The prototypes of nanozyme-based nanorobots

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Abstract Artificial nanorobot is a type of robots designed for executing complex tasks at nanoscale. The nanorobot system is typically consisted of four systems, including logic control, driving, sensing and functioning. Considering the subtle structure and complex functionality of nanorobot, the manufacture of nanorobots requires designable, controllable and multi-functional nanomaterials. Here, we propose that nanozyme is a promising candidate for fabricating nanorobots due to its unique properties, including flexible designs, controllable enzyme-like activities, and nano-sized physicochemical characters. Nanozymes may participate in one system or even combine several systems of nanorobots. In this review, we summarize the advances on nanozyme-based systems for fabricating nanorobots, and prospect the future directions of nanozyme for constructing nanorobots. We hope that the unique properties of nanozymes will provide novel ideas for designing and fabricating nanorobots.

Keywords Nanorobot, Nanozyme, Logic gate, Nanomotor, Motion control

INTRODUCTION

The biomolecules created by nature are able to manipulate subtle objects at nano/micro scales, which can be considered as most ideal nanorobots existing in the world. Proteins utilize ATP to perform sophisticated functions in cells, some of which even assemble into supermolecules to finish more complex tasks perfectly. Still, the proteins have never stopped evolving since the day they were created by nature. For decades, scientists have been working on masses of researches to figure out the basic characteristics of those biomolecules; however, there are still many questions left. Nowadays, inspired by these natural nanorobots, scientists are making an endeavor to follow the intelligence of nature by building artificial nanorobots.

Artificial nanorobots, the robots working at nanoscale, have been through tremendous development in recent years. Nanorobotics mainly focuses on two areas: one is the macroscale robots manipulating nanoscale materials; the other is the robots built at nanoscale (Sierra *et al.* 2005). The latter is capable of performing complex tasks at nanoscale, for example, manipulating atoms or molecules. Nanorobots may be programmed with specific tasks to automatically respond to the changing environment and switch their programs to execute corresponding functions (Loukanov *et al.* 2019a).

Building a nanorobot is much like the manufacture of a macroscale robot, while the difference is that a nanorobot needs more elaborate manipulation at nanoscale. Similar to the macroscale robots, the primary components needed for nanorobots include a logic control system, a sensing system, a driving system and a functioning system. When the logic control system receives information data from the environment, it operates logically based on the programmed reference

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and output message to other systems. Subsequently, other systems will instruct the nanorobot to finish the tasks, such as the motion control of the driving system or the switch of the function system. At the same time, the sensing system interacts with the environment and provides feedback to the logic control system, thus helping the nanorobot work properly (Celikten and Cetin 2016). These systems of nanorobots are similar to those of macroscale robots, however, building these systems at nanoscale is not as easy as macroscale. Besides the difficulties of assembling materials into an intact structure at nanoscale, the nano effect is also a big challenge, which will change the characteristics of materials at nanoscale. Therefore, more elaborate manipulations should be made to build advanced nanorobots. In the last decade, scientists have made great progress in this field. Among them, nanozyme (nanomaterials with intrinsic enzyme-like activities) may make a great contribution to nanorobotics.

Since the discovery of nanozyme in 2007 (Gao *et al.* 2007), it is very inspiring that researches on this subject increase explosively all over the world. Materials at nanoscale with intrinsic enzyme-like activities have been used in various areas, especially biomedical applications including disease theranostics (Zhang *et al.* 2020). Moreover, nanozymes possess advantages of higher stability, easier modification and lower manufacturing cost. Furthermore, as nanomaterials, the inherent physical and chemical properties of nanozymes provide a multimodal platform for manipulating nanorobots (Jiang *et al.* 2019b).

Is there any chance that nanozymes can make a difference in the fabrication of nanorobots? Indeed, nanozymes are able to help build the logic control system, sensing system, driving system, and functioning system of nanorobots. In this review, we will summarize the recent researches that fabricated nanorobots with nanozymes in different systems.

ELEMENTS OF NANOROBOTS

As we mentioned above, nanorobots are composed of several primary systems, while in some cases they are divided into certain nanomachines with incomplete systems.

In numerous reports, nanomachines and nanorobots are usually used as synonyms. In fact, nanomachines may be considered as a step of building nanorobots. Nanomachines consist of only one or a few systems of nanorobots, and therefore they may not be fully functional as that of nanorobots (Loukanov *et al.* 2019a). Nanomachines are partial components for the fabrication

of nanorobots, and we are able to build a whole nanorobot by putting them together. Nanomachines have been studied widely and scientists already created nanomotors, multifunctional nanoparticles, nano-biosensors, nanogears, nanojoints and other nanostructures (Yang *et al.* 2018). These nanodevices may not contain the entire systems of nanorobots. For example, some nanoparticles lack the driving system, and many nanomachines do not include the logic control system. In this review, some of the nanodevices we mentioned as follows belong to nanomachines.

Logic control system

Electronic information industry endows our daily life with astonishing convenience and progress, largely depending on Boolean algebra. Boolean algebra can be applied to any type of information expressed as 0 and 1, which is the fundamental operation for computers (Tregubov *et al.* 2018). Therefore, a robot at nanoscale also needs to be built on Boolean algebra. The input signal 0 or 1 are processed at the logic control system, after which the output signal 0 or 1 will be given to other systems, so that the latter can take an operation. Furthermore, there is another important component for the input information—the logic gate. As same as the computer language, the gate is capable of processing the input signal then the computed information will be transmitted to the control center, which may be the unary YES and NOT gates, as well as the binary AND and OR gates. These logic gates have been built by various nanomaterials and work in a number of entities at nanoscale.

Nanomaterials like DNA, protein and other molecules are appropriate for the fabrication of logic gates. Constructed by DNA strands, the nucleic acid-based logic gate could control AND and OR functions through modified fluorescence (Yoshida and Yokobayashi 2007). When the ligands were added to the system and matched with the corresponding aptamers, the fluorescence of corresponding ON (1) or OFF (0) information would be outputted (Fig. 1). For the AND gate, if both of the ligands were matched (the input signals are “1” and “1”), the change of fluorescence would transmit ON (1) as output, otherwise the output information would be OFF (0). The OR gate was different from the AND gate, that is, as long as one of the ligands were matched (input signals are “1” and “0”, “0” and “1”, “1” and “1”), the output would be ON (1). As we can see, the key point of logic gate is the threshold conditions for ON and OFF signal, and how to set the threshold depends on the materials and the way they were built.

Fig. 1 The working model of "AND" and "OR" gates of a DNA-based logic gate. Because of the quencher moieties, attenuated fluorescence means the "OFF" state, and enhancement of fluorescence means the "ON" state. Reproduced with permission of Royal Society of Chemistry (Yoshida and Yokobayashi 2007)

Driving system—nanomotor

As a nanomachine, nanomotor is driven by power instead of doing Brownian motion. Many kinds of micro/nanomotors have already been developed, such as nanowires (Guo *et al.* 2018; Wang *et al.* 2017a), helical motors (Li *et al.* 2014; Manesh *et al.* 2013), Janus particles (Ma *et al.* 2016; Qin *et al.* 2017), micro/nanorockets (micro/nanotubular) (Gao *et al.* 2012; Xu *et al.* 2018; Zha *et al.* 2018), *etc.* (Fig. 2). Some nanomotors obtain energy from external devices and convert it to motive power, meanwhile others catalyze fuels in the environment to move against the Brownian motion and other barriers. Therefore, nanomotors can be classified as fuel-free nanomotors and fuel-dependent nanomotors.

The fuel-free nanomotor receives energy from an external source such as magnetic, electric, acoustic and light fields, after which the driving system will convert the energy to power the nanomotor so that the nanorobot can overcome the obstacle of Brownian motion or resistance in fluid (Wang and Pumera 2015; Wang *et al.* 2019). While the fuel-dependent nanomotor does not need energy from an external source, it utilizes the non-biotoxic or biocompatible fuels in the environment. So far, the diverse fuels that have been reported include H_2O_2 , Br_2 , or I_2 solutions, hydrazine, acidic and alkaline solutions, and even methanol, diazomethane, azides, and glucose oxides (Mano and Heller 2005; Mirkovic *et al.* 2010; Wang and Pumera 2015).

A large part of micro/nanomotors are designed for applications in living bodies, in particular with

biomedical platforms (Gao *et al.* 2018; Wang *et al.* 2019). It is reported that excess H_2O_2 accumulated in tumor sites (Szatrowski and Nathan 1991), which provides favorable conditions for H_2O_2 -dependent nanomotors in cancer therapy. Moreover, tumor sites also show an acidic pH level (Vaupel 2004), which is partially caused by the elevated level of lactic acid (Kim and Dang 2006). Guix *et al.* built a CaCO_3 -based Janus particle to help deliver drugs for cancer cells by utilizing the acidic environment (Guix *et al.* 2016). The Janus particle, a hemispherical nanomotor decorated by CaCO_3 would generate CO_2 bubbles to power the motor in acidic environment, then the continuous reaction would dissolve the CaCO_3 shell leading to the release of drugs at the tumor site.

Furthermore, it is also important to control the pattern of motion, which means modulating the moving direction, speed, starting or stopping of the movement. To exert the control, we may search for solutions like external wireless influence or inner self modulation. Various methods have been applied to the motion control of the nanomotors, such as magnetic guidance, thermally control, chemical response, phototaxis, particle communication, *etc.* (Hong *et al.* 2010; Wang and Pumera 2015; Wang and Manesh 2010).

Sensing system

The sensing system is another crucial system for the operation of nanorobots/nanomachines. It communicates with the environment to obtain information, so that the control system acts upon these received data to modulate other systems. Nanomachines without control system may also depend on the sensing system for direct modulation. It may have an intimate connection with driving system and influence the motion, or it can switch the activation and inhibition of function systems. Zhang *et al.* built a jellyfish-like micromotor for DNA sensing, the motion of which was controlled by the DNA-dependent sensing system (Zhang *et al.* 2019). The micromotor was composed of an umbrella-shaped multi-metallic body, a bunch of DNA hybridization and catalase decoration (Fig. 3A). When the target DNA matched with the DNA of sensing units, sensing units disassembled and released power units, reducing the motion speed (Fig. 3B). The sensing system thus could modulate the motion and transmit the information about DNA detection by reducing the speed. In addition, the sensing system built by targeting molecules also affected the function system such as an artificial engineered platelet (Hu *et al.* 2016). Decorated with targeting molecules on the surface, the drug-encompassed platelet could sense and target myeloma cells via

Fig. 2 Different types of micro/nanomotors. **A** An electric-field-guided catalytic nanomotor. Reproduced with permission of American Chemical Society (Guo *et al.* 2018). **B** A magnetically powered enzyme-functionalized helical nanomotor. Reproduced with permission of Royal Society of Chemistry (Manesh *et al.* 2013). **C** A Zn nanozyme-based microrocket. Reproduced with permission of American Chemical Society (Gao *et al.* 2012). **D** A Pt nanozymes-based Janus particle. Reproduced with permission of American Chemical Society (Ma *et al.* 2016)

Fig. 3 **A** Steps of fabricating the jellyfish-like micromotor. **B** The working mechanism of DNA sensing. Reproduced with permission of American Chemical Society (Zhang *et al.* 2019)

alendronate and P-selectin. After internalization by myeloma cells, cell death would be induced through the release of bortezomib.

Function system

The function system is the most vital system, while all the other systems are here to help execute the functions. The final purpose of building nanorobots is to achieve subtle work at nanoscale in various areas, especially

medical therapy. There have been many nano/micro-motors endowed with medical functions, for instance, cancer-targeted delivery, diagnosis and imaging-guided therapy (Wang *et al.* 2019). Medical nano/micromotors are capable of delivering drugs to tumor sites like the Janus particle (Guix *et al.* 2016); or they may depend on the sensing system to detect target molecules for cancer diagnosis, such as the jellyfish-like micromotor for DNA sensing (Zhang *et al.* 2019). As for imaging-guided

therapy functions, fluorescent materials enabled nano/micromotors to monitor *in vivo* (Wan *et al.* 2019).

In this area, the nanoparticle is a burgeoning method for medical therapy. Nanoparticles, composed of multiple elements, are capable of performing smart work at nanoscales. In the progress of cancer nanomedicines, nanoparticles have made a remarkable contribution to drug delivery, tumor therapy, *in vivo* imaging, *etc.* (Loukanov *et al.* 2019b). However, many nanoparticles usually lack some systems, for example, the driving system, and make movement just following the environment. As we can see, nanoparticles are a great platform for multiple functions, and these functions need to be integrated into nanomachines or nanorobots, acting like a stack of diverse bricks for building nanomachines. The functions we required determine the applications of these nanomachines or nanorobots.

NANOZYMES AND NANOROBOTS

Nanozymes possess enzyme-like activities, indicating that the catalytic efficiency and mechanism are similar to that of natural enzymes. Most of the nanozymes follow the Michaelis-Menten kinetics, and there have already been standardized methods to study the catalytic activities of certain nanozymes (Jiang *et al.* 2018). By the end of May 2020, more than 900 nanomaterials have been reported to show enzymatic activity. Nanomaterials such as Fe_3O_4 , Co_3O_4 , CuO , Au , Ag , Pt and Pd *etc.* were found to perform catalytic activities comparable to natural enzymes (Yan and Gao 2020). In addition, those nanozymes possess enzyme-like activities including peroxidase-like activity, oxidase-like activity, catalase-like activity, superoxide dismutase-like activity, sulfite oxidase-like activity, protease-like activity and nuclease-like activity (Gao *et al.* 2020). Nanozymes may take place of the natural peroxidase or oxidase, even the protease and nuclease in artificial applications.

Enzyme-like activities and other properties

Peroxidase-like activity is a common property of many nanozymes, and peroxidase-like nanozymes reduce peroxide to generate transient reactive intermediates like free radicals, which further react with another substrate quickly. Catalase-like nanozymes catalyze the decomposition of H_2O_2 into molecular oxygen (O_2) and water (H_2O), with oxygen bubbles produced during the reaction. Besides, the oxidase-like nanozymes oxidize substrates in the presence of O_2 , among which, the glucose oxidase (GOx)-like nanozymes catalyze glucose to generate H_2O_2 and gluconic acid. These enzyme-like

activities are usually used to treat tumor cells or detect biomolecules *in vivo* or *in vitro*.

The oxidoreductase activities often catalyze the colorimetric reaction, the results of which are visualized and quantified. In tumor cells, these reactions play a role in modulating the cellular networks so as to treat cancer. Being biocompatible with low biotoxicity, nanozymes are favorable materials for biomedical applications and environment pollution (Munir *et al.* 2020). With high stability, low cost, easy large-scale production and simple modification, nanozymes act as a better choice for the substitution of natural enzymes. More importantly, some of them are endowed with several enzyme-like activities and catalyze cascade reactions just by one nanozyme (Fan *et al.* 2018b; He *et al.* 2013; Xu *et al.* 2019). This is a huge step for enzyme utilization. As natural enzymes, activators and inhibitors control their activities in various ways due to their physicochemical properties. For example, the gold nanozymes can be modulated by metal ions. Hg^{2+} and Pb^{2+} may endow Au nanozymes with the peroxidase-like activity. (Wang *et al.* 2012).

Apart from the enzyme-like activity, different nanozymes boast diverse physiochemical properties. For instance, iron oxide-based nanomaterials are able to respond to magnetic field, the color of cerium oxide nanozymes change with the states of Ce^{3+} and Ce^{4+} , and Au nanozymes are capable of absorbing near infrared (NIR) to generate heat.

How can nanozyme help nanorobots?

Activities of nanozymes are similar to that of natural enzymes, as activators and inhibitors also have an impact on nanozymes. Thus, it is proper to utilize nanozymes in the logic control system so that the "ON" and "OFF" of logic gate will be modulated by activators and inhibitors, and then transformed to the signal "0" and "1". Apart from the logic control system, the driving system is also suitable for these enzyme-like activities. For fuel-dependent nanomotors, enzyme-like activities of catalysts help power the motion, especially the catalase-like activity. In addition, nanozymes can not only catalyze the fuels for power but also control the motion. Decorated with targeting molecules, nanozymes have the potential to be applied in motion control. Some special features make nanozymes a promising material in the driving systems of nanorobots. For example, magnetic nanozymes help control the motion and guide the whole machine to the targeting position. Most importantly, their catalytic activities are powerful tools for the biomedicine applications, which provides multiple choices for the function systems. In conclusion,

nanozymes show great potential in nanorobots, and their applications will be discussed in detail in the following sections.

Nanozyme-based logic gate for control system

Signal “0” and “1” are the most important information for the control system as well as the ON and OFF of the logic gates. Therefore, activators and inhibitors function as proper signals for the logic gate and control system through modulating the ON and OFF activities of enzymes. There are some enzymes utilized in the logic gating function already, and the substrates and products functioned as the input and output information. With glucose oxidase (GOx), horseradish peroxidase (HRP), and invertase (INV) on the surface, these enzyme-coated carbon nanotubes generated spectroscopic and electrochemical output signals (Kim *et al.* 2011). Compared with natural enzymes, nanozymes are more easily to be modified with specific properties. Owing to reversibly-controlled enzyme-like activities, nanozymes are promising logic-gated nanomaterials for their simple instruction in the logic control system, as the exchange of their activity is able to present the signal “0” and “1”.

Au nanozymes modulated by metal ions

Metal ions may act as activators and inhibitors. By pairing with the ions in the environment, nanozyme-based logic gates are able to transmit output signals. Lien *et al.* utilized enzyme-like gold nanozyme to construct four types of logic gates combining with five metal ions including Ag^+ , Bi^{3+} , Pb^{2+} , Pt^{4+} and Hg^{2+} (Lien *et al.* 2013). These metal ions here were activators or inhibitors which could be utilized as input signals whereas the output signals were the color changes of chromogenic substrate induced by the multiple enzyme-like activities. For the OR gate which utilized the Hg^{2+} and Bi^{3+} as the input signals, the output signals would be 0 (OFF) only in the absence of both ions. Otherwise, either of the two ions would activate the catalase (CAT)-like activity of the Au nanozymes and the output signals would be 1 (ON) (Fig. 4A). Then the AND gate here was controlled by the Pt^{4+} and Hg^{2+} ions, and the presence of both Pt^{4+} and Hg^{2+} ions endowed the gate with oxidase (OX)-like activity leading to the 1 (ON) as output signal. Other three situations would make the 0 (OFF) (Fig. 4B). With regard to the INHIBIT gate, it inhibited the peroxidase (POX)-like activity of the Pb^{2+} -Au nanozymes by the Hg^{2+} ions, so that the Pb^{2+} -Au NPs without Hg^{2+} ions would come out 1 (ON) (Fig. 4C). Last, they built a XOR (Exclusive-OR) logic gate via regulation of the peroxidase (POX)-like

activity through Ag^+ and Bi^{3+} ions. This XOR logic gate could provide the output signals with 1 (ON) in two situations, only when one of the two ions Bi^{3+} and Ag^+ was deposited on the Au nanozymes (Fig. 4D). If the two ions Bi^{3+} and Ag^+ were both added to the gate at the same time, then the output would be 0 (OFF). These four logic gates—“ $\text{Hg}^{2+}/\text{Bi}^{3+}$ (OR)-Au NP_{CAT}”, “ $\text{Pb}^{4+}/\text{Hg}^{2+}$ (AND)-Au NP_{OX}”, “ $\text{Pb}^{2+}/\text{Hg}^{2+}$ (INHIBIT)-Au NP_{POX}” and “ $\text{Ag}^+/\text{Bi}^{3+}$ (XOR)-Au NP_{POX}”—designed by Lien and co-workers are promising components of the control system. These multiplex logic gates based on Au nanozymes opened a novel gate for the construction of Boolean algebra at nanoscale.

Later, Lien and his co-workers made use of the metal ion-based modulation of Au nanozymes into detecting applications. In this study, they induced Pb^{2+} , Hg^{2+} , Pt^{4+} and Bi^{3+} to fabricate the gates for the detection of ions- $\text{Pt}^{4+}/\text{Pb}^{2+}$ (AND) and $\text{Bi}^{3+}/\text{Hg}^{2+}$ (INHIBIT) via new combinations (Lien *et al.* 2014). Different from the former logic gates, Pt^{4+} -Au and Bi^{3+} -Au NPs are nanozymes with peroxidase-like activity, whereas the Pb^{2+} and Hg^{2+} ions are activators and inhibitors, respectively. These four metal ions acted as the input signals and the color reactions induced by the peroxidase-like activity were the output signals as well. In terms of the AND gate, only in the situation that the Pb^{2+} (1) and Pt^{4+} (1) were both deposited on the Au NPs logic gate simultaneously, the output would be 1 (ON), otherwise it would be 0 (OFF). As for the INHIBIT gate, with the Bi^{3+} (1) and without the Hg^{2+} (0) on the Au NPs, the gate transmitted 1 (ON) as output signal. In addition, 0 (OFF) appeared in the case of both Bi^{3+} (1) and Hg^{2+} (1), with Hg^{2+} (1) and without Bi^{3+} (1), or neither of the ions. This Au NPs logic gate was designed to detect the metal ions in liquids, and even more, they combined these two gates to a rational gate networking, a logic circuit that promoted the visual detection for metal ions (Fig. 5). The O_2 bubbles or reddish resorufin generated by enzyme reactions would show the 1 (ON) output directly.

As we can see, various ions play an active role in modulating the activities of nanozymes. With easy modification and multiple enzyme-like activities, nanozymes may be an appropriate material for fabricating multiplex logic gates. Furthermore, it opens a new horizon of the way to build logic control network as well.

The color change of cerium oxide nanozymes

Alongside with the enzyme-like activities, some inorganic nanozymes also possess many special physico-chemical properties related to the materials themselves.

Fig. 4 The working models of logic gates based on five metals. **A** The $\text{Hg}^{2+}/\text{Bi}^{3+}(\text{OR})$ -Au NP_{CAT} gate. **B** The $\text{Pb}^{4+}/\text{Hg}^{2+}(\text{AND})$ -Au NP_{Ox} gate. **C** The $\text{Pb}^{2+}/\text{Hg}^{2+}(\text{INHIBIT})$ -Au NP_{Pox} gate. **D** The $\text{Ag}^{+}/\text{Bi}^{3+}(\text{XOR})$ -Au NP_{Pox} gate. Reproduced with permission of Royal Society of Chemistry (Lien *et al.* 2013)

Among those nanozymes, cerium oxide nanozymes exhibit a unique characteristic—the color change of the nanozyme itself.

In 2007, Das *et al.* performed a series of experiments to investigate the auto-catalytic activity of ceria nanozymes and first observed the phenomenon of color change (Das *et al.* 2007). Later in 2008, Perez *et al.* further confirmed this result (Perez *et al.* 2008). At pH 7.4, when the hydrogen peroxide (H_2O_2) was added, the solution went through a rapid color change from yellow to orange. After 10 days, the H_2O_2 decomposed and the color returned to yellow. The color change happens because of the reversible variation of $\text{Ce}^{3+}/\text{Ce}^{4+}$ ratio on the surface of the nanozymes. Singh *et al.* also synthesized cerium oxide nanozymes and observed the addition of H_2O_2 lead to the color change from colorless to yellow and the recovery after 15 days (Singh *et al.* 2011).

This reversibility of Ce^{3+} and Ce^{4+} on the surface of ceria nanozymes indicated its potential role as a perfect switch signal for the ON and OFF of the logic gate. Therefore, there has already been a study applying the ceria nanozymes to the Boolean algebra. Lin *et al.* utilized CeO_2 nanozymes as signal transducer of the logic operation (Lin *et al.* 2012). This CeO_2 nanozyme-based logic gate took H_2O_2 as 1 (ON) then the signal would be transmitted by the color change from colorless to yellow. To reset the state of the gate back to OFF, it just needed a simple operation by heating the H_2O_2 to decomposition (Fig. 6A). As inputs, several enzymes in

combination were constructed to AND, OR and INHIBIT gate including β -galactosidase (β -Gal), glucose oxidase (GOx), xanthine oxidase (XO) and catalase (CAT) (Fig. 6B). For example, in the presence of lactose and oxygen, β -Gal and GOx would produce H_2O_2 , leading to ON as output signal. Similar to AND gate, the OR and INHIBIT gate processed information in the environment with glucose and oxygen in the solution. Unlike the Au nanozyme-based gate mentioned before which simultaneously dealt with input signals together, this CeO_2 nanozyme-based logic gate received the last information that has been through the cascading reaction. This design may offer a smarter logic algorithm for the control system. Even more, because of the relatively separated steps of the cascading reaction, the gates possess the ability to make an integration or a concatenation with each other (Fig. 6C). The computing ability may be regarded as a rudiment of the Boolean algebra calculation at nanoscale. Moreover, the complicated networks generated by these logic gates helped understand the complex biological systems. The CeO_2 nanozyme-based logic gate may be utilized to mimic the natural biological pathways in cells.

CuO:GNS nanozyme as the input signal

Natural enzymes can be applied to the logic gate as input signals, and so can the nanozymes. Sharma and co-workers fabricated a simple AND logic gate to detect

Fig. 6 The logic gates depended on the color change of CeO_2 NPs. **A** The “ON” and “OFF” states and their corresponding color change. **B** The combination designs of AND, OR and INHIBIT gates and their corresponding catalytic reactions. **C** The integrated computing results of all inputs and outputs. Reproduced with permission of John Wiley and Sons (Lin *et al.* 2012)

cholesterol by modifying the CuO nanozyme with graphene quantum dots (GQD) (Sharma and Mobin 2017). In the presence of cholesterol oxidase and chromogenic substrates (4-AAP and phenol), the modified CuO:GNS nanozyme with peroxidase-like activity and cholesterol were the input signal (1,1), which led to the colorimetric reaction as output signal (ON). The cholesterol oxidase generated H_2O_2 in the oxidation reaction of cholesterol, then the CuO:GNS nanozyme catalyzed 4-AAP and phenol to red products, suggesting the generation of H_2O_2 . Thus, the output signals could be detected by absorbance change. In addition, the modified CuO:GNS nanozyme has higher peroxidase-like activity than original CuO nanozymes. Therefore, the CuO:GNS nanozyme is also a good sensor for H_2O_2 . Although simple structure limited its function, the CuO:GNS nanozyme-based logic gate is of cytocompatibility. GNS modification not only increases its catalytic activity, but also decreases the toxicity of CuO by generating lower levels of ROS. Hence, it is more proper to utilize in the living body, and it may be applied to a smart sensing system at nanoscale especially for medical use.

Nanozymes with enzyme-like activities and other special properties foster the building of logic gate for the control system. Moreover, with complex designs, nanozymes may even take an important step of the Boolean algebra computations at nanoscale, which is a significant contribution to the fabrication of nanorobots. Nanozymes are able to be applied to the utilization *in vivo* and *in vitro*, making them promising materials over a wide range of fields.

Nanozyme-based driving system

Taking notice of the characteristics in the fabrication of logic gates, we found that the catalyst of H_2O_2 has played an important role. H_2O_2 is a common fuel for the self-propelled nanomotors. Therefore, nanozymes are widely used in the field of driving system.

Nanorobots need a driving system to keep them moving as required and reach the targeting site. As we mentioned before, there are fuel-free and fuel-dependent nanomotors. In order to convert the fuels to power, the fuel-dependent nanomotors need catalysts, and enzymes may play an active role in generating power. For example, a mesoporous silica drug delivery nanoparticle system decorated with urease enzymes, not only enhanced the drug delivery, but also increased the drug release capability (Hortelão *et al.* 2017). It may be caused by the increased diffusion of fuel-powered nanomotor and the flow rate on the surface of drug-loaded nanoparticle. Taking advantage of bioavailability and biocompatibility, it is ideal to convert the energy

from the catalytic reaction to drive the nanorobot compared with other methods (Wang *et al.* 2019). Therefore, as a kind of promising enzyme-mimic materials, nanozymes are a better choice to power the driving system in nanorobots.

Pt nanozyme-based linear motion

Pt nanozyme, one of the metallic nanoparticles, possesses catalase/peroxidase-like activity, catalyzing H_2O_2 to generate O_2 or oxidize other substrates. As we mentioned before, H_2O_2 is a common fuel for self-propelled nanomotors. Hence, Pt nanozyme with catalase activity has been widely studied in fuel-dependent nanomotors, and some were engineered with other metals to enrich the functions or improve the abilities.

In 2004, F. Paxton *et al.* designed Pt/Au nanorods as nanomotors, which could be considered as the initial application of Pt nanozyme to power the motion of nanomachines (Paxton *et al.* 2004). In H_2O_2 solution, the O_2 generated by Pt nanozyme formed an interfacial tension gradient to provide motion force (Fig. 7A), with the speed of approximately 2–10 body lengths per second. The movement of Pt/Au nanorods was considered to be related to the electrokinetic mechanism of the redox reaction. In order to investigate the motion characteristics of the self-propelled micro/nanomotors, R. Howse and co-workers used an asymmetric spherical particle (so called Janus particles now) that only based on Pt nanozyme as the model for the nanomotor (Howse *et al.* 2007). They concluded that this nanomotor was powered by a different propulsion mechanism. Since then, Pt nanozyme has become a popular material for micro/nanomotors, such as Pt nanozyme-based particles (Choi *et al.* 2018), enhanced Pt nanorods (Kline *et al.* 2005), and Pt Janus particles (Gibbs and Zhao 2009). In the process of developing Pt nanozyme-based motors, scientists are working to increase the flow speed as well. Pumera's lab fabricated a micromotor for self-propelled drug delivery by combination of carbon nanotubes (CNTs) and Pt nanozyme (Khezri *et al.* 2019). The inner layer was constructed with Pt nanozyme, which catalyzed the H_2O_2 as fuels to power the micromotor. Then the reduced nanographene oxide deposited as outer layer via template-assisted electrodeposition (Fig. 7B). The catalase-like activity of inner Pt nanozyme catalyzed the fuel H_2O_2 to oxygen and water, so that the generated O_2 could push the micromachine into movement by bubble ejection. The average velocity was 588 $\mu\text{m/s}$ in 3% H_2O_2 of the tubular micromachines, and the maximum reached 700 $\mu\text{m/s}$, which is noticeably faster than other Pt nanozyme-based motors. After the loading of doxorubicin (DOX), this micromotor could

Fig. 7 Pt nanozyme-based nanomotors. **A** The design of the first Pt nanozyme-based nanomotor. Reproduced with permission of American Chemical Society (Paxton *et al.* 2004). **B** The structure of Pt nanozyme-based carbon nanotubes. Reproduced with permission of John Wiley and Sons (Khezri *et al.* 2019)

deliver drugs to cancer cells. Considering that cancer sites are usually accumulated with H_2O_2 , Pt-based nanomotors may make a great contribution to cancer therapy.

Other materials and motion patterns

Pt nanozyme is the most common nanomaterial used to power the micro/nanomotors, probably because of its highly efficient catalytic property in the propelling utilization. However, there are other materials for building motors, which also possess catalytical activities or combine with Pt nanozyme to help the construction. Besides, based on multiple materials, these motors may act in other ways like rotation.

Fournier-Bidoz *et al.* designed a nanorod by means of decomposing H_2O_2 on the surface of nickel nanorods to generate O_2 bubbles (Fournier-Bidoz *et al.* 2005). The two segments of these nanorods were made of gold and nickel respectively and the gold end was anchored to the silicon substrate, so the whole nanorods made a rotational movement at a speed of 1.5 ± 0.2 rad/s. He *et al.* further designed a boomerang-like structure for the rotation (He *et al.* 2007). Si made up of L-shape backbones with a longer arm and a shorter arm, and the Pt nanozymes deposited on the longer arm asymmetrically (only on one side of the nanorod) which allowed the L-shape nanorod to do rotary motion. (Fig. 8A, B). Then they also deposited Ag to the side of nanorods, and found they moved faster than Pt nanozyme (Fig. 8C). H_2O_2 was catalyzed on the surface of Ag nanozyme and generated O_2 bubbles to propel the rotation, similar to the Pt nanozyme. Furthermore, two Ag-based nanorods were even linked to form a nanospring resulting in a helically rotating movement (Fig. 8D). However, the biotoxicity of Ag nanozymes largely restricts its applications. Vicario designed a rarely used material, manganese, to catalyze H_2O_2 fuels, the main body and Mn-based power engine of which were independent parts

and linked by a tether (Vicario *et al.* 2005). Functioning as an engine, molecular $\text{Mn}(\text{ClO}_4)_2$ possessed the catalytic activity to generate O_2 from H_2O_2 . Interestingly, linear and rotary movements were both observed in these experiments (Fig. 8E, F).

Nanozyme guidance in motion control

Based on above analysis, we have enabled the autonomous movement of nanomotors with fuels, and there comes a further problem: how can we control the movement? Nanomotors without control will just be propelled to do random motion, so they are not useful for practical application. Thereby, we need to present nanorobots with the ability of reaching the expected place through directed trajectory. Taking the nanomotor as the engine of a car, we need steering wheels, a braking and an accelerator to manage the speed and orientation, so that nanomotors are able to get to the targeting position. Hence, the control of motion will help the nanomotor get to the appointed place with minimum fuels and fast speed, and without unwanted movement. Magnetic or chemical approaches play a part in the external or internal control, which boost the utilization of nanozymes. Consequently, nanozymes with magnetism and other abilities are favorable in motion control by responding to the environment or signals.

On the contrary of nanomotors, some nanorobots are not endowed with driving systems, but they also need to reach the targeting place. When those nanoparticles are injected into living bodies, their movement usually depends on the blood flow and they accumulate in the tumor site through the enhanced permeability and retention (EPR) effect. Therefore, some nanoparticles are modified with antibodies to target the cancer cells. Nanozymes are easy to be modified with cancer-targeting antibodies, and for this reason, these nanozymes are suitable materials to help guide the nanorobots to the targeted places.

Fig. 8 The fabrication (A), propelling mechanism and force (B) of the Pt-nanozyme based L-shape nanomotors. The fabrication (C), nanospring and helically rotating movement (D) of the Ag-based L-shape nanomotors. Reproduced with permission of American Chemical Society (He *et al.* 2007). The structure (E) and catalytic molecule (F) of the Mn-based nanomotor. Reproduced with permission of Royal Society of Chemistry (Vicario *et al.* 2005)

Magnetic guidance

Magnetic field is a common choice for wireless control of many devices at macroscale, microscale or even nanoscale, and the iron oxide nanozyme is a general material for magnetic guidance. Some microorganisms possess nanometer-sized magnetosomes inside the cells, so they take advantage of the magnetic field to help the movement. This property inspired some scientists to design a kind of bionic micro/nanorobots to mimic the movement of magnetotactic bacteria. For example, Kim and co-workers employed iron-oxide nanozymes (magnetite) to create an artificial *Tetrahymena pyriformis* (Kim *et al.* 2010) (Fig. 9A–C). The man-made cells could move much more quickly than many microorganisms, with an average speed at 786.7 $\mu\text{m/s}$.

In the former part we have described the fuel-dependent motors powered by metals, which have a strong engine. However, nano/micromotors need a steering wheel to guide their direction, and magnetic metals have shown their potential. Fe_3O_4 nanozyme is a most common nanozyme with magnetism, therefore it has been used in many nanomotors for the magnetic guidance. Villa engineered a multifunctional Janus

particle decorated with Pt nanozyme as a fuel-powering engine, which could be self-propelled in H_2O_2 solution. (Villa *et al.* 2018). Coated with a porous polymeric shell, the iron oxide nanozymes were encompassed in the inner part of the Janus particle, endowing it with magnetic features to manipulate the motion of microrobots in external magnetic field. In addition, the outside surface of this microparticle was decorated with tosyl groups to capture the cancer cells or deliver DOX. When controlled by a magnetic field, the particles would form a chain-like spherical structure, and the cells released by trypsin would bind with the decorated microparticles (Fig. 9D). By adjusting the magnetic guidance, the Janus particles could alter their direction and took the cells into movement. The cells attached to the surface of the particles firmly, without breakage of bonds while moving with the chain-like particles. In addition, six to seven Janus particles generated adequate force to drag one or even more cancer cells. On the other hand, loading with DOX, the self-powered microrobots were guided to the cancer site by magnetic field, then released drugs to cancer cells. This multifunctional designment will provide a great inspiration for nanorobot fabrication.

Fig. 9 Normal status without artificial modification (A), internalization of iron oxide nanozymes into cells (B), magnetization of internalized iron oxide nanozymes (C) of *T. pyriformis*. The scale bars are 10 μm . Reproduced with permission of AIP Publishing (Kim *et al.* 2010). D The dragging of cancer cells by chain-like particles. Reproduced with permission of John Wiley and Sons (Villa *et al.* 2018)

Furthermore, magnetic guidance is able to combine with other methods to steer the motion. The gold/iron oxide nanozyme-based nanorods made by Zhou were manipulated by the visible light and magnetic field (Zhou *et al.* 2017). These nanorods with properties of semiconductors transferred light energy to chemical energy by taking advantage of the photoelectric effect. Therefore, the visible light could control the power of the nanorods in H_2O_2 solution—the switch of on and off, and the adjustment of speed. With the magnetic features of iron oxide nanozyme, the whole nanorods are able to be directed by magnetic field.

Environment-responsive chemical control

Apart from the wireless control from external devices, the motion of nanorobots also depends on the response to environment. Some nanomachines have the sensing system, so they attain information from surrounding environment through the sensing system, then send instructions to the driving system. While the others can be instructed by the environment directly. The concentration of fuels affects the speed control. Unlike the machines at macroscale which contain fuels inside, micro/nanomachines usually utilize fuels in the environment. Hence, by altering the concentration of fuels in the aqueous solution, the velocity will be modulated accordingly. In a similar way, components in the aqueous solution have an impact on the speed as well. Laocharoensuk and his partners made an effort to modulate self-propelled nanomotors by changing components in solutions. They fabricated the nanomotor by adding carbon nanotubes (CNT) into the Au/Pt nanozyme-based nanotubes and tested the speed in concentration gradient of H_2O_2 solution (Laocharoensuk *et al.* 2008). This nanomotor was as same as others, speeding up as the concentration increased. Notably,

hydrazine induced an acceleration, demonstrating that certain components in the environment accelerated the self-powered nanomotor (Fig. 10). In addition, silver ions were reported to accelerate an Au-Pt nanozyme-based nanowire powered by H_2O_2 solution (Kagan *et al.* 2009). Among 11 metal cations in the solution, it was found that Ag^+ dramatically increased the speed (Fig. 11). This might result from the underpotential deposition of Ag metals on the surface of the Au-Pt nanozyme-based nanomotor, which affected its catalytic efficiency similar to the control of nanozyme-based logic gates discussed before. Speed changes are able to be used for detecting silver ions. By virtue of altering the components in the complex solutions, it is convenient to control the motion of nanomotors via a novel method.

Through altering components in the environment, this way of motion control seems a little rough at nanoscale, but it still provides a reference. Furthermore, it may be a better idea to adjust the concentration in the environment for motion control, which is similar to the chemotaxis of microorganisms. Living cells are able to orientate the movement of themselves by following the lead of concentration gradients. This phenomenon not only happens within microorganisms but also appears in the cells of multicellular organisms (Van Haastert and Devreotes 2004). Once again, inspired by the intelligence of nature, scientists are seeking for the applications of chemotaxis in the guidance of artificial micro/nano devices. R. Howse and his partners studied the motion of Pt nanozyme-based nanomotors and observed the speed-concentration relationship and the feature of directions (Howse *et al.* 2007). They found that Pt nanozyme-based nanomotors exhibited a directed motion in a short time, although this phenomenon disappeared at longer times. And the higher the concentration of H_2O_2 solution was, the longer time of the directed motion lasted. This might be

Fig. 10 Influences of hydrazine on the CNT nanomotors. Tracking lines about the movement of nanomotors in the solution without (A) and with hydrazine (B). Scale bar is 50 μm . C Illustrating of the speed distribution without (red) and with (blue) hydrazine. Reproduced with permission of American Chemical Society (Laocharoensuk *et al.* 2008)

Fig. 11 Motion of nanomotors in solutions containing 11 different metal ions respectively. Tracking lines about the movement of nanomotors (A) and illustrating of the speed (B) in solutions with 11 different metal ions respectively. Reproduced with permission of American Chemical Society (Kagan *et al.* 2009)

the first glance at the chemotaxis of artificial micro/nano devices outside the biological system. Ayusman Sen's team built the first Pt nanozyme-based nanomotor in 2004 (Paxton *et al.* 2004), and later in 2007, they continued to study the chemotaxis of their nanomotor (Hong *et al.* 2007) (Fig. 12). Experiments demonstrated that many of the nanomotors accumulated at the site with high concentration. In addition, in the model of concentration gradients, the number of nanomotors gathered in 10% H_2O_2 solution was larger than that of 1%. These results presented the chemotaxis of nanomotors. Moreover, two types of nanomotors were demonstrated to follow the rule of chemotaxis although powered by different propulsion mechanisms (Baraban *et al.* 2013). In this experiment, the Janus particles were more sensitive than the tubular microjets when put in the concentration gradient of H_2O_2 solution, which was related to their shape. Therefore, the characteristics of chemotaxis are relevant to the size and shape as well. Considering that the cancer site possesses higher concentration of H_2O_2 , chemotaxis may be a promising guidance for the micro/nanomotors applied in the living body.

In addition, pH is also a good tool for steering the orientation, such as the novel submarine-like nanomotor designed by Liang's lab (Guo *et al.* 2019). This nanomotor seemed like a submarine minimized to nanoscale, for the mechanisms modulating it was just the same as the real submarine-related density functional theory (DFT). Metal-organic framework (MOF) nanozyme acted as the propelling engine, which mimicked the catalase (CAT) activity. And MOF nanozymes were decorated with special pH-responsive materials as the sensing system (Fig. 13A). Polymer

Fig. 12 Solution fields for the chemotaxis detection of nanomotors. **A** A gel contained 30% H_2O_2 in the center of the water solution with nanomotors. **B** Four gels with H_2O_2 gradient in the water solution with nanomotors. Reproduced with permission of American Physical Society (Hong *et al.* 2007)

poly(2-diisopropylamino) ethyl methacrylate (PDPA) could shift the phase of hydrophilicity or hydrophobicity, helping the nanomotor respond to the environment change. The MOF nanozymes catalyzed the generation of O_2 bubbles in H_2O_2 solution, and when pH was above 6.4, the bubbles would attach to hydrophobic PDPA, and then accumulated buoyancy force was strong enough to lead the nanomotor to flow up. On the contrary, if the pH was below 6.4, bubbles would dissociate with hydrophilic PDPA, leading to the downward movement. The movement of this nanomotor could be achieved at centimeter scale, and even could be visualized via bare eyes (Fig. 13B). This original idea opens a new gate for the strategies of motion control.

Chemical motion control depending on the environment is an available way to fabricate the nanomotors. Because of the complexity and easy-modulation of the aqueous environment, it is always a popular strategy.

Modified nanozymes for targeting

For the nanodevices used in living body, there is also a convenient way to help guide them to accumulate at the targeting positions or to interact with objects: decorating the target molecules on the surface, such as ligands for receptors on the cells. It seems like a simple sensing system that senses objects in specific places, and then the decorated nanodevices will attach to the objects and further transmit information to the whole nanorobots. These nanodevices only function when the distance is close enough, so most of the nanodevices without driving system depend on the blood flow inside the body. The artificial engineered platelet we discussed before is a typical example (Hu *et al.* 2016).

Recently, Ding *et al.* built exosome-like nanozyme vesicles for clinical cancer diagnosis *in vivo* (Ding *et al.* 2018). The horseradish peroxidase-like graphene quantum dot nanozyme (GQDzyme) together with the 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) was encompassed in the natural erythrocyte membranes (RM) to form the vesicle. Folate acid (FA) was conjugated on the outside surface of the particle, so that the nanoparticles were able to target nasopharyngeal carcinoma (NPC) cells through the interaction with the overexpressed folate receptors (FR) on these cancer cells. With horseradish peroxidase (HRP)-like activity and the high level of H_2O_2 in the cancer tissues, GQDzyme inside the nanoparticles oxidized ABTS, and the near-infrared (NIR) absorbance of oxidized ABTS would be a suitable contrast agent for photoacoustic imaging (PAI).

Decorating target molecules are indeed a good strategy, and a nanocage exhibiting intrinsic targeting ability is a favorable choice for nanoparticle fabrication. Human H-ferritin (HFn) binds to transferrin receptor 1 (TfR1) on many cells without extra modification, especially the ones overexpressed in tumor cells (Fan *et al.* 2012). With a cage-like structure, ferritin is a perfect nanocarrier itself. Moreover, recently it has been reported that HFn has the ability to cross through the blood brain barrier (BBB) (Fan *et al.* 2018a). Because TfR1 is also overexpressed on the surface of the BBB endothelial cells (ECs), Dox-loaded HFn was found to deliver drugs to glioma cells by overcoming the BBB (Fig. 14A). In addition, ferritin can be easily modified via a genetic engineering approach (Jiang *et al.* 2019a). By linking the hepatocellular carcinoma (HCC)-targeting peptide SP94 to the subunit of ferritin, the specific binding ability for particular tumor cells largely increased. Meanwhile, the modified ferritin could still self-assemble and exhibited SP94 on the exterior surface. As a proper nanocage for carrying materials, the

Fig. 13 The pH-responsive submarine-like MOF micromachines. **A** The fabricating materials and illustrating of pH-responding movement. **B** The visible movement of pH modulation. Reproduced with permission of Elsevier (Guo *et al.* 2019)

Fig. 14 **A** HFn crossed the BBB through TfR1. Reproduced with permission of American Chemical Society (Fan *et al.* 2018a). **B** The antibody-decorated microrocket captured CTCs. Reproduced with permission of John Wiley and Sons (Balasubramanian *et al.* 2011)

modified ferritin contained horseradish peroxidase-like Co_3O_4 nanozyme was demonstrated to stain the clinical HCC tissues in the presence of H_2O_2 and DAB.

It seems a little crude to apply this targeting strategy to the motion control for unpowered nanoparticles, but it increases the precision in powered micro/nanomachines. A decorated microrocket was reported to catch the circulating tumor cells (CTCs) in fluids because of the target ligands on the surface (Balasubramanian *et al.* 2011). The engine of this microrocket was built by Pt nanozymes in the inner layer and the middle layer is constructed by ferromagnetic (Fe) nanozymes to guide the engine with external magnetic fields. Finally, the

monoclonal antibody (mAb) was conjugated to the outer gold surface. The anti-carcinoembryonic antigen (anti-CEA) has been demonstrated to be overexpressed in some common cancer cells, so the anti-CEA mAb could guide the micromachine to catch CTCs, and then took them to directed place (Fig. 14B). This microrocket might contribute to the early diagnosis of cancers including colorectal, gastric, and pancreatic carcinoma.

Nanozymes with magnetism and chemical-responsive properties are favorable for the motion control of micro/nanomachines. In addition, their easy-modification also provides a convenience for the

guidance of targeting molecules, in which case, ferritin is especially noticeable.

Nanozyme for the function system

Nanorobots are widely studied in medical applications. Many smart nanodevices have been designed to realize more complex functions than before. In addition, smart nanodevices perform tasks efficiently *in vitro*. However, they usually lack the driving system and get to the target site by EPR effect and contact with the objectives with or without modified targeting molecules.

To enhance the practical utilization of nanorobot, scientists selected nanodevices with smart functions and endowed them with systems like driving system and sensing system to build useful nanorobots. In many cases, nanozymes play an important role in the endeavor of providing functions for the nanodevices. Here, we list some designs of functions which have been achieved by nanozymes such as the detection and therapy of tumor and antimicrobial applications, *etc.* These examples may offer novel ideas to help design the function system.

Tumor theranostics

Tumor theranostics remains a troublesome problem for many years and scientists have taken a number of endeavors to investigate it. After the discovery of nanozyme in 2007, scientists found that nanozyme may be a proper choice for tumor theranostics and some of them have already been utilized for tumor detection and therapy.

nanozymes have shown potential in tumor therapy. Based on the ROS damage of cells, Qu's lab designed a multi-nanozyme nanoflowers to kill tumor cells (Wang *et al.* 2018) (Fig. 15A, B). They combined two types of nanozymes, which were the PtCo nanozymes with intrinsic oxidase-like activity and the MnO₂ nanozymes mimicking catalase (CAT). These materials were able to self-assemble into a whole structure step by step. Especially, the PtCo nanozymes could direct the growth of MnO₂ nanozymes. The MnO₂ nanozymes with the intrinsic catalase-like activity converted high level of H₂O₂ in tumor cells to O₂, then the PtCo nanozymes catalyzed the cascades of oxidation reaction via oxidase-like activity. Therefore, the generated ROS damaged a large part of components in the cancer cells resulting in apoptosis and necrosis. This function system did not need an external supply of O₂ to generate ROS and this MnO₂@PtCo nanoflower exhibited high catalytic activity in the acid solution (Fig. 15C). This characteristic means that the

MnO₂@PtCo nanozyme is very appropriate for destructing tumor cells, which contain high level of H₂O₂ and are of acid pH. Moreover, the results showed little cytotoxicity towards normal cells, thus it is an ideal choice for *in vivo* therapy.

Antimicrobial functions

Besides the applications for tumor theranostics, nanozyme-based particles are developing in the area of antimicrobes as well.

Nanozymes such as cerium oxide (CeO₂) and iron oxide (Fe₂O₃) nanozymes (Masadeh *et al.* 2015), Fe₃O₄ nanozymes (Gao *et al.* 2014) and Au nanozymes (Ayaz Ahmed *et al.* 2014; Mohamed *et al.* 2017; Wang *et al.* 2017b; Yang *et al.* 2017) are employed for the obliteration of unwanted microbes. These nanozymes are capable of generating ROS to destruct biofilms of bacteria. Among the antimicrobial applications, there is a special scheme which functions in the seawater environment (Natalio *et al.* 2012) (Fig. 16). Vanadium pentoxide nanozyme with peroxidase-like activity could produce hypobromous acid and singlet molecular oxygen under seawater conditions, against the marine bacteria, which promote the prevention of marine biofouling on the shells of ships. Besides the stability of such nanozymes, it has been demonstrated that the vanadium pentoxide nanozymes are not harmful to marine biota.

Other functions

As we can see, nanozymes are more easily combined to work as multi-functional catalysts compared with natural enzymes. Particularly, the metal-organic framework (MOF) possesses large surface and highly ordered porous structure. Zhang's lab took advantage of this characteristic and built a function system to mimic natural cascade reactions (Huang *et al.* 2017). The MOF nanozyme possessed intrinsic peroxidase-like activity, then the Au nanozyme with glucose oxidase (GOx)-like activity grew on the surface of MOF nanosheets. Therefore, the two catalytical activities were combined together, and in the presence of O₂, the multifunctional nanozyme oxidized glucose to gluconic acid and H₂O₂ and the latter would continue reacting with TMB because of the peroxidase-like activity. The multifunctional nanozymes were used to detect glucose and helped investigate the mimicking of natural enzymic cascade reactions. Moreover, as a biocompatible material, Au-modified MOF is suitable for the *in vivo* therapy and has been studied in cancer treatments. In this scheme, decorated with Au nanozymes, the newly synthesized MOF nanozyme possessed GOx-like and

Fig. 15 Multi-nanozyme nanoflowers for killing tumor cells. **A** The fabricating materials and processes. **B** The mechanism of killing tumor cells. **C** The catalytic activities of MnO₂@PtCo nanoflowers at different pH values. Reproduced with permission of Springer Nature (Wang *et al.* 2018)

Fig. 16 Schemes of vanadium pentoxide nanozyme killing bacteria. **A** Nanozymes on a metal surface. **B** The bacteria attack. **C** The activities of nanozymes catalyze the generation of hypobromous acid. **D** The destruction of bacteria. Reproduced with permission of Springer Nature (Natalio *et al.* 2012)

catalase-like activities. With the capability of converting NIR light to generate $^1\text{O}_2$, the MOF nanozyme further killed the cancer cells (He *et al.* 2020). Glucoses were depleted by MOF nanozymes in tumor cells, leading to the loss of nutrition in these cancer cells. Meanwhile H_2O_2 was produced in this reaction and the catalase-like activity catalyzed H_2O_2 to generate O_2 . Upon NIR light irradiation, the nanozyme continuously converted the generated O_2 to $^1\text{O}_2$, wounding the cells finally. This design demonstrated that MOF nanozyme is a promising

nanomaterial for multifunctional utilization, especially *in vivo*.

As for practical utilization, we will discuss a real smart biomedical machine for *in vivo* applications. This machine was not at nanoscale, but its function systems were built on nanomaterials (Son *et al.* 2015) (Fig. 17). The function systems were comprised of ceria nanozymes and gold nanorods decorated with mesoporous silica (AuNR@MSN). Ceria nanozymes with superoxide dismutase activity could scavenge ROS to reduce inflammations and AuNR@MSN held a post of drug carrier. Thanks to NIR-responsive property, AuNR@MSN received wireless instructions by the photothermal signal, then the heat would result in the diffusion of drugs. Together with other systems: flow/temperature sensors and resistance random access memory (RRAM), the whole machine was an electronic stent for handling artery blockage. Ceria nanozymes induced in the novel stent could alleviate inflammations resulting from traditional mechanical stents.

Showing their capabilities in applications such as tumor therapy and antimicrobial utilization, nanozymes offer us a variety of ideas for building the function system. By selecting proper ones, we can endow the function system with multiplex functions. Especially, the nanozyme-based multifunctional nanoparticles may be utilized in the fabrication of nanomachines or nanorobots. At present, we are able to construct tiny smart machines like the electronic stent above, but we need to overcome the problems arousing in the manufacture of nanodevices such as the supply of power energy and the processing of instruction in the logic control system at nanoscale.

Fig. 17 The bioresorbable electronic stent. **A** The structure illustration. **B** The image of applications *in vivo*. Reproduced with permission of American Chemical Society (Son *et al.* 2015)

NANOZYME AS THE BRIDGE FOR CONNECTION OF SYSTEMS

Complicated functions and integrated systems should be combined together to fabricate nanorobots. However, the nanomachines which lack some partial components may limit the abilities of nanorobots. For instance, many functional nanoparticles lack a driving system (a motor), while some of the micro/nanomotors are not provided with function parts. In addition, the sensing system and logic control system are absent in a numerous of nanomachines. Therefore, the combination of properties of individual nanomachines will make a great contribution to build more powerful nanorobots. Nanozymes with multiple characteristics can be employed in various systems to connect different components, for their properties may simultaneously work in several systems.

Besides the enzyme-like activities, some characteristics of nanozymes make it possible to integrate separated systems, and Fe_3O_4 nanozyme is one of the examples. The magnetism of Fe_3O_4 nanozyme makes it a common component in the movement of the nanomachines. Trau's group made a platform for the isolation of *in vitro* circulating tumor cells (CTCs) that merely depended on the Fe_3O_4 nanozymes (Li *et al.* 2017). They linked Fe_3O_4 magnetic nanozymes (30 nm) with antibodies targeting melanoma cells (anti-MCSP). After incubation with cell suspensions, the Fe_3O_4 nanozymes attached to the melanoma CTC and the external magnetic field guided the isolation. The Fe_3O_4 nanozymes with separated CTCs would catalyze the colorimetric reaction based on the intrinsic peroxidase-like activity (Fig. 18A). This method offers a rapid and convenient way to detect CTCs *in vitro*. Referring to the

micro/nanomotor-based methods for isolation and the motion guidance of Fe_3O_4 nanozymes in driving system, this idea may provide an approach for the *in vivo* CTC detection, combining the function system with driving system.

Furthermore, gold nanozymes possess multiple characteristics as well. In one design, the CD-decorated gold nanozymes (CD@AuNPs) combined sensing, self-assembling and cascading enzyme-like catalysis together (Zhao *et al.* 2016). Au nanozymes accepted energy and participated in the fluorescence resonance energy transfer (FRET). After modified with cyclodextrin (CD), the new CD@AuNPs were appropriate for fluorescence sensing (Fig. 18B). Blood cholesterol assay was studied as the model, in which CD@AuNPs were added to rhodamine B (RB) molecules, and the combination of both materials led to the quenching—the sensing system was built. If the cholesterol were added to this sensing system, RB molecules would be taken place by cholesterol and dissociated from CD@AuNPs, back to the status of fluorescence recovery. This sensing system showed favorable results in the detection of blood cholesterol. Previous studies found that Au nanozymes exhibited glucose oxidase (GOx)-like activity, and some also possessed the peroxidase (HRP)-like activity. Here the CD@AuNPs with intrinsic GOx-like activity and HRP-like activity were able to catalyze cascade reactions, oxidizing glucose to generate H_2O_2 and catalyzing TMB (Fig. 18C). Finally, CD@AuNPs self-assembled into a well-ordered structure with tetrakis(4-carboxyphenyl)-porphyrin (TCPP) acting as a mediator (Fig. 18D). Endowed with various properties, Au nanozymes are very likely to help the combination of the sensing and function systems.

Fig. 18 **A** The detection of CTCs *in vitro* by Fe₃O₄ nanozymes. Reproduced with permission of Royal Society of Chemistry (Li *et al.* 2017). **B** The fluorescence-based sensing system of CD@AuNPs. **C** The enzyme-like activities of CD@AuNPs and the cascade reactions. **D** The self-assembly of CD@AuNPs through TCPP. Reproduced with permission of American Chemical Society (Zhao *et al.* 2016)

CONCLUSION

In this review, we have summarized recent progress on the nanozymes-based micro/nanodevices. Producing a smart machine at nanoscale demands well-performed nanomaterials, and nanozyme is one of the nanomaterials waiting to be exploited. The modulation of activities is proper for the construct of logic gates, and the catalytic activities of nanozymes are able to power the movement or help with the motion control. Other properties like magnetism may also be of good assistance. Nanozymes are easy to be modified with extra abilities, which are fit for the structure of the nanorobots as well. The multiple enzyme-like activities of one nanozyme will enhance the catalytic performance and favor the nanodevices with more than one function.

Some powerful nanomachines have already been built. To take a further step we should find methods to integrate these nanomachines to construct a whole multiplex nanorobot. Nanozymes with catalytic activities, physicochemical properties may be an important key for the combination of components. With high biocompatibility and low biotoxicity, nanozymes now have been widely used for clinical applications, which catalyze the H₂O₂ or glucose at the tumor sites. These molecules, especially high level of H₂O₂ act as fuels to power the micro/nanomotors. For example, hollow mesoporous organosilica nanoparticles (HMOSs) decorated with catalase-like MnO_x nanozymes were studied for the ultrasound (US)-triggered sonodynamic therapy (SDT) (Zhu *et al.* 2018). MnO_x nanozymes decomposed

H₂O₂ in the tumor microenvironment (TME) to generate O₂. These nanoparticles may be constructed to Janus particles—the MnO_x nanozymes are only linked to the hemispherical surface, so the generated O₂ could provide power for driving. In this way, the functional nanoparticles are able to help with the motion and sonodynamic therapy (SDT) simultaneously. More importantly, driving power may help the nanodevices go deep into the inner part of the tumor sites. We may need to break through the barrier that H₂O₂ in the TME is not enough to drive the movement currently. In addition, the TME offers modulations for chemical-responsive control, and problems may still remain in the complexity of the TME.

In conclusion, nanozymes are promising materials for the further fabrication of nanodevices such as nanomachines and nanorobots, and there are extensive opportunities for us to explore.

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Compliance with Ethical Standards

Conflict of interest Jiaying Xie, Yiliang Jin, Kelong Fan and Xiyun Yan declare that they have no conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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