNPs onto V_2O_5 nanowires as glucose oxidase and peroxidase mimics, respectively. Reprinted with permission from reference [104]. Copyright (2014) John Wiley and Sons.

As indicated by Figure 2b, when other oxidases are used, their corresponding substrates as targets of interest can be detected. Choline, D-alanine, lactate, uric acid, and xanthine have been determined with the strategy shown in Figure 2b.[64, 74, 122-124] For example, when $NaYF_4$:Yb,Er nanoparticles as a peroxidase mimic was combined with uricase, uric acid has been determined.[124] The proposed method had good selectivity against several biomolecules, such as creatinine,

ascorbic acid, glucose, cholesterol, triglyceride, and urea. More, the uric acid in clinical human serum sample was successfully measured via the developed method, which matched well with the established method.

Several studies also demonstrated that targets of interest as substrate 0 could be determined if they could be converted into oxidase substrates (Figure 2c).[123, 125-127] Using acetylcholinesterase, choline oxidase and Au/Ag nanoparticles as the peroxidase mimic, Wang et al. reported the sensitive detection of acetylcholine.[125] With Wang's method, a detection limit of 0.21 nM was obtained. Based on the inhibition of acetylcholinesterase's activity with organophosphates, Liang and co-workers later developed a rapid and sensitive strategy for detecting organophosphorus pesticides and nerve agents (such as Sarin).[126]

2.3 Sensing targets of interest by modulating peroxidase mimics (or oxidase mimics) catalyzed reactions

As shown in Figure 6, by modulating the peroxidase mimics catalyzed reactions, the targets of interests can be detected.[62, 128-138] So far, these targets already covered a wide range of molecules, such as ascorbic acid, biothiols (e.g., cysteine), catechol, dopamine, melamine, phosphate, trypsin, etc.[62, 128-138]

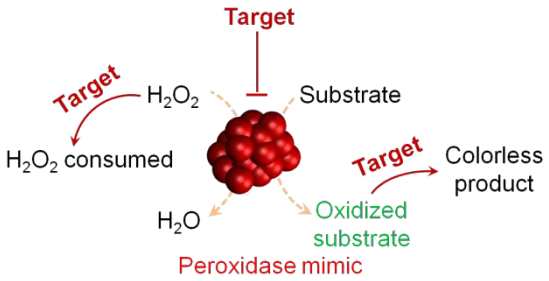

Figure 6. By modulating the peroxidase mimics catalyzed reactions (e.g., inhibiting the nanozymes' activity, consuming H_2O_2, or converting the coloured oxidized substrate to colourless product), the targets of interests can be detected.

By using C-rich DNA as the template, Sun et al. synthesized bimetallic Au_xPt_y and studied their peroxidase mimicking activities.[134] Their results revealed that the nanozymes' activities could be tuned by manipulating the ratios of x:y. After demonstrating the high peroxidase mimicking activity of Au_2Pt_1 nanozyme, they then used it for detection of biothiols (i.e., cysteine and homocysteine), which was based on the thiol-induced inhibition of nanozyme's activities. The proposed strategy showed good selectivity against non-thiol-containing amino acids. More, with Sun's sensing strategy, cysteine spiked in human serum was successfully detected with good recovery. Lin et al. suggested that the presence of cysteine not only inhibited the nanozyme's activities but also reduced the oxidized substrate (such as oxidized TMB).[135] Due to such a synergetic effect, a detection limit of 1.2 nM was obtained for cysteine detection. Ascorbic acid, one of the physiologically important neurochemicals,[139] was detected on the basis of its inhibition effect on CuNPs@C nanocomposites' peroxidase-like activity.[131] Several ions such as phosphate and uranyl ions have been detected based on their inhibition effects on peroxidase-like nanozymes.[136, 137]

By reacting with and consuming H_2O_2, a number of bioactive small molecules (such as ascorbic acid, catechol, dopamine, GSH) have been detected.[62, 130-133] For example, catechol in Yellow river was determined using Fe_3O_4 MNPs as peroxidase mimic.[132]

An innovative concept for chemiluminescence detection of pesticides was reported.[140] The Fe_3O_4 MNPs as peroxidase mimic catalyzed the generation of chemiluminescence from luminol, which could be quenched by ethanol. However, the quenching was reversed when pesticides were bound onto Fe_3O_4 MNPs. By "turning on" the chemiluminescence of luminol, nonredox active pesticides were sensitively detected. More interestingly, Fe_3O_4 MNPs with different surface ligands exhibited unique chemiluminescence patterns towards different pesticides. Thus, simultaneous detection of pesticides could be achieved via the developed method.

Oxidase uses oxygen to oxidize its substrates (Scheme 2). Similar with natural oxidase, nanomaterials-based oxidase mimics have been used for sensing the corresponding substrates.[141-144] Hayat et al. evaluated the oxidase mimicking activity of nanoceria and developed colorimetric assay for dopamine and catechol.[143] By carefully choosing the nanoceria type, buffer composition and pH, etc., they demonstrated good selectivity for dopamine and catechol detection with respect to several interferences.

$$A_{red} + O_2 + H_2O \xrightarrow{\text{Oxidase}} A_{ox} + H_2O_2 \quad (2a)$$

$$A_{red} + O_2 \xrightarrow{\text{Oxidase}} A_{ox} + H_2O \quad (2b)$$

$$A_{red} + O_2 \xrightarrow{\text{Oxidase}} A_{ox} + O_2^{\bullet -} \quad (2c)$$

Scheme 2. The reactions catalyzed by oxidase.

Sulfite is an important additive in food and wine. It can tune the oxidase mimicking activity of $CoFe_2O_4$ nanoparticles. Zhang et al. discovered that sulfite at low concentration inhibited the oxidase mimicking activity of $CoFe_2O_4$ nanoparticles while high concentration of sulfite exhibited enhancement effects.[141] On the basis of this phenomenon, they reported a chemiluminescent assay for sulfite determination in white wines. Sulfite in food was also measured by exploring its inhibition effect on the oxidase mimicking activity of Co_3O_4 nanoparticles.[142]

2.4 Nanozymes for nucleic acid sensing

Several strategies have been developed for nucleic acid detection using nanozymes.[104, 145-155] The reported protocols can be roughly classified into two types. One type of assay uses nanozymes as alternative tags to classic dyes (or enzymes) to label nucleic acid probe strand while the other type employs nucleic acids to tailor the nanozymes' activities.

For example, graphene-supported ferric porphyrin, acting as the peroxidase mimic, was bioconjugated onto streptavidin for electrochemically detecting the target DNA (Figure 7a).[146] The hairpin DNA was immobilized onto a AuNPs-modified electrode via Au-S interaction. In the presence of target DNA, the hairpin structure was opened and the pre-conjugated biotin was thus available for binding to the streptavidin-nanozyme conjugates. With the developed electrochemical sensor, as low as 22 aM of target DNA was detected. Thiramanas and co-workers reported the detection of bacterial DNA with Fe_3O_4 MNPs as peroxidase mimic via a sandwich assay.[147] The developed assay was used for monitoring bacteria in drinking and tap water.

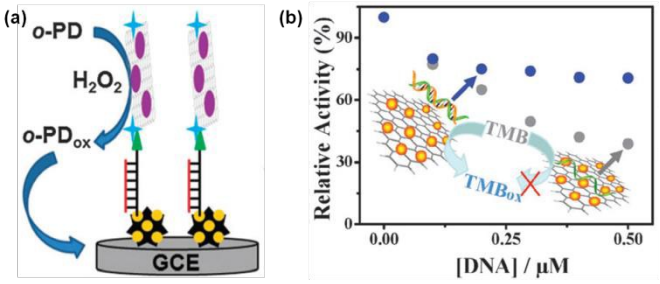

Figure 7. Nucleic acid detection with nanozymes. (a) Electrochemical detection of DNA with graphene-supported ferric porphyrin as a peroxidase mimic. (b) DNA detection based on modulating the peroxidase mimicking activity of AuNPs/graphene hybrids with ssDNA and dsDNA. (a) Reprinted with permission from reference [146]. Copyright (2013) Royal Society of Chemistry. (b) Reprinted with permission from reference [156]. Copyright (2012) Royal Society of Chemistry.

Single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA) exhibit different affinities towards several nanozymes. By modulating the peroxidase mimicking activity of AuNPs/graphene hybrids with ssDNA and dsDNA, Liu et al. reported a colorimetric method for DNA detection (Figure 7b).[156]

Despite the current progress, no RNA detection with nanozymes has been reported. Future efforts should also be focused on RNA detection, which is critical for disease diagnostics, etc.

Interestingly, while some reports showed that DNA could enhance the activity of several nanozymes,[157, 158] others demonstrated that DNA could also inhibit the activity of certain nanozymes.[156, 159, 160] Liu et al. suggested that the enhanced activity of Fe_3O_4- and nanoceria-based peroxidase mimics by DNA was attributed to (i) the electrostatic interactions between the positively charged substrate TMB and the negatively charged phosphate backbone and (ii) the aromatic stacking between the DNA bases and TMB.[158] On the other hand, the much stronger binding between ssDNA and gold nanoparticle-based nanozyme could completely prevent the interaction between the nanozyme and the substrate (even for positively-charged TMB), therefore the inhibition effects were observed.[156, 159] However, since the enhancing/inhibiting effects of DNA on the nanozymes' activity depend on many factors (such as the nature of nanozymes, the substrates, the DNA sequence and structures, etc), more systematic studies are needed to deep under the mechanisms.[161]

2.5 Nanozymes for aptasensors

Aptamers are selected short nucleic acid sequences, which are capable of recognizing specific targets and thus have been widely used for constructing various aptasensors.[162-177] Recently, nanozymes have been employed to develop numerous aptasensors for bioactive small molecules, proteins and metal ions.[154, 157, 159, 160, 178-183]

By making use of the AuNPs' peroxidase mimicking activities and an S-18 aptamer's high affinity and specificity to acetamiprid, a colorimetric assay for rapid pesticide monitoring was demonstrated.[159] The aptamer inhibited the nanozyme's activities due to its binding-induced surface passivation. Acetamiprid present in samples would interact with its aptamer and thus prevent the aptamer's binding onto AuNPs, which in turn recovered the AuNPs' catalytic activities. With Weerathunge's approach, as low as 0.1 ppm of acetamiprid was detected within 10 minutes, which met the requirement of United States Environmental Protection Agency. The same group also showed their approach was applicable to wide range of targets, such as antibiotics (kanamycin).[178]

Using the corresponding aptamers, several studies reported the detection of proteins, such as thrombin and lysozyme.[179-182] For example, sensitive and selective detection of thrombin was achieved in a recent study by Xu and co-workers.[180] The aptasensor for thrombin employed a multiple amplification strategy, in which peroxidase-like MnO_2 nanoflowers, PtNPs, toluidine blue, and hemin/G-quadruplex were co-assembled together onto multi-walled carbon nanotubes (CNTs). It demonstrated that the designed multiple-catalysts were superior to other catalyst assemblies. The detection of thrombin in 10-fold-diluted human blood serum was also demonstrated. Using DNA stabilized At/Pt nanoclusters as peroxidase mimic, Zheng et al. reported a colorimetric aptasensor for thrombin detection.[181]

Based on the highly specific interaction between Hg^{2+} and T-rich DNA (i.e., T-Hg^{2+}-T base pairing), Kim et al. reported a colorimetric approach for Hg^{2+} detection using Fe_3O_4 MNPs based peroxidase mimic.[160] The binding of T-rich DNA onto Fe_3O_4 MNPs inhibited the peroxidase mimicking activity. The presence of Hg^{2+} would recover the Fe_3O_4 MNPs' catalytic activity by Hg^{2+}-mediated release of T-rich DNA via T-Hg^{2+}-T coordination. In another study, it showed G-rich DNA could enhance the AuNPs' peroxidase mimicking activity.[157] Since the G-rich DNA could specifically interact with K^+ by forming a G-quadruplex structure, a signal-off approach to K^+ detection was proposed.

In future, other functional nucleic acids-based sensing systems (such as DNAzymes-based sensors) should also be investigated, which will broaden the nanozyme research.[164, 184]

2.6 Nanozymes for metal ions sensing

Quite a few studies have been devoted to metal ions sensing with nanozymes.[154, 157, 160, 185-196] In an early report, a sensitive and selective sensor for Cu^{2+} was developed by using Cu^{2+}-based click chemistry.[185] Via the click chemistry, CNTs and magnetic silica nanoparticles were assembled together, leading to synergistic enhancement for CNTs' peroxidase mimicking activity. As low as 1 μM of Cu^{2+} was detected with the sensor.

As discussed above, Hg^{2+} has been detected based on T-Hg^{2+}-T coordination.[160] Other strategies were also studied for developing Hg^{2+} sensors.[186, 190, 193] For example, Li et al. prepared 2 nm PtNPs with BSA as the template and studied their peroxidase mimicking activity.[193] Interestingly, they found that Hg^{2+} specifically inhibited the nanozyme's activity due to Hg^{2+}-Pt^0 metallophilic interactions. They therefore developed a sensitive and selective sensor for Hg^{2+} detection. The sensor had a linear range of 0-120 nM and a detection limit of 7.2 nM. It has been applied for monitoring Hg^{2+} in drinking water. On the basis of Ag^+ inhibition effect on $CoFe_2O_4$ nanoparticles' peroxidase mimicking activity, a chemiluminescent sensor for Ag^+ was reported recently.[192]

2.7 Nanozymes for immunoassay

Enormous efforts have been made to develop immunoassays with nanozymes.[11, 50, 53, 197-216]

Several formats have been employed for immunoassays using nanozymes as signalling elements. For example, Gao et al. reported antigen-down immunoassay format and capture-detection sandwich immunoassay format.[11] Later, many research groups adopted classic sandwich immunoassay format for detection using peroxidase and oxidase mimicking nanozymes.[50, 197, 201, 204, 206, 210, 212] For example, Kim et al. prepared a highly active peroxidase mimic by encapsulating Fe_3O_4 MNPs and PtNPs within porous carbon.[206] They then used the nanozyme as the signalling element for labelling antibodies. With their nanozyme-labelled detection antibody, as low as 1.5 ng/mL of HER2 (human epidermal growth factor receptor 2) was detected within 3 minutes via a sandwich assay. More, diarrhea causing rotavirus was also successfully detected with the developed immunoassay. Gao and co-workers fabricated urchin-like Au@Pt core shell nanostructures as a highly efficient peroxidase mimic.[210] They then developed a sandwich assay for prostate specific antigen (PSA) detection. Using their nanozyme-labelled anti-PSA antibody as the detection antibody, as low as 2.9 pg/mL of PSA was determined. More excitingly, PSA concentrations in clinical serum specimen were analyzed, which exhibited very good correlation with the referenced method. These studies suggested that nanozymes could be used as alternatives to conventional natural enzyme-based immunoassays in future.

Recently, several studies demonstrated that nanozymes can be used for point-of-care (POC) (Figure 8).[207, 211, 213, 216] To combat highly infectious diseases such as Ebola virus, it is critical to perform rapid diagnosis, especially rapid local detection with portable devices. To meet this challenge, Duan and co-workers recently reported a nanozyme-based strip for Ebola virus detection, which exhibited 100 times more sensitivity compared with AuNPs-based strip (Figure 8a).[211] They showed that as low as 240 pfu/mL of pseudo-EBOV could be detected within 30 minutes. As shown in Figure 8b, Kim et al. developed a similar strip for hCG detection.[213] With the help of a smart phone (or other portable devices), the concentration of hCG could be readily quantified and communicated with patients/physicians and other clinical workers.

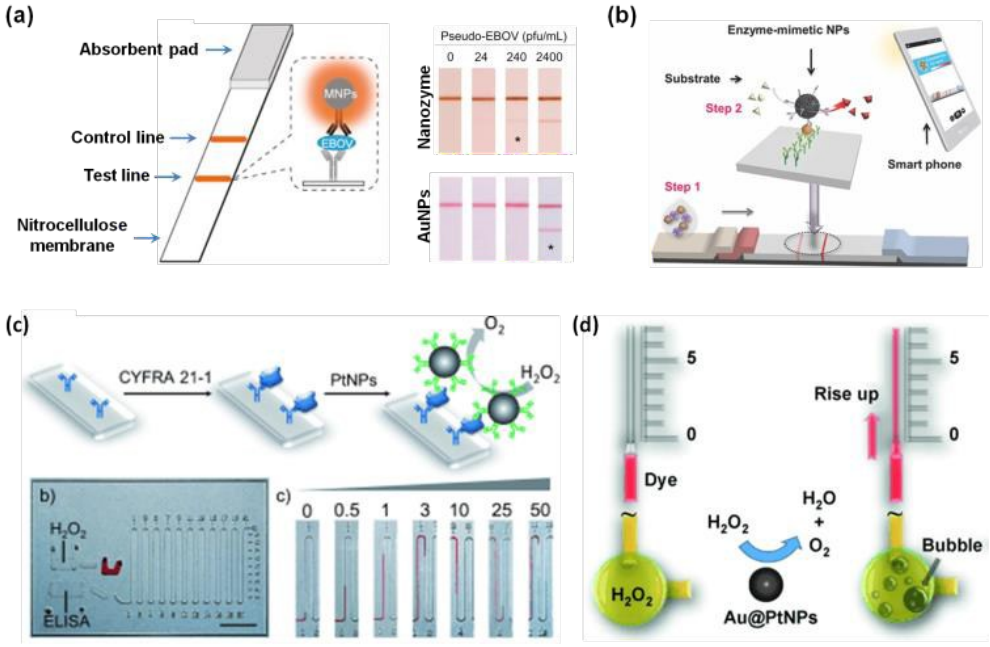

Figure 8. Nanozymes for immunoassay. Nanozyme-based strips for Ebola detection using Fe_3O_4 MNPs as peroxidase mimic (a) and for hCG detection using hierarchically structured PtNPs as peroxidase mimic (b). PtNPs (c) and Au@PtNPs (d) as catalase mimics for immunoassay on a volumetric bar-chart chip. (a) Reprinted with permission from reference [211]. Copyright (2015)

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Catalase catalyzes the decomposition of H_2O_2 into H_2O and O_2 gas (Scheme 3). Though many nanomaterials have been used to mimic catalase, only a few studies have been focused on their applications.[1, 207, 216] Recently, Song et al. showed that the O_2 gas from catalase mimic-catalyzed H_2O_2 decomposition could be used for diagnosis (Figure 8c).[207] They used PtNPs as the catalase mimic, which were then used to label detection antibody for signalling. To efficiently and conveniently measure the produced O_2 gas, they developed a microfluidics platform called volumetric bar-chart chip, which could easily gauge the volume of O_2 gas with coloured solution in the chip channel. With such a device, they have detected cancer biomarker cytokeratin 19 fragment (CYFRA 21-1) in serum and HER2 expressed on three breast cancer cell surfaces. By pre-encapsulating the catalase mimic (i.e., Au@PtNPs) within an aptamer hydrogel, Zhu and co-workers devised a similar bar-chart chip for cocaine detection (Figure 8d).[216]

$$2H_2O_2 \xrightarrow{\text{Catalase}} 2H_2O + O_2 \qquad (3)$$

Scheme 3. The reaction catalyzed by catalase.

2.8 Nanozymes for detection of cells and bacteria

Cells (usually cancer cells) and bacteria have been detected with nanozymes.[53, 198, 202, 205, 209, 217-220]

Cancer cells over-express characteristic receptors as cancer biomarkers. Therefore cancer cells can be detected with the corresponding antibodies or ligands, which recognize the receptors specifically. When an antibody or a ligand is conjugated with nanozymes, the conjugates can be employed for cancer cells detection. For example, Asati et al. employed antibody conjugated ceria nanoparticles for detection of folate receptor over-expressed lung carcinoma cells (A-549) and EpCAM over-expressed MCF-7 cells.[217] Recently, several studies also showed that folate receptor over-expressed cancer cells could be detected with various folate-modified nanozymes.[53, 198, 205, 209] In Wang and co-workers' study, they discovered that chitosan stabilized silver halide (AgX) nanoparticles exhibited interesting peroxidase mimicking activities (Figure 9a).[205] In the absence of H_2O_2, the AgX nanoparticles could still oxidize the substrate (such as TMB) if stimulated by light irradiation. Using AgI nanoparticles as the nanozyme, folate receptor over-expressed MDA-MB-231 cells were detected under light irradiation.

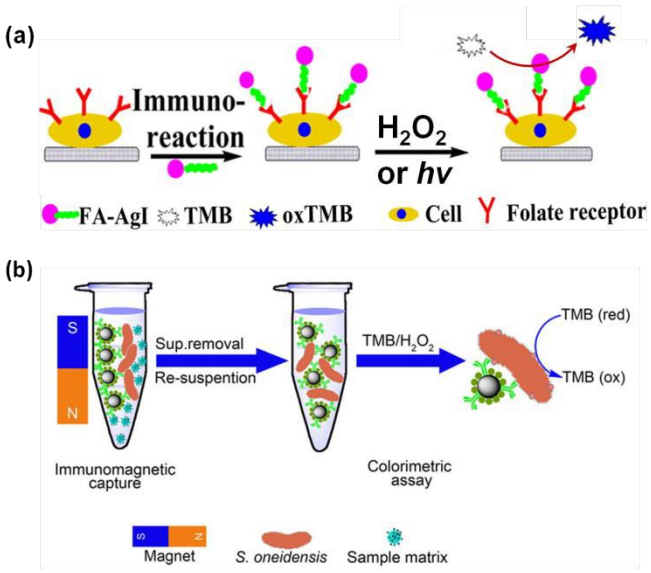

Figure 9. Nanozymes for cancer cell (a) and bacteria detection (b). (a) Reprinted with permission from reference [205]. Copyright (2014) American Chemical Society. (b) Reprinted with permission from reference [202]. Copyright (2014) Nature Publishing Group.

Wen reported the colorimetric detection of *Shewanella oneidensis*, a facultative anaerobic bacterium, on the basis of immunomagnetic capture of the bacteria and bacterial intrinsic peroxidase mimicking activities for signalling (Figure 9b).[202] The developed method exhibited good selectivity toward *S. oneidensis* and has been used for identifying spiked *S. oneidensis* in river water.

2.9 Nanozymes for imaging

Fan et al. reported the imaging tumour tissue by staining them with magnetoferritin nanoparticles as peroxidase mimic (Figure 10).[221] Due to the presence of over-expressed transferrin receptor 1, the tumour tissues were specifically stained with the magnetoferritin nanoparticles, which were coated with recombinant human heavy-chain ferritin. For the 474 patient specimens examined, the nanozyme-based imaging technique successfully distinguished cancer samples from normal ones with a sensitivity of 98% and specificity of 95%. Recently, Cai and co-workers also reported the staining and imaging tumour tissues with the magnetoferritin nanoparticles, which confirmed Fan's discovery.[208]

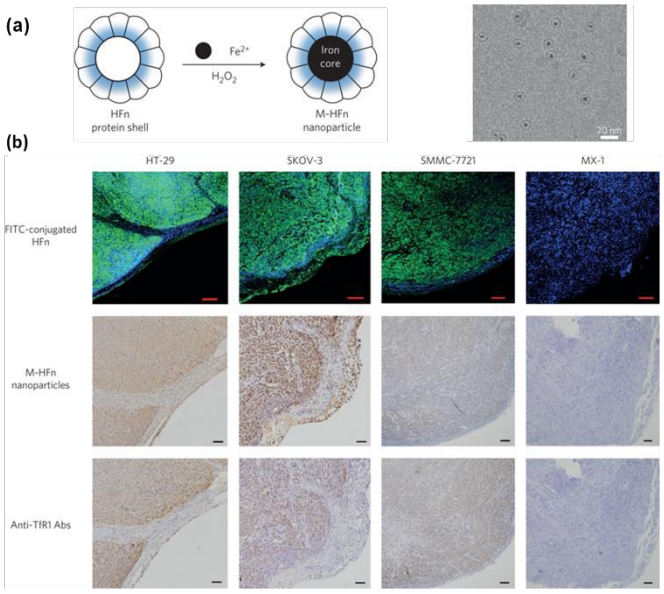

Figure 10. Magnetoferritin nanoparticles as peroxidase mimic for tumour tissues staining and imaging. (a) Preparation of magnetoferritin nanoparticles. (b) Magnetoferritin nanoparticle staining of tumour tissues. Reprinted with permission from reference [221]. Copyright (2012) Nature Publishing Group.

3. Nanozymes for therapeutics

By mainly eliminating reactive oxygen species (ROS) and/or reactive nitrogen species (RNS), nanozymes have been exploited for potential therapeutics.[13-17, 25, 209, 222-237] The nanozymes' ROS scavenging capabilities are mainly originated from their SOD mimicking activities, which convert superoxide into H_2O_2 (Scheme 4). In this section, the therapeutic effects of nanozymes are discussed, which cover anti-aging effects, anti-inflammatory effects, anti-oxidation effects, neuroprotection, and promotion of stem cell growth, etc.

$$2O_2^{\bullet -} + 2H^+ \xrightarrow{\text{SOD}} H_2O_2 + O_2 \qquad (4)$$

Scheme 4. The reaction catalyzed by SOD.

3.1 Neuroprotection

Fullerene derivatives are among the first nanozymes used for therapeutic studies.[14, 15] Dugan et al. pioneered the use of carboxyfullerenes as SOD mimics to protect neural cells from free radical damage.[14, 15] In a later study, Dugan's group not only investigated the SOD mimicking activity of $C_{60}[C(COOH)_2]_3$ and the associated catalytic mechanism but also studied the nanozyme's therapeutic effect on SOD2 knockout mice (Figure 11).[222] For the $Sod2^{-/-}$ mice, which cannot express mitochondrial manganese superoxide dismutase (MnSOD), their life span has been increased by 300% after either utero or postnatal treatment with the $C_{60}[C(COOH)_2]_3$ nanozyme. Since the nanozyme has been detected within mitochondria, it was proposed that the nanozyme may functionally replace MnSOD.

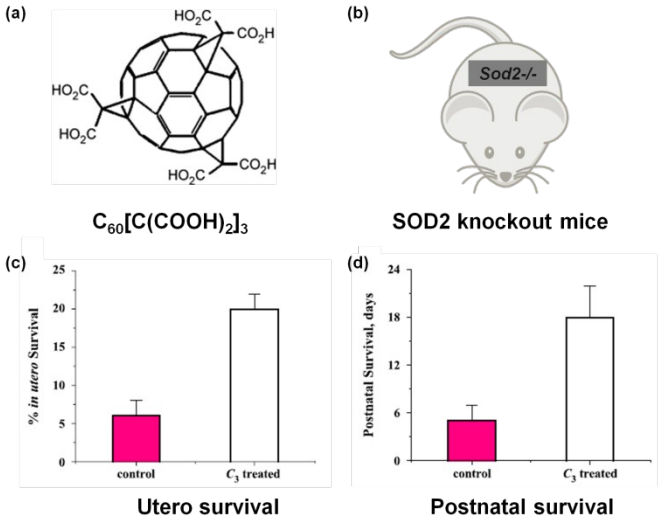

Figure 11. Treatment of SOD2 knockout mice with $C_{60}[C(COOH)_2]_3$. (a) Structure of $C_{60}[C(COOH)_2]_3$. (b) SOD2 knockout mice. Utero (c) and postnatal (d) survival of SOD2 knockout mice after treatment with $C_{60}[C(COOH)_2]_3$. Adapted with permission from reference [222]. Copyright (2004) Elsevier.

Ceria nanoparticles could also mimic SOD and exhibit interesting neuroprotective activity.[17, 227, 230] Chen and co-workers demonstrated that ceria nanoparticles could prevent retinal neuron cells from ROS damage, which was induced by intracellular hydrogen peroxide.[17] Remarkably, their animal studies also demonstrated that the ceria nanoparticles-based nanozyme exhibited protective activity towards light-induced rat retina photoreceptor cells degeneration.

ROS, generated and accumulated during ischemia, plays a critical role in ischemic stroke and associated neural injuries and diseases.[238] By eliminating the ischemic ROS, it would be possible to protect brain against ischemic stroke. For the first time, Kim et al. demonstrated that PEGylated ceria nanoparticles indeed exhibited excellent protective activity against ischemic stroke.[227] The animal studies showed that ceria nanoparticles of optimal dosage reduced ischemic brain damage (Figure 12).

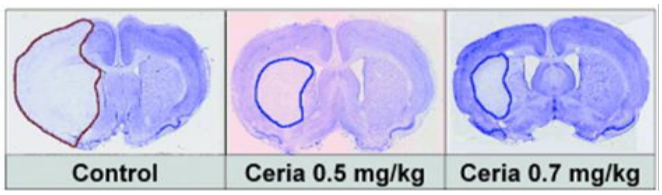

Figure 12. Ceria nanoparticles protect against ischemic stroke. Reprinted with permission from reference [227]. Copyright (2012) John Wiley and Sons.

RNS and amyloid beta (Aβ) peptides are involved in Alzheimer's disease (AD). However, effective therapy towards AD with proper antioxidants is still lacking. To address this challenge, Dowding and co-workers studied the protective roles of nanoceria against RNS and Aβ-induced mitochondrial fragmentation and neuronal cell death.[230] The electron

microscopic studies showed that nanoceria were internalized by neurons and localized at the mitochondrial outer membrane and inner leaflet of the plasma membrane, where most of RNS were produced.[230] Due to the switchable oxidation states between Ce^{3+} and Ce^{4+}, ceria nanoparticles could scavenge RNS and thus protected the neurons against degeneration. The results demonstrated that ceria nanoparticles protected neurons from nitrosative-associated mitochondrial fragmentation, DRP1 S616 hyperphosphorylation and neuronal cell death.

3.2 Anti-aging

It is known that redox reactions participate in aging process. For example, the detoxification of ROS is involved in regulating aging. Therefore, the ROS scavenging nanozymes may help to detoxify the ROS and thus prevent aging-related diseases. To this end, Quick et al. showed that $C_{60}[C(COOH)_2]_3$-based SOD mimic exhibited interesting anti-aging effects and improved wild-type mice's cognition ability.[224] Detailed studies revealed that the nanozyme decreased the age-associated mitochondrial superoxide production and thus improved the mitochondrial biological function, which in turn rescued age-related cognitive impairment due to its localization within mitochondrial.[224]

3.3 Anti-inflammatory

ROS can induce inflammatory responses, which may lead to endothelial dysfunction and tissue injury.[239] By scavenging ROS with SOD or its mimics, it can protect cells and tissues from ROS-induced inflammation. Several nanozymes have exhibited interesting anti-inflammatory effects due to their ROS scavenging properties.[232, 240] Hirst et al. studied the anti-inflammatory properties of ceria nanoparticles.[240] They demonstrated that the biocompatible ceria nanoparticles inhibited the production of ROS and radical nitric oxide (the two key inflammatory mediators) in J774A.1 murine macrophage cells. In a recent report, Son and co-workers integrated ceria nanoparticles as anti-inflammatory agents onto a bioresorbable electronic stent, which was a therapeutics device for endovascular diseases (Figure 13).[232] Using human umbilical vein endothelial cells as a model, they demonstrated that the nanozyme was able to improve the cell viability under oxidative stress. More, they showed that the nanozyme also exhibited excellent anti-inflammatory effects in animal models after implantation of the device in the canine common carotid artery. The nanozyme's anti-inflammatory properties were attributed to their ROS scavenging effect. This study offers a new direction of nanozyme research.

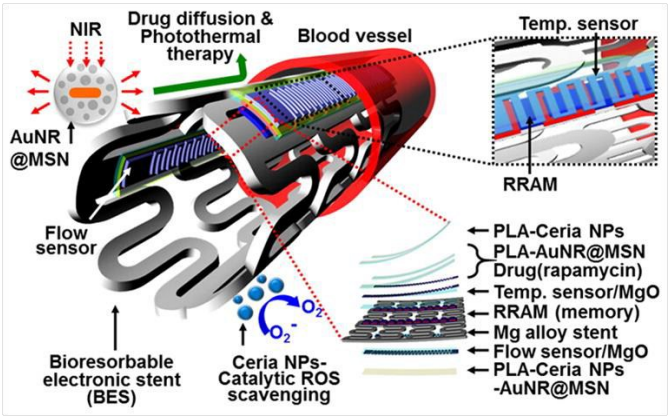

Figure 13. Ceria nanoparticles as anti-inflammatory agents in a bioresorbable electronic stent for endovascular diseases. Reprinted with permission from reference [232]. Copyright (2015) American Chemical Society.

3.4 Anti-oxidation

The anti-oxidation effects of several nanozymes have been investigated.[13, 234, 241] Early studies demonstrated that nanoceria possessed interesting anti-oxidation properties.[241] On the basis of self-regenerating antioxidant mechanism, nanoceria protected cardiac progenitor cells from H_2O_2-induced cytotoxicity for one week.[241]

Su et al. examined the protective effects of PVP-stabilized iridium nanoparticles against H_2O_2-induced oxidative damage to A549 lung cancer cells.[234] They showed the IrNPs significantly reduced intracellular ROS levels and thus enhanced cell viability in a dose-dependent manner. Vernekar and co-workers studied the cytoprotective effect of vanadia (V_2O_5) nanowires (Figure 14).[13] They found that the vanadia nanowires exhibited interesting glutathione peroxidase (GPx) mimicking activity (Figure 14a). More, by combining the nanozyme with glutathione reductase (GR), the GSH was recycled. Using genetically encoded H_2O_2-specific probe HyPer, they showed that the nanozyme indeed exhibited ROS scavenging properties against both extrinsic H_2O_2 and intrinsic cellular peroxide (induced by $CuSO_4$) in HEK293T cells (Figure 14b). The cytoprotective effects of the nanozyme were further confirmed by staining the cells with H_2O_2-specific dye Amplex Red and ROS-sensitive fluorescent dye DCFDA-H2 (Figure 14c). In a following study, it demonstrated nanoceria could also mimic GPx and protected cell via anti-oxidative effects.[233]

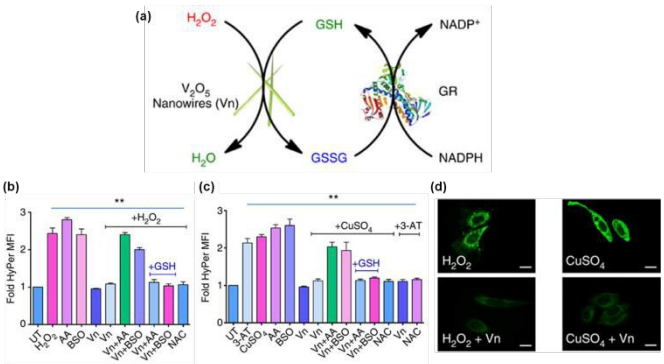

Figure 14. Vanadia nanowires as anti-oxidation nanozyme for cytoprotection. (a) Schematic depicting the glutathione peroxidase (GPx)-like antioxidant activity of vanadia nanowires (Vn) and GSH recycling by glutathione reductase (GR). Extrinsic H_2O_2 (b) and intrinsic cellular peroxide (induced by $CuSO_4$) (c) scavenging activities of Vn measured using genetically encoded H_2O_2-specific probe HyPer in HEK293T cells. Cells were either left untreated or pretreated with various agents. (d) Hela cells were treated with Vn before the treatment with H_2O_2 or $CuSO_4$ and then stained with 15 μM DCFDA-H2 dye. Reprinted with permission from reference 13. Copyright (2014) Nature Publishing Group.

3.5 Anti-biofouling

Nanozymes have also been used for anti-biofouling.[231, 242, 243] Tremel's group discovered that vanadia nanowires could mimic haloperoxidase.[244] They further investigated the vanadia nanowires' anti-biofouling properties in a subsequent report.[242] They carried out a long-term (60 days) *in situ* study of the nanozyme's activity by fixing the testing samples to a boat hull. Remarkably, because of its excellent anti-biofouling activity, the nanozyme-coated stainless steel plates significantly prevented marine biofouling when compared with the uncoated stainless steel plate. Due to its high efficiency and low toxicity to marine biota, the nanozyme may be used as an alternative to conventional anti-biofouling agents.

Gao et al. recently studied the Fe_3O_4 MNPs-enhanced oxidative cleavage of biofilm components (such as nucleic acids, proteins, oligosaccharides, and bacteria).[231] They used the Fe_3O_4 MNPs as a peroxidase mimic, which efficiently eliminated biofilms and thus prevented their formation in the presence of H_2O_2. Due to the nanozyme's unique penetrating property into the protective, organic matrix, the developed Fe_3O_4 MNPs-H_2O_2 system may provide a new approach to biofilm elimination in oral health, etc.

3.6 Other therapeutic applications

Nanozymes have also found other interesting therapeutic potentials, such as promoting stem cell growth for tissue engineering and regulating iron homeostasis.[25, 226, 228, 229, 237, 245-247]

In Kito's report, they investigated the effects of Fe_3O_4 MNPs-containing liposomes on the proliferation of induced pluripotent stem (iPS) cells (Figure 15).[228] The proliferated iPS cells would form the cell sheets, which were then used for angiogenic cell therapy. It was found that the extracellular matrix (ECM) alone did not form truly sheet-like structure and thus could not promote angiogenesis effectively. Surprisingly, when ECM was combined with Fe_3O_4 MNPs-containing liposomes for iPS cell proliferation, the formed iPS cell sheets significantly accelerated revascularization of ischemic hindlimbs after implanting the sheets in nude mice. The Fe_3O_4 MNPs-enhanced angiogenesis was attributed to the peroxidase-like anti-oxidative activities. The presence of Fe_3O_4 MNPs also improved the sheets' mechanical property, providing sufficient strength for handling.[228] This study provides an interesting approach to tissue engineering for reparative angiogenesis.

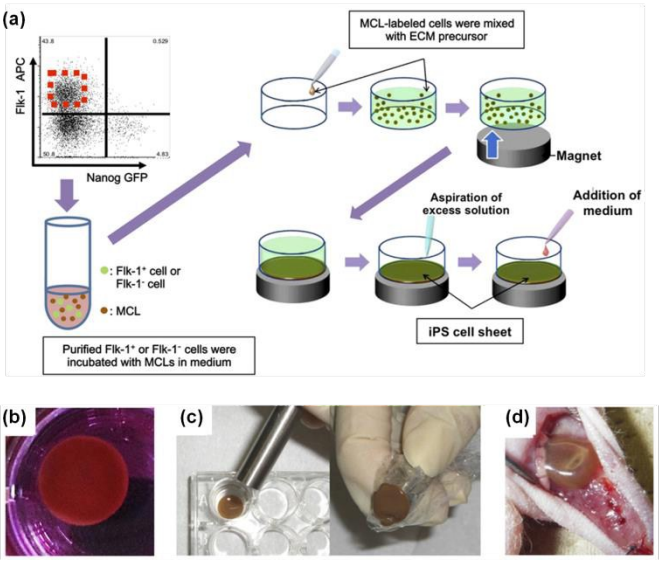

Figure 15. Fe_3O_4 MNPs-facilitated formation of iPS cell sheets for reparative angiogenesis. (a) Procedure for construction of iPS cell-derived cell sheet. (b) An alnico magnet was positioned on the surface of the culture medium. The Flk-1 cell sheet floated up to the surface of the culture medium without disruption. (c) The magnetized Flk-1 cell sheet attached to an Alnico magnet covered with polyvinylidene difluoride membrane via a magnetic force. (d) Flk-1 cell sheets were placed on the adductor muscles of nude mice using the Alnico magnet. Reprinted with permission from reference [228]. Copyright (2013) Nature Publishing Group.

Li et al. prepared the PtNPs within L-chain apoferritin cages, which showed ferroxidase mimicking activity.[25] They further showed that the nanozyme could regulate the iron homeostasis, providing great promise for therapeutic applications. Molybdenum trioxide nanoparticles exhibited sulfite oxidase mimicking activity.[229] Cellular study showed that the nanozyme could act as an alternative to natural sulfite oxidase, suggesting the potential use for treating sulfite oxidase-defect diseases.

4. Other applications

Nanozymes have also found other exciting applications, such as in constructing logic gates, pollutant removal and water treatment, etc.[23, 65, 187, 189, 247-255]

4.1 Logic gates

Several logic gates have been constructed with various nanozymes.[187, 189, 248, 249]

As shown in Figure 16, when the ceria nanoparticles were combined with natural enzymes, label-free, resettable, and colorimetric logic gates have been fabricated.[248] For ceria nanoparticles, they were colourless when Ce^{3+} were dominant on the nanoparticles' surface. However, they would turned into yellow colour when surface Ce^{3+} was oxidized to Ce^{4+} with H_2O_2. More, by heating, the yellow coloured ceria nanoparticles would return to colourless (Figure 16a). Lin et al. exploited the unique colour change of the ceria nanoparticles

as signalling readout to construct various logic gates. For example, when the ceria nanoparticles were combined with β-galactosidase and glucose oxidase, an "AND" logic gate was built. "OR" and "INHIBIT" logic gates were also obtained (Figure 16c). Due to the thermally responsive colour changing properties, the ceria nanoparticles could be transformed into colourless, which in turn reset the logic gates. The potential application of the logic gates for multiplex detection was also studied.

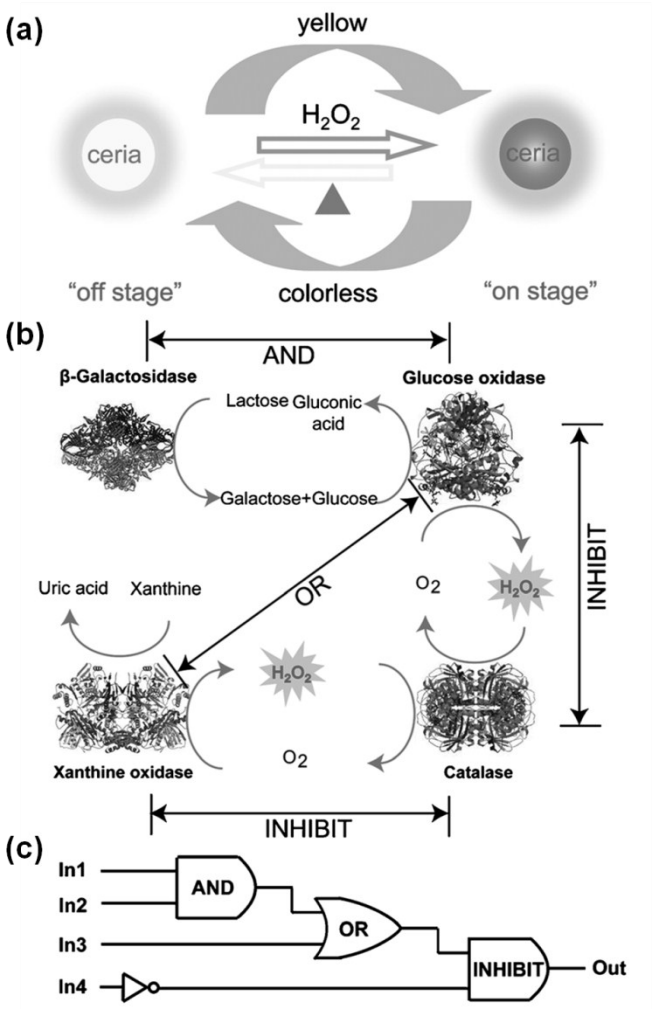

Figure 16. Ceria nanoparticles for colorimetric logic gates. (a) Illustration of a thermally responsive switch based on CeO_2 nanoparticles. (b) The operation of logic gates based on biocatalytic reactions. (c) Logic circuitry for the integrated logic system. In1=β-galactosidase, In2=glucose oxidase, In3=xanthine oxidase, In4=catalase. Reprinted with permission from reference [248]. Copyright (2012) John Wiley and Sons.

Lien and co-workers reported several logic gates on the basis of tuning AuNPs' multiple enzyme-like activities with metal ions.[187, 189] For example, both Be^{3+} and Hg^{2+} enhanced AuNPs' catalase mimicking activity, respectively. Thus, an "OR" logic gate was developed using Be^{3+} and Hg^{2+} as inputs and the AuNPs' catalase activity as the output (Figure 17a).[187] To enhance AuNPs' oxidase mimicking activity, both Pt^{4+} and Hg^{2+} were necessary. On the basis of this phenomenon, an "AND" logic gate was fabricated (Figure 17b). Similarly, an "INHIBIT" logic gate was developed by tuning AuNPs' peroxidase mimicking activity with Pb^{2+} and Hg^{2+} (Figure 17c). Pb^{2+} enhanced the peroxidase mimicking activity while Hg^{2+} exhibited inhibition effect. The presence of both Pb^{2+} and Hg^{2+}, however, also inhibited the mimicking activity. An "XOR" logic gate was also reported by tuning AuNPs' peroxidase mimicking activity with Ag^{+} and Bi^{3+} (Figure 17d).

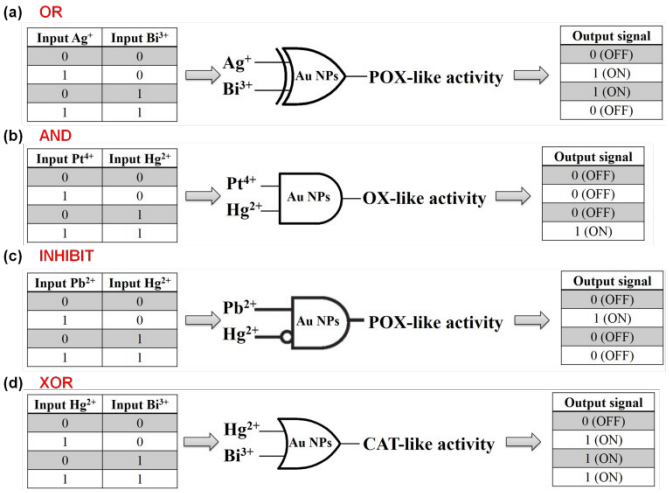

Figure 17. Logical regulation of the enzyme-like activity of AuNPs by using metal ions. "OR" (a), "AND" (b), "INHIBIT" (c), and "XOR" (d) logic gates on the basis of tuning AuNPs' enzyme mimicking activities with various metal ions. Reprinted with permission from reference [187]. Copyright (2013) Royal Society of Chemistry.

4.2 Pollutant removal and water treatment

Yan's group reported the removal phenolic pollutants from aqueous solutions using Fe_3O_4 MNPs-based peroxidase mimic.[250] After that, numerous studies have been devoted to pollutant removal and water treatment with nanozymes.[23, 65, 250-252]

In a recent report, Janos et al. investigated the phosphatase mimicking behaviour of the CeO_2/γ-Fe_2O_3 nanocomposites.[23] Due to the adsorption and phosphatase mimetic properties, the nanozyme has been used to decompose organophosphorus pesticide parathion methyl as well as the chemical warfare agents Soman and VX at ambient temperature. Since the nanozyme still retained the magnetic properties, it could be recycled and used in various decontamination strategies.[23]

5. Mechanisms

Though relative few studies have been focused on elucidating the mechanisms of the nanozymes based catalysis, several mechanisms have been established.[32, 222] In this section, the catalytic mechanisms of fullerene-based SOD mimic and nanoceria-based SOD and catalase mimics are discussed,

which should be helpful for understanding the mechanisms of other nanozymes in the future.

5.1 $C_{60}[C(COOH)_2]_3$ based SOD mimic

The detailed mechanism of $C_{60}[C(COOH)_2]_3$ based SOD mimic has been proposed by Ali and co-workers.[222] By combining the experimental results (such as electron paramagnetic resonance (EPR) measurements and kinetics studies) with semiempirical quantum-mechanical calculations, they proposed the mechanism shown in Figure 18.[222] Their study suggested that the electron-deficient regions on the $C_{60}[C(COOH)_2]_3$ nanozyme attracted the substrate anions (i.e., $O_2^{\bullet -}$) towards surface of the nanozyme electrostatically and then directed the substrate for further dismutation. The whole process was facilitated by the protons from the carboxyl groups of the nanozyme and/or surrounding water molecules around the nanozyme.[222]

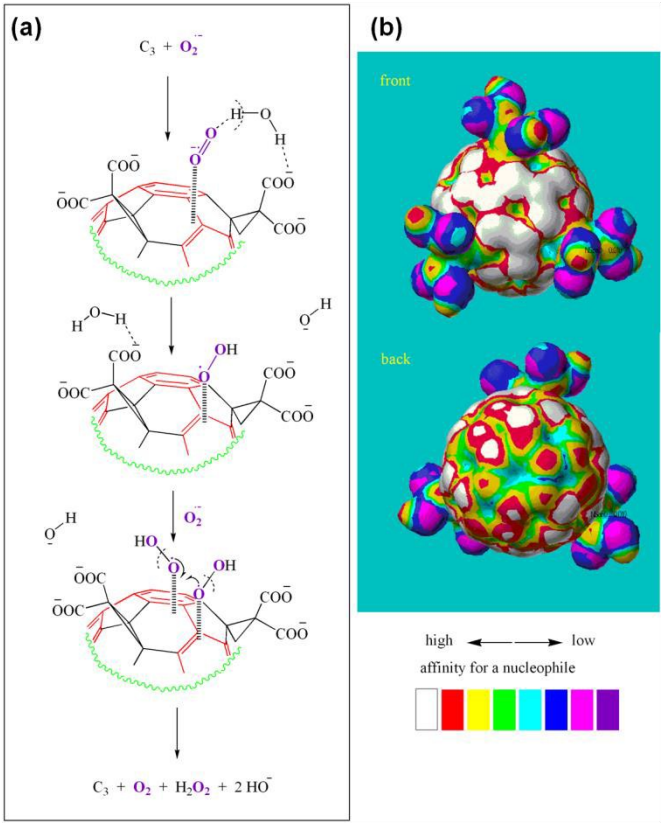

Figure 18. Proposed mechanism of $C_{60}[C(COOH)_2]_3$ based SOD mimic. Reprinted with permission from ref. [222]. Copyright (2004) Elsevier.

5.2 Nanoceria based SOD mimic

The SOD mimetic activity of nanoceria has been validated by the competitive assay against cytochrome c.[256] Based on EPR measurements, kinetics studies as well as other observations, Self's group proposed a dismutation mechanism of nanoceria-based SOD mimics, which is similar to the mechanism of Fe- and Mn-SOD.[256] As shown in Figure 19, an alternative mechanism was proposed by Celardo et al., which showed the redox cycle between Ce^{3+} and Ce^{4+}.[32]

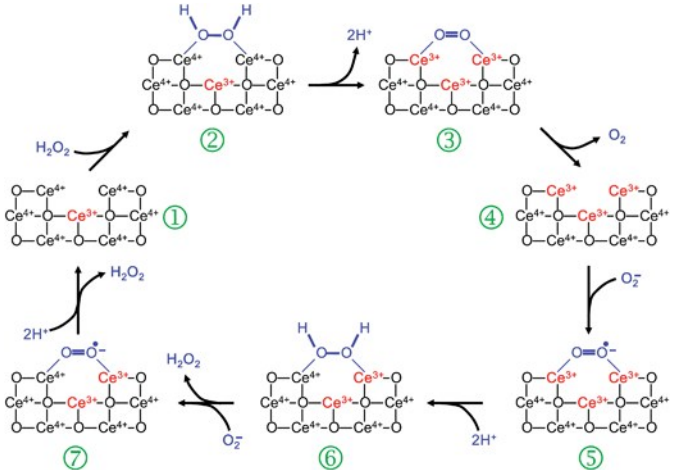

Figure 19. Proposed mechanism of nanoceria based SOD mimic. Reprinted with permission from ref. 32. Copyright (2011) Royal Society of Chemistry.

5.3 Nanoceria based catalase mimic

Nanoceria has also showed catalase mimetic activity. Figure 20 shows a possible mechanism for the reaction cycle similar to the one of natural catalase.[32] The overall reaction involved in Figure 20 can be expressed by the equation (3) in Scheme 3.

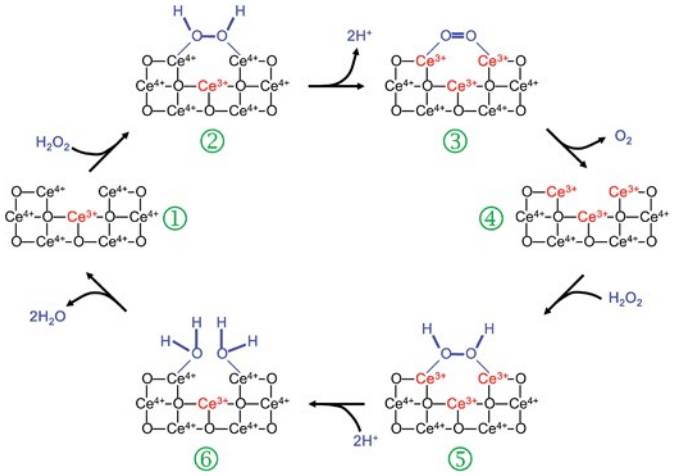

Figure 20. Proposed mechanism of nanoceria based catalase mimic. Reprinted with permission from ref. 32. Copyright (2011) Royal Society of Chemistry.

6. Summary and outlook

This review highlights the recent progress of nanozymes, especially their applications in bionanotechnology. Using selected examples, the broad applications in various areas (such as sensing, imaging, therapeutics, logic gates, pollutant removal and water treatment) were discussed.

As evidenced by the above-mentioned examples, the research field of nanozyme has grown substantially. To fulfill their great potentials, there are still numerous challenges remain to be tackled.[1]

First, though many nanomaterials have been exploited to mimic various natural enzymes,[81, 101, 257-267] currently the redox

enzyme mimics are still dominant in the developed nanozymes. Therefore, new strategies are needed to design and prepare other types of nanozymes. Recent progress in theoretical and computational protein design has enabled to design new functional proteins, including enzymes.[268, 269] Such a lesson should also be applicable to nanozyme design by combining experiments with theoretical and/or computational strategies.

Second, nanozymes are superior to natural enzymes in their enhanced stability, recyclability, low-cost, etc.[105, 270] Their catalytic activity and selectivity, however, still cannot compete with natural enzymes. By further understanding their mechanisms, high-performance nanozymes could be rationally designed in future.[271-274] For example, by taking advantage of synergistic effect, nanozymes with improved activities have been prepared.[275]

Third, natural enzymes usually work together within a confined environment. To truly mimic natural enzymes, cascade reactions catalyzed by nanozyme assemblies (or assemblies of nanozyme and natural enzyme) should be further exploited.[238, 276, 277]

Fourth, like natural enzymes, nanozymes' activities can be regulated.[47, 78, 158, 278-285] For example, by tailoring the nanozymes' composition, their activities could be tuned.[78, 278] pH and even light have been investigated for modulating nanozymes' activities.[280, 281, 283, 284] Despite the current progress, more approaches and factors are still needed to intentionally modulate nanozymes catalytic properties. Among them, biomolecules will play critical roles in manipulating nanozymes' catalytic behaviours.[47, 158, 286-290]

Fifth, for biomedical applications, more broad targets should be considered. More importantly, translational studies should be carried out whenever it is possible in future. For example, when the nanozyme-based test strips are combined with available telemed devices, they may help us address the need for point-of-care and even precision medicine. For the therapeutic nanozymes, their effective windows should be carefully optimized to avoid potential toxicity.

Sixth, for biomedical applications, the toxicity of nanozymes should be systematically studied. Though previous reports have shown that several nanozymes have been employed for therapeutics studies in animal models, their translation into clinical applications remains a great challenge. Currently, a few FDA approved superparamagnetic iron oxide nanoparticles, such as Resovist (Ferucarbotran), have exhibited peroxidase-like activity and been used for promoting stem cell proliferation.[237] However, the toxicity of other promising nanozymes should be tested for clinical trials.

Finally, chiral catalysis using nanozyme has been reported recently.[255] Here we speculate that nanozymes may be even involved in the original of life since there are must be some catalysts to carry out the catalysis before biocatalysts evoluted.

7. Acknowledgements

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8. Abbreviations

4-AAP	4-aminoantipyrine
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
CNTs	carbon nanotubes
DPD	N,N-diethyl-p-phenylenediamine
DRP1	dynamin-related protein 1
ECM	extracellular matrix
EpCAM	epithelial cell adhesion molecule
EPR	electron paramagnetic resonance
FDA	Food and Drug Administration
GPx	glutathione peroxidase
GSH	glutathione
hCG	human chorionic gonadotropin
HER2	human epidermal growth factor receptor 2
5-HIAA	5-hydroxyindole-3-acetic acid
HPLC	high-performance liquid chromatography
iPS	induced pluripotent stem
LOD	limit of detection
MNPs	magnetic nanoparticles
MS	mass spectrometry
NPs	nanoparticles
OPD	o-phenylenediamine
POC	point-of-care
PSA	prostate specific antigen
PVP	polyvinylpyrrolidone
rGO	reduced graphene oxide
SERS	surface enhanced Raman scattering
SOD	superoxide oxidase
TMB	3,3',5,5'-tetramethylbenzidine

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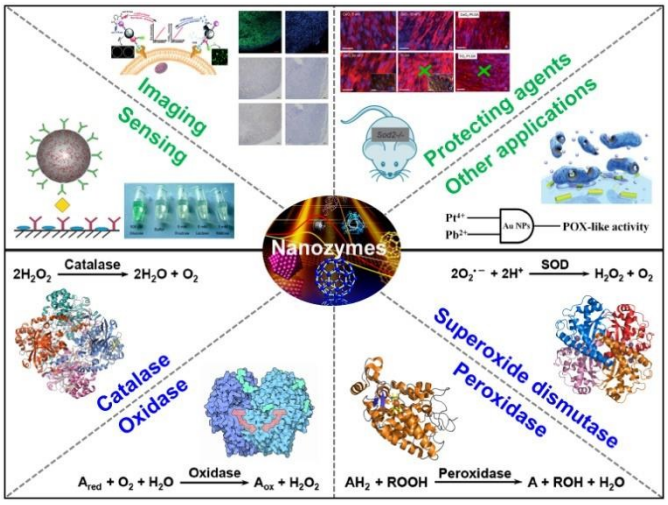

Nanozymes are nanomaterials with enzyme-like characteristics, which have found broad applications in various areas including bionanotechnology and beyond.