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REVIEW

Micromotor-derived composites for biomedicine delivery and other related purposes

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Abstract

Biocompatible designed micromotor has attracted more and more concerns in the field of biomedicine due to their self-propulsion and delivery abilities. Such micromotors, mostly consisting of alkali earth metals, hydrogels, or other motile biomaterials, can effectively transform chemical energy into mechanical or kinetic energy to achieve the expected delivery of cargos to the sites of action. Except for conveying power, the modifiable surface and inner cavity of micromotors guarantee that their potential as versatile delivery systems for therapeutic agents. Here, this review generalizes the propelling mechanisms, composites, and shapes of micromotors. Besides, the application of micromotor-derived composites for biomedicine delivery and other versatile purposes are also discussed.

Keywords Micromotor · Propulsion · Targeted delivery · Retention · Penetration

Introduction

People have witnessed rockets marching into the space propelled by liquid hydrogen fuel under the navigation of the ground control. Those rockets were exerted with the mission of delivering astronauts and cargoes, such as satellites and Mars probe to establish novel functions for people on earth or explore the deeper space. Get inspired by such beneficial huge inventions, scientists started to anticipate the prospect of scaling down these real rockets to microscale. Even though medical robotic devices have reached an advanced level and markedly excavated tremendous novel treatments, miniaturizing and employing them into the internal human bodies still face plenty of challenges for the entirely different operating environment and high safety requirements. The real external rockets' motion and carrying ability owe much to the strong and continuous propulsion stemming from fuels. Meanwhile, incorporated remote control parts instruct the rockets to fulfill directional locomotion according to the control tower. Nevertheless, realizing these conditions in vivo is not that simple. To overcome this difficulty, micromotor science came into the presence through years of efforts and the rapid growth of medical robotics. Various tiny (usually less than microscale) and mobile motors, possessing the ability to move inside human bodies and to carry relatively considerable cargos, keep emerging from concepts. Ismagilov et al. [1] firstly fabricated a tiny plate (< 1 cm) with a small area covered by platinum which helps it move under the impulse of bubbles generated by the platinum-catalyzed decomposition of hydrogen peroxide, depicting the rudiment of micromotors.

Subsequently, versatile materials were employed to build motors with diverse features and the size turned smaller and smaller with the minimum reaching nanoscale. Alkali earth metals, including Mg [2] and Zn [3], are usually used to construct the body of micromotors through electrodeposition, as well as some inert metals like platinum. These metals hold great importance in developing micromotors for their potential reaction with adequate medium and the ensued chemical propulsion upon themselves. Furthermore, some metal-based micromotors can be navigated to the targeted sites even in unprocessed bio-medium by the external magnetic field due to the exerted magnetic interaction. Many preliminary studies showed that this wireless and untethered navigation ability makes it possible to deliver drugs controllably [4], diagnose diseases [5, 6], and detoxify certain mediums

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[7, 8]. Apart from metals, scientists also employed polymer, hydrogel, protein, and motile biomaterials to assemble biocompatible micromotors. Fabricated by appropriate materials, some micromotors can vanish of itself after the mission is done, barely leaving anything toxic. Such biodegradable feature brought immense prospects for micromotors to be applied to in vivo therapeutical payloads delivery. Herein, we summarize the general design of micromotors, including the propelling mechanisms, composites, and various shapes. Subsequently, we mainly discuss the attractive advantages and potential challenges in biomedicine delivery. Through these introductions, we expect a practical clinical use of micromotors 1 day.

Propelling mechanisms

Unlike the traditional rockets with a Reynolds number of 10^6, microscale "rockets" have a lower Reynolds number, which is 10^{-4}. Such a low Reynolds number means inertia devotes a little affection on the motion, and there can only be instantaneous motion caused by instantaneous force [9]. That is to say, if we want the microscale rockets to achieve a continuous in vivo move, we should exert them a continuous thrust through the whole moving process. Once we withdraw the thrust, the microscale rockets will cease to move in no time. Besides, when it comes to motions in the microscale, there is one factor we cannot neglect—Brownian motion which also remains a big challenge to the locomotion of microscale rockets [10, 11]. Consequently, the first challenge to construct preconceived microscale rockets is providing a stable and sustainable propelling force. Different from the actual rockets, it is impossible to burn liquid hydrogen or other fuels inside human bodies. Hence, scientists have invented several propelling mechanisms such as chemical propulsion [3], acoustic propulsion [12], biological propulsion [13], and so on. With these propulsions, micromotor can swim inside human bodies, and it thus turns into dynamic from static by swimming capability. Amid current researched propulsion mechanisms, self-electrophoresis occupies the domain position for these nano/microscale motors [14–16]. In self-electrophoresis powered ones, an electric field generated by the charged microparticles may result in an asymmetric distribution of ions, driving the motors to move. In this review paper, we primarily talk about chemically powered micromotors which always take advantage of the local gradients of concentration, electrical potential, and gas bubbles to propel in the aqueous solution [17, 18].

Chemical propulsion

As widely known, the pH of the gastric fluid is acidic, as well as the tumor microenvironment. This feature attracts much attention from researchers. Dr. Sattayasamitsathit et al. [19] present a novel zinc-based micromotor which is able to fulfill cargo loading, delivering, and releasing. This micromotor utilizes the redox reaction of zinc in an acidic environment and the following generation of hydrogen bubbles to realize self-propulsion. Once the bubbles are produced, the micromotor gets a counterforce, and such force poses an instant movement on it. Accordingly, the duration time of bubbles generation decides the lifetime of micromotor's movement, that is to say, the distance it can move [3]. Inspired by the same principles, Karshalev et al. [20] build spherical micromotors, using the reaction of magnesium and acid, and load them into tablets for oral drug delivery, proved to have higher cargo retention onto the stomach lining compared to orally administrated free micromotors and passive microparticles. Apart from two types of chemical propulsion talked above, people also harness the decomposition of hydrogen peroxide (H_2O_2) under the catalysis of central Co^{2+} in zeolitic imidazolate framework-67 or enzyme immobilized on the motors' surface [21, 22]. Herein, micromotors are driven by oxygen bubbles. However, this strategy still needs to be optimized for the requirement of relatively high H_2O_2 concentration which is toxic to sustain mammalian cellular functions.

Acoustic propulsion

The sound wave is able to transmit through solid, liquid, and air mediums to trigger propulsion on motors from the outside without causing damages to human bodies. Furthermore, using the sound wave to propel means there is no need to supply fuels. Considering the easiness of establishing acoustic conditions, acoustic propulsion also carries tremendous prospects for applications of micromotors. Garcia-Gradilla et al. [23] fabricated three-segment Au–Ni–Au nanowire motors propelled acoustically by mechanical waves at a constant speed, following the predefined trajectories. They functionalized this nanowire with bioreceptors and a drug-loaded polymeric segment and endow this metal wire with magnetic guidance, unearthing the potential applications' prospect of acoustic propulsion micromotors.

Photic propulsion

As an easily accessible and environmental-friendly energy source, light has been more and more utilized to drive micromotors. It is widely reported that the light-driven methodology enables the instant on–off switch and the manipulation of the moving direction via remote control [24, 25]. Unlike other kinds of micromotors, the light-driven ones have a unique characteristic—photocatalytic property which is based on photoactive materials such as Cu_2O/Au, bismuth oxyiodide, TiO_2, or C_3N_4 nanomaterials [26, 27]. The application of light on a micromotor can activate

its movement behavior based on either the photochemical reaction, photothermal effect, or photochromism, and the propulsion mechanisms of light-driven micromotors can be classified as light-induced self-diffusiophoretic propulsion, light-induced bubble propulsion [28]. A Janus micromotor driven by multi-light for enhanced bio-detoxification of bacterial endotoxins and heavy metals was fabricated via polymer polycaprolactone and photoactive materials [29]. The designed micromotor can be robustly activated by visible light (470–490 nm), and such strong photoactive activity can induce the generation of a gradient of products around the micromotor surfaces to accordingly be propelled in peroxide or glucose media continuously. Moreover, varying the light intensity can modulate the propulsion speed. Sun et al. [24] constructed a light-driven sheet-like micromotor with polypyrrole nanoparticles which can be activated by near-infrared (NIR) light. To tune the movement, they just have to adjust the incident light angle and thus attain precisely controlled motion behavior.

Magnetic propulsion

In recent years, another important propulsion method—magnetic propulsion has come into the stage. Like the photic propulsion, it can propel the micromotors without any fuel and brings no harm to human bodies. To fabricate the magnetically driven micromotors, the magnetic materials are essentially needed to respond to the external magnetic field. Wei et al. [30] reported a flexible magnetic nickel–silver nanoswimmer which was given a successive motion by a rotating magnetic field. This magnetic metal body has a magnetic interaction with other magnetic objects and thus was used to capture and carry magnetic payloads in their research. The results demonstrated the nanoswimmer could capture various-sized and drug-loaded magnetic polymeric microspheres and tow them along with the propulsion. What's worth mentioning is the application of magnetic materials in constructing micromotors brought in the practical control and guidance for the propulsion by the magnetic field.

Electric propulsion

Except for converting photic energy or magnetic energy into propelling source, micromotors with electrical propulsion also suggest that an electric field can be an alternative or even better candidate for offering micromotors energy [18, 31, 32]. Due to the high variability and controllability of electric fields, the capture, delivery, and release of cargos through induced dipolar interactions between a Janus motor and the cargos can be realized more easily [33]. Electric propulsion always leverages the asymmetrically distributed active chemicals which can develop a gradient of cations and anions to generate electrophoresis and thus the self-propulsion on the micromotors [34–36]. Demirors et al. [37] fabricated autonomous active Janus particles as colloidal shuttles and realized trap, transport, and release cargo particles through dielectrophoretic interactions induced by an AC electric field. The stable propulsion could also be directed by incorporating the nickel layer, demonstrating the promising application of electric propulsion.

Biological propulsion

Compared to other propulsions, utilizing the biomaterial possessing moving ability to propel can distinctly improve the biocompatibility and safety of micromotors. A micromotor driven by motile sperm cells can be fabricated as a targeted drug delivery system, guided by a magnetic field. Because of the cell membrane fusion between sperm cells and tumor cells, such micromotor is capable to swim into the tumor and deliver anti-cancer drugs [13]. Promisingly, this sperm-driven biohybrid micromotor's speed is adjustable [38]. There are other examples transforming microorganisms, like bacteria [39] and flagella [40], and endogenous organisms, like neutrophil [41], into designed motors with endowed motile ability. Propulsion ability brings micromotors swimming motion, active targeting, and drug-loading capacity, attracting a number of scientists to devote themselves to facilitating novel applications.

Composites and shapes

Those advanced micromotors are based on plural materials including metal [42], high-molecular polymer [43, 44], hydrogel [45, 46], protein [47], organic materials [48], and even motile biometerials [13]. Most of those motors consist of metals like zinc [3] and magnesium [49] for that such metals not only provide robust frameworks that bring huge potential to load drugs but also can have chemical reactions with gastric acid and generate bubbles, giving feedback of propelling force. Some articles also take advantage of metal complexes to synthesize the artificial motile flagella [4, 50, 51] and optimize the performance of designed micromotors [52, 53]. As the newly invented materials with metal ions and organic linkers, metal–organic frameworks (MOFs) have also been widely employed in fabricating self-propelled micromotor devices due to their high surface areas and tunable pore structure and exhibited ideal performance [54–56].

Except for synthetic materials, various types of cells, including red blood cells, leukocytes, and macrophages [49, 57–60], have been utilized to compose active micromotors. Motile biomaterials attract peoples' attention as well for their high biocompatibility and outstanding in vivo motion behaviors. Xu et al. [13] build a micromotor containing a driving part of motile sperm, and thus, this whole system has

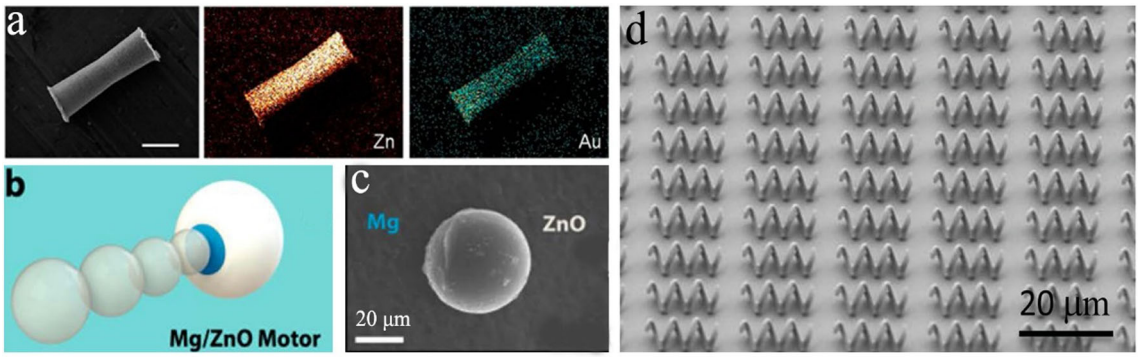

Fig. 1 Schematic display of different shapes of synthetic micromotors. **a** SEM image of an AuNP-loaded PEDOT/Zn micromotor (left) and EDX analysis proving the presence of Zn (middle) and Au (right) within the motor, reproduced with permission from Ref. [61] (https://pubs.acs.org/doi/full/10.1021/nn507097k, further access is available through this ACS webpage), copyright 2015 American Chemical Society. **b** Concept scheme of transient Janus microsphere motors with Mg cores and generation of hydrogen bubbles. **c** SEM images of typical Mg/ZnO Janus micromotors. The core particle extends out is Mg and the shell is ZnO. **b**, **c** Reproduced with permission from Ref. [62], copyright 2016 American Chemical Society. **d** Optical images of helical artificial bacterial flagella micromotors, reproduced with permission from Ref. [40]

an intrinsic swimming ability in biological media. In addition, Magdanz et al. operated studies into the influencing factors including the length of micromotor body, coupling efficiency, and addition of caffeine on the performance of such kind of spermbots [38] firstly, and then, it turns out there are more influencing factors such as physical confinement of the single-cell and the interaction with biomolecules. Fangyu et al. [49] employed macrophages to engulf magnesium microparticles and thus produced biohybrid motile micromotors while still maintaining the viability and biological functionality of macrophage cells. The preparation of micromotors based on different materials involves diverse fields of knowledge, and it still leaves us suspended questions about how to maximize the micromotors' performance.

Intelligent scientists have fabricated plenty of micromotors in different shapes such as tubular type [23, 61], helical type [40], spherical type [8, 62], dodecahedron [21], tadpole-like [63], and so on (Fig. 1). It is worth noting that a rectangle slice micromotor based on polypyrrole which induces the light-triggered doping behavior exhibited a controllable motion ability, representing attractive potential in controlled drug delivery and release [24]. In addition to this rectangle shape, Manesh et al. designed a helix-like micromotor (Fig. 1d), which is constituted of three different metal segments, possessing a rotation-based motile ability in a magnetic field [64]. Su et al. realized the construction of polymer-based autonomous micromotors in diverse shapes and structures, utilizing the polydimethylsiloxane template [65]. Different shapes of micromotors that can be applied to different situations all possess propulsion ability no matter the reaction layer is fabricated outside or inside. Specifically, the same with those micromotors whose bubbles are from the inside cavity, even the bubbles are generated on the surface of the outside zinc mono-layer, they still exert propelling force on micromotors. This phenomenon is quite different from common sense. Commonly, the outside layer gets exposed to the acid environment, and thus, redox reaction happens nearly all over the surface, namely bubbles release to every direction. Under such circumstance, the micromotor is subject to forces from all directions at the same time, and it should come to no propulsion or just goes on irregular motions like self-rotation theoretically. Surprisingly, a double-conical zinc-based micromotor with merely zinc monolayer can be self-propelled in the 0.7 M HCl solution at a speed of 180 $\mu m\ s^{-1}$, almost 8 body lengths per second. Even loaded with SiO_2 particles, it still can reach a fast movement of speed at 110 $\mu m\ s^{-1}$, nearly 5.5 body lengths per second [19]. Regardless of versatile shapes or constituents, this interesting feature leaves quite considerable space for the design of micromotors and expands micromotors' solid application prospects.

Advantages in biomedicine delivery

With powerful self-propulsion and controllable navigation, this type of microscale robots can play an important role in biomedicine delivery effectively. Present applications in biomedicine include targeted drug delivery, precision surgery, medical diagnosis, and detoxification [10]. Traditional drug carriers always rely on systemic circulation and have no navigation ability, while such micromotors equipped with propelling force, payloads carrying capability, high retention, controllable motion, and tissue penetration, bring novel tremendous prospects for drug delivery. Herein, the following paragraphs mainly review the applicable traits for application in biomedicine delivery of micromotors from oral and parenteral aspects.

Oral administration

Gastrointestinal propulsion

Current oral administrations mostly depend on the random contact with the gastrointestinal (GI) tract to be absorbed. However, irregular motion and distribution, as well as the slow contact process, restrain the drugs from being timely uptaken. Surprisingly, the advent of new micromotor technology is promising to alleviate the problem effectively with its basic attracting function—robust propulsion. As discussed in Propelling mechanisms, there are numerous principles and methods to generate propulsions while chemical reaction with acid is the main strategy in oral administration. Gao et al. [3], for the first time, presented the acid-powered Zn-based tubular micromotors, propelled by the bubbles from the redox reaction between zinc and acid (Fig. 2a, b). The propelling force coming from the redox reaction is relatively strong and steady to afford an ultrafast propulsion speed (as high as 100 body lengths per second). Such directional locomotion, different from what we talked in Shapes chapter under the circumstance that the motor's body was exposed to the medium thoroughly, stems from the formation of the galvanic cell between the zinc and the sputtered gold layer which is introduced in during the preparation process [66]. They also tested the propulsion ability in the different kinds of acid and acidified human serum, which attested the prospective and robust mobility of this motor. In addition, zinc is a metal trace element and in sync with generating bubbles, and it also has the function of maintaining positive appetite, promoting wound healing, etc. This tubular structure symbolizes a high loading capacity and provides more possibility of clinical combination therapies. A monolayer zinc tubular micromotor was readily electrodeposited and used to co-encapsulated different drugs [19]. Fully loading combined drugs (up to 74% of the entire motor body), this micromotor still displayed considerable propulsion capacity. After completing propulsion, zinc would be run out, like self-destruction, leaving nothing undegradable and autonomously delivering and releasing drugs to targeted sites.

In addition, some designed micromotors can also propel themselves without exploiting the acid in the gastric environment, whereas attaining the same robust propulsion. Arqué et al. modified hollow silica microcapsules with urease, acetylcholinesterase, glucose oxidase, and aldolase, respectively, to make use of the propulsion generated by the enzymatic conversion of substrates into products [67]. They studied how the four enzymes with four different turnover numbers above modulate the enzyme-powered propulsion behavior and attested the promising application of prepared micromotors in GI drug transport and delivery. These studies demonstrated the robust motion ability of micromotors which apparently increase the chance of contact between drugs and the GI tract, laying a solid foundation for more promising merits including but not limited to strong penetration and high retention.

Mucus penetration and retention

There are many in vivo biological barriers for the absorption of drugs and some medicines' inherent penetration is puny, posing limits on their bioavailability [68]. For example, the gastric luminal epithelial surfaces are covered by a mucus layer dominantly composed of water and high molecular weight polymeric mucins, shielding epithelial cells from damaging substances on one hand, but preventing some carriers and drugs from being absorbed on the other hand [69, 70]. Positively, active propulsion of micromotors imparts a fresh pathway to increase the movement and absorption in biological media. Walker et al. [71] presented an artificial magnetic micropropeller with a helical structure which can be actuated and propelled in a homogeneous magnetic field. They employed this micropropeller to overcome the mucus barrier in the GI tract and inventively to combine the motion of micropropeller and the pH-dependent sol–gel transition of the mucus layer to substantially augment the penetration performance. Mimicking the strategy of *Helicobacter pylori* to pass through the mucus layer, they immobilized urease onto the surface of a magnetically propelled micromotor to degrade urea into ammonia, increasing the local pH of gastric mucin and turning it into the liquid state. Accordingly, the resistance that micromotor faces when penetrating the mucus layer decreases distinctly and the penetration efficiency increases relatively due to the double facilitation of propulsion and liquidation. Acoustically propelled micromotors showed great application potential in tissue penetration as well. Kagan et al. fabricated a tubular-type microbullet integrated with biocompatible fuel source perfluorocarbon which can be expanded and vaporized by acoustic actuation and then exerts an extremely fast speed (~6.3 $\mu m\ s^{-1}$: over 100 times faster than currently published micromachines) on the microbullet [12]. The ultrasound-triggered propulsion experiments they performed revealed this powerful thrust helped microbullets deeply penetrate and deform lamb kidney tissues. In their study, different scales of microbullets were tested and it turned out the scalable size did not impair the performance of propulsion and penetration, opening doors for more biomedical applications with high requirement of devices' size. Moreover, scientists have studied diverse coatings and surface passivation techniques to reduce mucoadhesion [72–74], weakening the resistance when penetrating the mucosal tissues.

With the aforementioned robust propulsion and strong penetration, the micromotors can locomote rapidly in gastric acid and reach the mucus layer even the GI tissues quickly before being excreted. Planted in the mucus layer, these

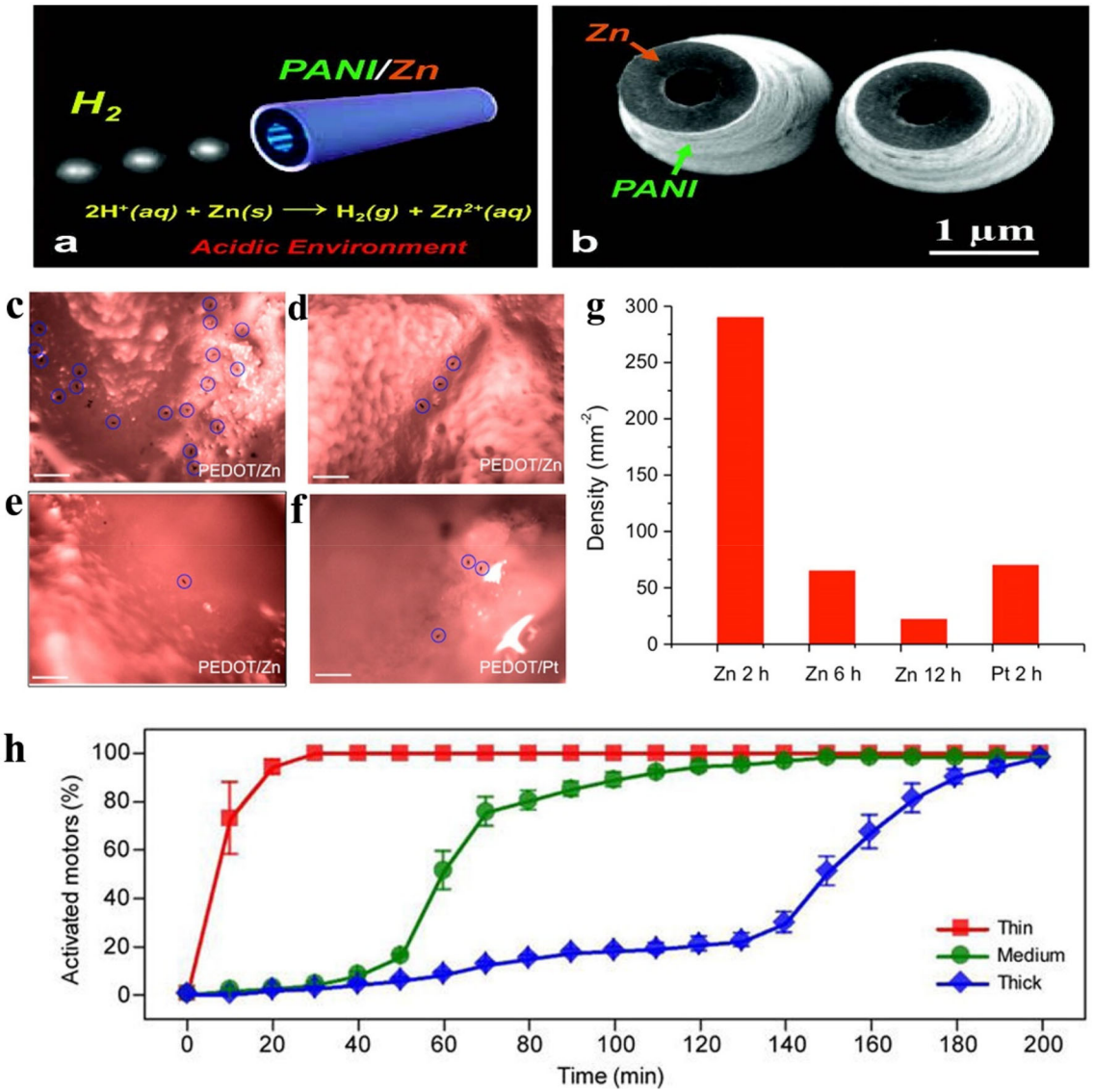

Fig. 2 **a** Schematic of chemical propulsion in an acidic environment and **b** top view SEM images of PANI-Zn micromotors. Reproduced with permission from Ref. [3]; Tissue retention performance of dynamic micromotors. **c**–**f** Microscopic images illustrate the retained micromotors on the stomach tissues collected at **c** 2 h, **d** 6 h, and **e** 12 h post-oral administration of PEDOT/Zn micromotors and **f** 2 h post-oral administration of PEDOT/Pt micromotors (serving as a negative control). Scale bars, 100 μm. **g** Enumeration of the density of PEDOT/Zn and PEDOT/Pt micromotors retained on the stomach tissues at the different times after the administration, **c**–**g** reproduced with permission from Ref. [61], (https://pubs.acs.org/doi/full/10.1021/nn507097k, further access is available through this ACS webpage), copyright 2015 American Chemical Society. **h** Quantitative analysis of the percentage of activated micromotors with different enteric coatings in the intestinal fluid at different time points ($n = 6$ with 400 micromotors in each test). Reproduced with permission from Ref. [75], copyright 2016 American Chemical Society

micromotors would not be washed away easily by the GI fluid and hence acquire prolonged retention in the GI tract, which is demonstrated by in vivo animal tests. PEDOT/Zn bilayer micromotors were intragastrically administrated into the stomachs of living mice, loading gold nanoparticles as model drugs [61] (Fig. 2c–g). Then, researchers evaluated the biodistribution and retention inside stomachs, and it turned out a mass of micromotors retain on the walls of living mice stomachs, 2 h after the oral administration. On the contrast, in the control group—PEDOT/Pt micromotors which generate no bubbles or propulsion, there were no distinct retained micromotors on the stomach walls. PEDOT/Zn bilayer micromotors even can be observed at 12 h post-administration. As reckoned, the strong propelling force promoted the micromotors' penetration into the 170-μm-thick mucus layer comprised of cross-linked and staggered

mucin fibers covering the inner surface of the stomach [68]. After successful penetration, these micromotors will be bound in the mucus layer and retained for a long while. The existence of the PEDOT polymeric layer greatly fortified the propulsion and prolonged micromotor's lifetime. An enteric-coating Mg-based micromotor utilized the enteric polymer coating to escape from the gastric segment into the intestine and activated its propulsion to realize localized tissue penetration and high retention [75].

Through current researches, the magnesium-based micromotors have been proved with robust and continuous propulsion, endowed protons depletion, and high retention within gastric walls [76]. Researchers encapsulated magnesium particles into the coating PEDOT tubular framework as the propellant for the particles can react with water to generate hydrogen bubbles, namely, the spontaneous propulsion in the intestine segment where there is no effective acid "fuel". They studied the retention of the synthesized micromotors with medium enteric coating in the GI tract and the result showed that high biodistribution in the jejunum and micromotors remained at the site at 12 h, which was about fourfold longer than typical gastric emptying times in mouse GI tract [77]. Besides, adjusting the thickness of the enteric coating polymeric layer can thereby tailor the pH-responsive releasing time and location in the intestine (Fig. 2h). Except for encapsulating magnesium microparticles, there is still the capacity to load some therapeutic payloads like small molecule drugs. Upon reaching the intestine tract, the coating polymer would dissolve quickly and make the magnesium particles exposed to the water which subsequently generates propulsion, biodistribution, and retention. Herein, magnesium is also a biocompatible trace element crucial to human body activities. Usually, these micromotors triggered by external or internal factors move in disorder, while Karshalev et al. [20] integrated magnesium-based micromotors with diluents and disintegrating agents and transformed them into swallowable pills, achieving a more collective motion of micromotors compared to orally administrated free micromotors and static motors. Simultaneously, more micromotors attached to the gastric mucus layer with speed barely affected in parallel to the non-pill micromotors experiment.

Protons depletion

For the oral administration pathway, there is also a knotty but crucial factor—strongly acidic gastric environment which is adverse to the stability of protein drugs or the efficacy of antibiotics. Whereas, the aforesaid chemical propulsion mechanism through the reaction with gastric acid brings the eradication of the protons in the stomach and elevates the pH to a neutralized level [78]. It was later proved that this elevation is transient and exerts no affection on the normal gastric function with no adverse effects—no apparent gastric histopathologic change or inflammation. Temporary change in the pH of gastric fluid would make it possible for those unstable in acid therapeutic drugs to be orally administrated.

It is reported that long-term exposure to PPIs is associated with increasing the risk of chronic kidney disease, kidney disease progression, and end-stage renal disease [79, 80]. This may be because PPIs irreversibly bind to the proton pumps and suppress secreting acid [81] and thereby influence the normal function of the stomach. This proton-depletion feature of micromotor technology presents us with an alternative to proton pump inhibitors (PPIs) without any potential adverse effects probably made by PPIs [80]. de Ávila et al. [82] harnessed this feature to build an Mg core micromotor, loaded with clarithromycin (CLR) treating *H. pylori* infection in the stomach. The *H. pylori* bacteria, existing in almost half of the world's population, can cause diverse gastric diseases. It was proved that the appropriate dosage of PPIs has the ability to conserve the efficacy of co-administrated antibiotics when treating stomach infection. Therefore, de Ávila and his group, for the first time, combined the micromotors' retention ability and protons depletion to ameliorate the harsh acidic condition in the stomach in case it decreases the antibacterial efficacy. They synthesized Mg/TiO_2/PLGA microspheres, coated with chitosan layer to raise the adhesion to the gastric wall, to load anti-gastric-infection drug CLR. Thereafter, they developed a mouse model of gastric infection by *H. pylori* bacteria and compared the efficacy of CLR-loaded Mg micromotors and CLR + PPIs, evaluating by enumerating and comparing *H. pylori* counts retrieved from each mouse stomach. To fully examine the advantage of the synthesized motors, they also administrated the model mice with static drug carriers (CLR-loaded SiO_2 particles) and CLR-loaded Mg micromotors, respectively, and it turned out the dynamic carriers possess a better retention ability and a better treatment to infection. This strongly validates the potential value of micromotors in vivo therapeutic applications.

Vaccines through oral routes are always highly desirable for their benefits of ease of administration, high patient compliance, and generating a broader response by stimulating mucosal immunity [83]. However, the instability of vaccines in an extreme gastric acid environment and the poor retention in the GI site deter vaccines from operating maximum efficacy. Scientists thus started to pay attention to the newly developed micromotors, in order to achieve high vaccine potency and specificity. Wei et al. [84] synthesized a spherical micromotor with a Mg–TiO_2 core by sequential coating procedures, possessing improved cargo delivery ability, protons depletion, and enhanced retention. They coated prepared Mg–TiO_2 micromotor with a layer of the red blood cell (RBC) membrane inserted with toxins to simulate invasive infection. Herein, RBC membrane coating was used to neutralize and immobilize a model bac-

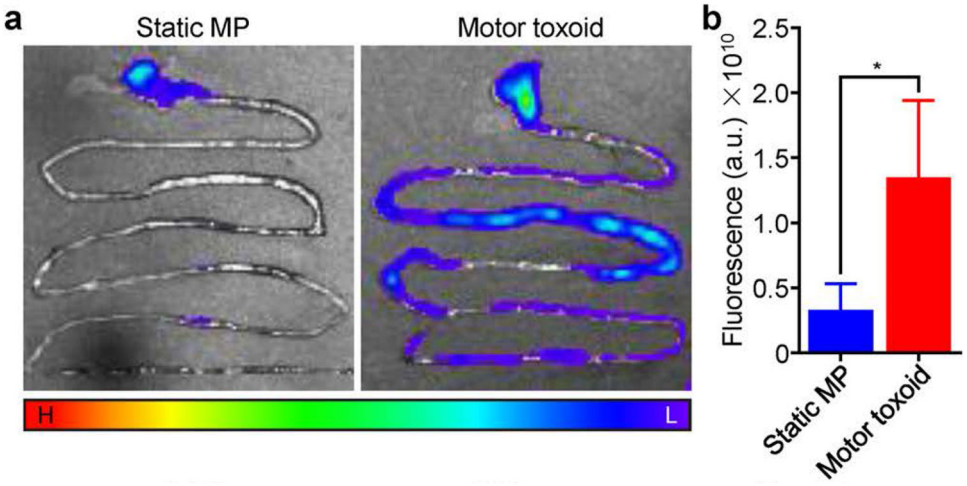

Fig. 3 **a** Representative images of the gastrointestinal tract of male CD-1 mice 6 h after administration of DiD-labeled static microparticles (MP) or motor toxoids by oral gavage (H: high fluorescence, L: low fluorescence). **b** Quantification of the fluorescence from (**a**) ($n = 3$, mean + SD), **a**, **b** reproduced with permission from Ref. [84]

terial toxin onto the micromotor's surface, no need to assure the protein function intact. So as to combine the adhesion ability to the mucosal wall of the intestine [85, 86] and intestinal localization, the coating of a positively charged mucoadhesive chitosan layer and pH-responsive polymer layer (Eudragit L100-55) ensued. The in vitro uptake properties were evaluated and the observed increased uptake of membrane materials implied the propulsion capability may contribute to facilitating the cellular contact and prolonging the retention in absorbing sites (Fig. 3a, b). At last, this research group performed the in vivo test on model mice via oral administration to explore the ability to induce immune responses against α-toxin. They assessed IgA antibody titers with an enzyme-linked immunosorbent assay method and judged from the absorbance values, the toxin-loaded micromotors significantly boost the antitoxin IgA titer production by almost 1 order of magnitude compared to those mice administrated with static α-toxin microparticles. This test suggests that there is a significant strength in fabricating a toxoid platform and delivering antigenic payloads by micromotor technology.

Parenteral administration

Transcellular penetration

Not only beneficial in the oral administration, but the strong penetration also benefits the payloads delivery into cells in parenteral administration. de Ávila et al. [87] combined synthetic nanomotors with DNA nanotechnology to have fabricated an acoustically powered gold nanowire modified with the interfering RNA's payload, achieving an accelerated siRNA delivery and high silencing response (Fig. 4). Their experiment showed that such gold nanowire can pierce and penetrate into HEK293-GFP cells efficiently driven by ultrasound and cause minimized cell damage, successfully delivering drugs into cells under magnetic navigation. This effective penetrating performance is promising to make up for the lack of traditional carriers in penetration and clearly can improve bioavailability. Wang et al. fabricated an acoustically powered gold nanorod (3 μm long × 300 nm diameter) and found rapid autonomous axial propulsion (peak axial speed of about 200 $\mu m\ s^{-1}$) in the water when excited by the 4 MHz acoustic resonance [88]. They placed the nanorods in a HeLa cell aggregate and tracked their trace under acoustical activation. Surprisingly, these nanorods not only can move between HeLa cells with robust propulsion but also can attach persistently to the cells at their tips or sides and even move into the cells. After moving into the living cells, the propulsion still existed and such intracellular propulsion had no apparent influence on the viability of the HeLa cells. Therefore, ultrasound powered nanorods with effective propulsion bring more possibility for delivering payloads into cells and controllably manipulating intracellular organelles. Xu et al. [13] presented a sperm-driven micromotor capable of swimming and delivering the drug into a cancer cell through the cell membranes fusion. They trapped a motile sperm into the cavity of the tubular body of a tetrapod, and thus, the sperm started to push the tetrapod forward, giving this micromotor propulsion and increasing its biocompatibility.

While local administration is widely applied in delivering drugs to the posterior part and treating diseases of eyes, the efficacy is not satisfying as a result of the lacrimal fluid–eye barrier and the retina–blood barrier [89, 90]. Microparticles can realize the targeted delivery though, the high viscosity of vitreous body blocks them from rapid drug delivery and low absorption still diminishes the effect. Hence, it is necessary and crucial to find a method to help microparticles drug delivery systems overcome the barriers. Wu et al. [91] firstly demonstrated a novel dynamic micromotor with a slippery liquid coating to carry the drugs to the nidus of eyes effectively. This micromotor is helical in shape and has a

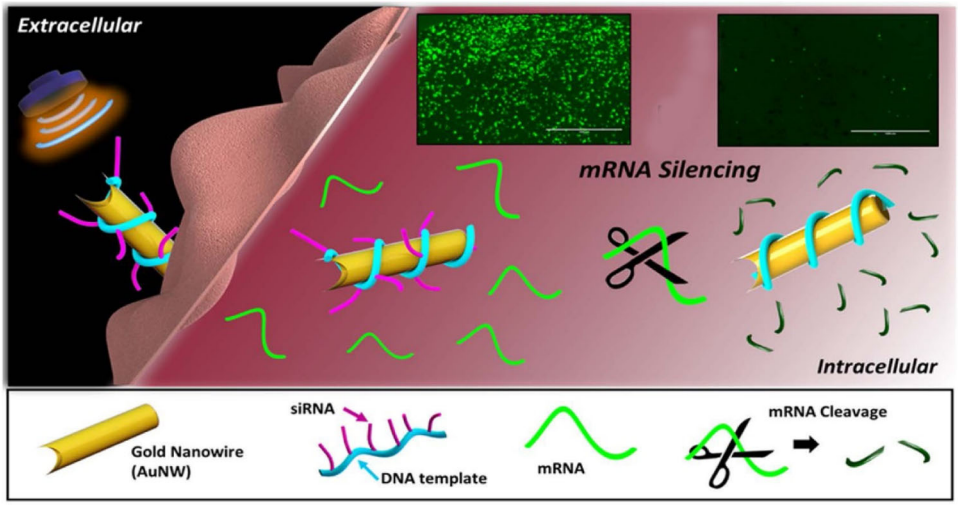

Fig. 4 Schematic of strong penetration mechanisms in micromotors. Penetration inside a HEK293-GFP cell and composition of GFP/RCA-AuNW micromotors to perform intracellular gene-mRNA silence. Reproduced with permission from Ref. [87]

size of ~500 nm which is comparable to the mesh size of the vitreous. The slippery coating constituted of perfluorocarbon helps shrink the interaction of the micromotor with biopolymers like collagen bundles and boosts the motion in biological mediums. Therefore, this micromotor can easily penetrate through the tight macromolecular matrix and reach the retina of eyes with the locomotion actuated wirelessly by an external field.

Moreover, what is necessary to be noticed is that the administrated micromotors are directly exposed to the human tissues amid the penetration, raising the safety issues to some extent. On improving the biocompatibility, scientists have invented diverse differently characterized micromotors. Wu et al. [47] fabricated a biodegradable functionalized micromotor through the template-assisted layer-by-layer method. This synthesized micromotor incorporated a heat-sensitive gelatin hydrogel core, greatly increasing the encapsulation capacity, and released cargos-gold nanoparticles, doxorubicin, and catalase in this case by a near-infrared trigger. Peters et al. [92] proposed a degradable superparamagnetic polymer composite micromotor through simple and facile device fabrication, wirelessly actuated by the magnetic field. The degradants showed low cell damage and possessed potential excretion pathways from the human body. Using biodegradable materials to fabricate micromotors can expand the application area in the human body and enrich the delivery types, bringing more values to this new carrier as a result. Overall, the advent of these strategies to increase the penetration performance of micromotors greatly improved the bioavailability and reinforced the potential application of micromotor delivery systems. It is worth noting that the strong penetration into tissues or cells distinctly helps motors get entry into these sites and ameliorates both the retention and the distribution there, which sufficiently guarantees the collection in targeted tissues or cells and improve the targeting efficiency.

Targeting delivery

Currently, most applied nano/microcarriers are delivered through the carriage systemic circulation because of the lack of propulsion and navigation. To these novel micromotors, after possessing the propulsion ability, a little extra navigation may thus endow them with the ability of localized delivery which helps transport drugs directly to the diseased sites, bringing increases in therapeutic efficacy and decreases in systemic toxicity. The majority of researchers used the magnetic technology, namely incorporating a magnetic layer into the micromotor structure, to restrain motors in their predetermined paths [30, 92–94], and numerous researches have been conducted to prove the feasibility. Chen et al. [52] demonstrated a hybrid magnetoelectric core–shell composite nanowire (a magnetostrictive core and a piezoelectric shell) loaded with the anticancer drug, being able to realize targeted motion and onsite controlled drug release. The drug is loaded by the interaction between the drug molecules and polydopamine, and released by being exposed to an alternating magnetic field. The magnetic field also plays a role in maneuvering the micromotor to the targeted lesion when being rotated, leaving no significant cell death. Gao et al. [95] reported a RBC-mimicking micromotor, consisting of RBC-shaped hemoglobin particles including Fe_3O_4 nanoparticles and aiming to overcome the hypoxia in tumors and the low tumor-targeted accumulation capability of photosensitizers via delivering oxygen and controllable locomotion. Through exerting external ultrasound waves whose power can be modulated, this fuel-free micromotor can reach a high speed of up to 56.5 $\mu m\ s^{-1}$ (28.2 body lengths s^{-1}) and its velocity can be adjusted to the strength of ultrasound waves. Plus, the loaded magnetic Fe_3O_4 nanoparticles allow for precise directional control under a variable magnetic field which thereby can deliver oxygen and therapeutical cargos to the predetermined sites. Following the same principle,

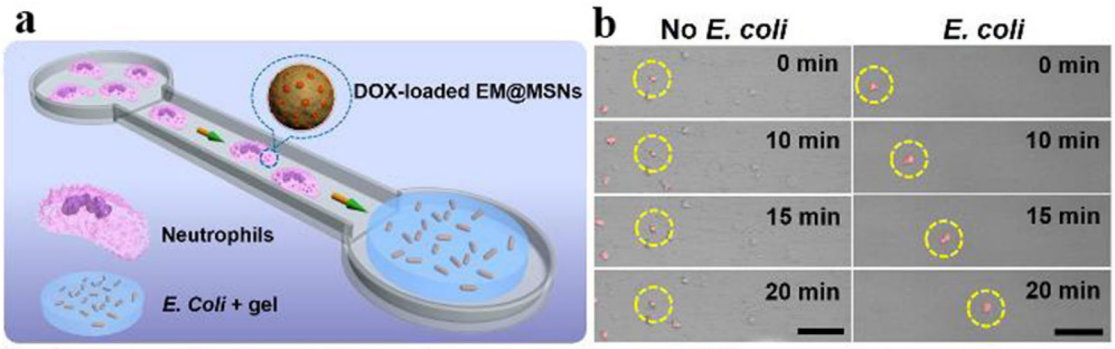

Fig. 5 **a** Schematic illustration showing the chemotactic motion of hybrid neutrophil micromotors toward the gel containing *E. coli* in a microfluidic channel. **b** time-lapsed CLSM images of hybrid neutrophil motors with (right) and without (left) *E. coli* in the gel. Scale bar = 50 μm. **a**, **b** Reproduced with permission from Ref. [41]

Wu et al. [22] integrated citrate-stabilized Fe_3O_4 nanoparticles into polymer-based multilayer nanorockets and thus attained magnetic guidance toward cancer cells. To reduce the risk of immune attacks of synthetic materials, they also employed human red blood cells as functional micromotors, loaded with iron oxide nanoparticles asymmetrically [96]. The regular distribution of magnetic particles allows directional alignment and guidance according to the magnetic field when propelled by acoustic propulsion.

The aforementioned sperm-driven micromotor presented by Xu et al. [13] is capable of swimming and delivering the drug into a cancer cell through the cell membranes fusion. Sperm cells were trapped into a magnetic tetrapod with a tubular body and four flexible arched arms protruding from one opening of the microtube in a curved manner. This designed microdevice utilized the in vivo motion of sperms and navigated it through modulating the external magnetic field, representing the tremendous application in detecting and treating cancer or other diseases in the female reproductive tracts.

Except for the navigation from external stimuli, another strategy is to harness the special affinity with the endogenous substances. Chemotaxis represents the trend of bacteria or immune cells self-guiding toward chemical attractants or away from repellants. The combination of substances with chemotaxis phenomenon and micromotors is promising to produce more practical and convenient targeting delivery methods. As an immune cell, neutrophil can spontaneously locomote along the chemoattractant gradients (i.e., chemoattractant produced by *Escherichia coli*) toward the inflammatory sites and extinguish the pathogens (like bacteria and virus) by phagocytosis [97–99]. Shao et al. [41] inventively blended mesoporous silica nanoparticles (MSNs) with neutrophil cells leveraging the engulfing capability of neutrophils and then coated such biohybrid micromotors with membranes derived from the *E. coli* bacteria. They hoped to combine MSNs' high drug-loading capacity and biocompatibility and neutrophils' ability to move toward inflammatory sites. As their experiments tested, the intrinsic chemotaxis ability of neutrophil cells facilitated micromotors moving along the chemoattractant gradients produced by the *E. coli* (Fig. 5a, b), remaining the cellular activity and motility of neutrophils and low leaking of loaded drugs. Instead of relying on the systemic circulation, current research progress in micromotor science draws more upon spontaneous motion and special affinity as guidance. These researches indicate a new trend in novel targeted drug delivery systems in an active way, paving way for more effective therapeutical treatment compared to the traditional passive methods.

Apart from the targeting ability toward the lesion sites, the interaction between motors and therapeutic cargos also opened the door to manipulating and transporting drugs directionally. If micromotors can recognize and approach to the determined cargos, it will be realistic to fulfill the directional accumulation of special drugs and even the isolation and clearance of toxic substances [100, 101]. Kagan et al. [102] encapsulated iron oxide nanoparticles into drug-loaded poly-D,L-lactic-*co*-glycolic acid (PLGA) particles to generate a magnetic interaction with the nickel segment of catalytic alloy nanomotors. In their experiment, those nanomotors demonstrated a quick and smooth pick-up, transport, and release of PLGA particles through predefined routes under magnetical guidance. The nanomotor grabs the PLGA particles during the move toward them via magnetic attraction and reaches an instantaneous release at the fast reversal of direction brought by the modulation of the external magnetic field.

Overall, compared to the traditional delivery pathways depending on the random, passive diffusion of drug molecules, system circulation and uptake characteristics of the absorption sites, the application of micromotor tech-

nology can provide us a controllable and rapid delivery of therapeutical payloads.

Other related purposes

Not only endowed with autonomous and robust motion but also equipped with diversely-featured surfaces easily to be functionalized, these proposed micromotors performed promisingly in other applications. Currently, reported methods to fabricate the biorecognition layer include sputtering a gold layer which can be functionalized with the alkanethiol monolayer and covalent coupling of bioreceptors onto the metal copolymer/micromotors surface and simply co-electropolymerized the functional monomer in the outer layer [5, 103–105]. Garcia-Gradilla et al. [23] employed an acoustically propelled three-segment Au–Ni–Au nanowire motor whose Au segments were functionalized with lectin and antiprotein A antibody bioreceptors to capture and transport *E. coli* and *Staphylococcus aureus* bacteria, respectively. In their designed experiments, the nanowire locomoted under acoustic stimuli and directionally captured the pre-planned targets via the affinity between targets and bioreceptors, revealing to be promising to capture and isolate biological targets even in unprocessed real-life biological and environmental media. DNA hybridization represents the exclusive combination of two complementary sequences as well. Under appropriate conditions, two complementary sequences can autonomously bind and form a stable duplex structure. Van Nguyen et al. [106] incorporated a thiol layer onto the inner gold layer of a PEDOT/Au microtube modified with 11-mercaptoundecanoic acid and then attached a certain DNA sequence to the gold layer by the standard EDC/NHS coupling reaction. The ensued micromotors thus display a "signal-on" motion in the presence of assumed DNA analytes, detecting and capturing the specific DNA strands.

Traditional immunosensors mainly indicate optical, mass-sensitive, and electrochemical types, but the long assay time limited their applications. The advent of autonomously locomote and orient micromotors brought new opportunities to immunosensing. Yu et al. [6] constructed a gold nanoparticle-modified self-propelled polyaniline/Pt (AuNP/PANI/Pt) micromotor functionalized with capture antibody as a microsensor (Fig. 6a). They electrostatically assembled a gold nanoparticle-modified polyaniline/Pt (AuNP/PANI/Pt) micromotor and then integrated the capture antibody (Ab1) into the gold layer. In fuel-enhanced media, the micromotor can move fast and selectively recognize the protein target. Once recognizing the target, the micromotor will load the secondary antibody-modified glycidyl methacrylate microspheres (GMA) and slow down. Researchers distinguish the concentration of carcinoembryonic antigen by the velocity of microsensors and the number of GMA conjugated on the microsensor.

Furthermore, the functionalized surface and carrying ability of micromotors exhibit the possible removal of targets from media. Considering the hazardous metal ions have been threatening humans' health, some scientists laid their attention on the micromotors [107–109]. Yang et al. [110] built a tubular micromotor based on metal–organic frameworks consisting of calcined layered double hydroxides and MnO_2 and functionalized with ethylene diamine tetraacetic acid (EDTA). The incorporated MnO_2 helped micromotors with self-propulsion by decomposition of hydrogen peroxide and EDTA chelated Fe^{3+} during the motion to effectively remove metal ions from environmental media (Fig. 6b). Plus, the aforementioned biomembrane-coating tactic was also employed to camouflage micromotors for effectively biodetoxifiation [111, 112]. As the camouflaged micromotors propelled acoustically, the RBC membranes could specifically decoy the membrane-damaging toxins in biological fluids, holding great potential to protect normal cells and profoundly constructing a broad-spectrum detoxification robotic platform.

Conclusion and prospectives

Herein, we overviewed a bunch of different micromotors with various propulsion, actuation, and navigation mechanisms, and outstanding merits in diverse applications are involved, respectively, as well. Both in vitro and in vivo animal tests displayed the micromotors' feature of fast motion generated by self-propulsion or external power. Fast motion ability has already been translated into cargo towing force and payloads carrying function by researchers which made it promising for the designed micromotor to be a novel drug carrier. Concluding from the micromotors talked above, innovative surface functionalizations and structures are able to bring motors navigation, penetration, retention, and cell-manipulation advantages, and these functions all show a stable and bright application future. Nonetheless, in vivo tests in animals still have a quite long distance away from clinical use. Plus, short lifespan and ensued short moving distance, the maximum distance of cargo-loaded micromotor is 6.6 cm, inevitably limited the application. In addition, some of the tubular micromotors' fabrication methods are highly complicated and technique required, which may block this technology from practical use. The already-proved improvement in penetration is mainly enhanced by propulsion force physically, namely, drugs penetrate into the gastric-gel layer wall in a form of solid mass instead of molecules. The increase in the uptake of drugs is not that considerable theoretically.

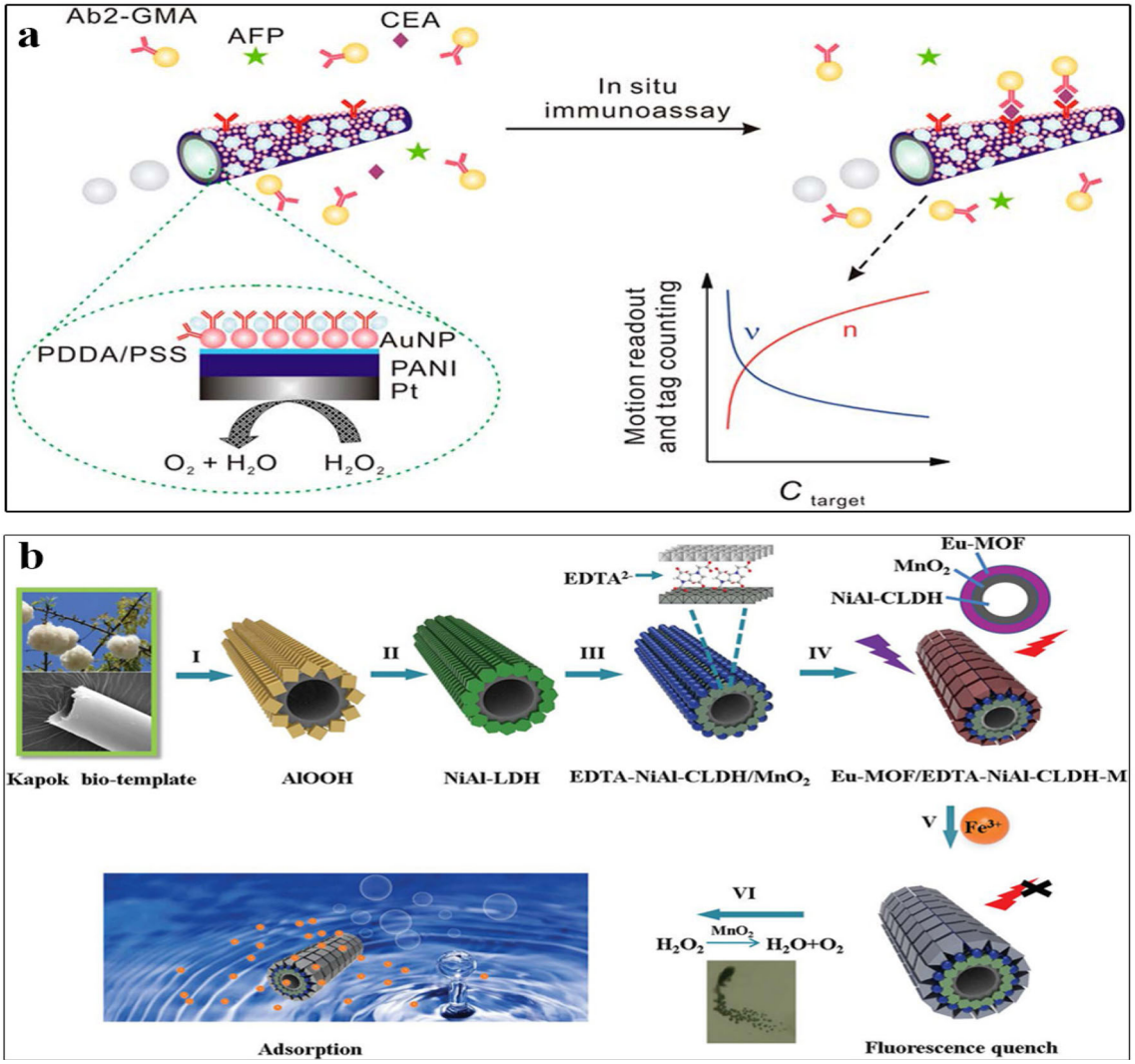

Fig. 6 **a** Schematic illustration of a motor-based microsensor for in situ visualization immunoassay of cancer biomarkers through velocity readout or tag counting. Reproduced with permission from Ref. [6]. **b** Schematic illustration of the preparation and composition of Eu-MOF/EDTA-NiAl-CLDH–M micromotor based on a bio-template for sensing and removal of Fe^{3+}. Reproduced with permission from Ref. [110]

As reviewed, the present main in vivo animal tests are orally administrated, and there are a lot of other administration forms to be tested like injection which yet might cause gas embolisms in blood vessels from gas-propelled micromotors. This may enlighten us to apply external power-driven micromotors in injection. Innovations in administration forms can optimize this miniaturized device, especially for the biomedicine field such as specific diagnostic functions, precision surgery, and removal of toxic substances. To accomplish this goal, entangled subjects knowledge is highly required including materials science, inorganic chemistry, biochemistry, and pharmaceutics. The biocompatibility is also highly required to be tested deeper, especially immunocompatibility, to prove the safety in clinical application. We anticipate and put stock in that with close communication between various fields, micromotors technology will come into vigorous practice in the short future.

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Compliance with ethical standards

Conflict of interest The authors declare no competing financial interest.

Ethical approval This manuscript does not contain any studies with human or animal subjects performed by any of the authors.

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