Artificial nanomotors: Fabrication, locomotion characterization, motion manipulation, and biomedical applications

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Abstract
Artificial nanomotors are nanoscale machines capable of converting surrounding other energy into mechanical motion and thus entering the tissues and cells of organisms. They hold great potential to revolutionize the diagnosis and treatment of diseases by actively targeting the lesion location, though there are many new challenges that arise with decreasing the size to nanoscale. This review summarizes and comments on the state-of-the-art artificial nanomotors with advantages and limitations. It starts with the fabrication methods, including common physical vapor deposition and colloidal chemistry methods, followed by the locomotion characterization and motion manipulation. Then, the in vitro and in vivo biomedical applications are introduced in detail. The challenges and future prospects are discussed at the end.

KEYWORDS
biomedical application, fabrication, locomotion characterization, motion manipulation, nanomotor

1 | INTRODUCTION

Artificial micro-/nanomotors (MNMs) are microscale and nanoscale machines that can convert diverse other energy into mechanical movement and forces.[1–5] Owing to the autonomous movement property, MNMs display significant potentials in various biomedical applications,[6–20] such as active drug delivery,[6–10] precision surgery,[11,12] medical diagnosis,[13–16] and detoxification.[17–19] The existence of biological barriers in vivo environments generally requires biomedical MNMs to have a size comparable to the application scenarios.[21,22]
The Zn- and Mg-based micromotors have dozens of micron in diameter and are chemically powered by bubble recoils. They were demonstrated to dramatically improve the retention of their payloads usually in the easily accessible gastrointestinal tract of living mice through gavage administration. Liquid perfluorocarbon-coated magnetic helical micropellers that have a diameter (0.5 µm in diameter and 2 µm in length) are able to propel through the vitreous humor to reach the retina of a porcine eye over centimeter distances, holding potential for future ophthalmological therapies. For the treatment of some major diseases (e.g., tumor and cardiovascular disease), the drug carriers need to transport in the blood circulation system and have to encounter diverse biological barriers during the transportation. Pharmacokinetics shows that the nanostructures with a size smaller than 6 nm will be rapidly filtered out and cleared by the kidneys, while those larger than 200 nm will be rapidly retained by the spleen. For the enhanced permeability and retention (EPR)-based tumor targeting, nanostructures with dimensions in the range of 30–200 nm show superior retention by the tissue resistance, shifting the equilibrium toward extravasation and leading to enhancement in tumor accumulation. Moreover, the extracellular matrix (ECM) has a pore size of 100–300 nm. Thus, nanomotors with sizes of about 30–200 nm are expected to have applications related to the blood circulation system, especially for cellular level applications in comparison to micro-sized motors.

As the size of motors is reduced to the nanoscale, their fabrication, motion characterization, and manipulation pose great challenges not found at microscopic scales. For instance, the commonly used methods for the fabrication of micro-sized motors do not work for nanomotors. In addition, due to the optical diffraction barrier presented in classical white-light optical-microscopy setups, it becomes a challenge to examine the motion trajectories of nanomotors. Moreover, owing to the huge influences of the stochastic Brownian forces, the nanomotors always exhibit a weak driving force and it is difficult to manipulate their motion behaviors. Despite all these challenges, great breakthroughs have been made in the last decade. For example, various nanomotors with controllable sizes, shapes, and components can be fabricated by developing physical vapor deposition and colloidal chemistry methods. The propulsive forces of nanomotors have been greatly increased to move from enhanced diffusion into directional movement. More recently, some proof-of-concept nanomotor-based active drug delivery systems demonstrated greatly enhanced therapeutic effects in tumor and cardiovascular disease therapy compared to their static counterparts.

In this review, state-of-the-art nanomotors (<500 nm) are presented. In Section 2, we summarize the fabrication techniques of reported representative nanomotors, as well as discuss their respective advantages and limitations in terms of the driving force. Sections 3 and 4 describe the recently developed characterization techniques for analyzing the motion behaviors of nanomotors and then discuss motion manipulation methods for nanomotors. Afterward, we highlight in Section 5 the developments of active drug delivery based on nanomotors. Finally, the current challenges and future prospects are also envisioned to realize the biomedical applications of nanomotors following some concluding remarks. With a systematic knowledge frame and increasing attraction about biomedical nanomotors, this review provides insights to explore biomedical nanomotors, especially for active drug delivery in the future.

2 | FABRICATION TECHNIQUES OF NANOMOTORS

The key to preparing nanomotors is to make active components asymmetrically distributed on a nanoparticle. With the rapid development of nanotechnology, a variety of strategies and techniques have been used for the preparation of nanomotors, which, however, are facing the most exciting challenges. In this section, we enumerate the fabrication techniques of reported nanomotors with representative examples and discuss their respective advantages and limitations (Table 1). The fabrication techniques presented here are mainly divided into two categories: physical vapor deposition and colloidal chemistry methods.

2.1 | Physical vapor deposition

Physical vapor deposition is a vaporization coating technique for depositing thin layers of target materials on the surface of the substrate in a vacuum or partial vacuum environment. This technique has been widely used to fabricate micromotors. By tuning the size of templates to the nanoscale, it can also be utilized to fabricate nanomotors. So far, two types of physical vapor deposition techniques, sputtering and electron beam evaporation, have been used for the preparation of nanomotors. The first typical procedure for preparing nanomotors by physical vapor deposition techniques is to form a self-assembled monolayer of nanoparticles by depositing a droplet of nanoparticle suspension on a
| Fabrication techniques | Nanomotors | Structure | Size (nm) | Fuel or energy source | Application scenarios | Advantages and limitations | References |
|------------------------|------------|-----------|-----------|-----------------------|-----------------------|---------------------------|------------|
| Physical vapor deposition | Ellipsoidal Pt−Au Janus nanomotor | Janus | 30 | H$_2$O$_2$ | – | Advantages: easy to fabricate Janus nanostructures. | [35] |
| Physical vapor deposition | Pt (catalase)−mSiO$_2$ Janus nanomotor | 40–90 | H$_2$O$_2$ | – | Limitations: expensive and complicated equipments, laborious and time-consuming, difficult to prepare small-sized nanoparticles, and low yield. | [36,37] |
| Physical vapor deposition | Enzyme (catalase, urease, glucose oxidase)-powered mSiO$_2$ Janus nanomotor | 400 | H$_2$O$_2$/urea/glucose | – | | [38] |
| Physical vapor deposition | NIR-driven Janus mSiO$_2$−Au nanomotor | 50–120 | Light | – | | [39,40] |
| Physical vapor deposition | Cap-like Au/TiO$_2$ nanomotor | Hollow | 175 | Light | – | | [41] |
| Physical vapor deposition | Helical nanopropeller | Helical | 500 | Magnetic field | – | | [42] |
| Colloidal chemistry method | Urease−Au−mSiO$_2$ nanomotor | Symmetrical | 500 | Urea | Medical imaging | Advantages: easy to regulate the shapes, sizes, and components of the nanostructures. | [16] |
| Colloidal chemistry method | Fe$_3$O$_4$−mSiO$_2$ nanomotor | 290 | Magnetic field | Detoxification | | [19] |
| Colloidal chemistry method | Urease-powered mSiO$_2$ nanomotor | 300–480 | Urea | Tumor therapy | | [43–45] |
| Colloidal chemistry method | Lipase-powered mSiO$_2$ nanomotor | 430 | Triacetin | Triglyceride degradation | | [46,47] |
| Colloidal chemistry method | NIR-driven mesoporous-macroporous SiO$_2$−Pt nanomotors | 200–400 | Light | Cardiovascular disease and tumor therapy | | [48,49] |
| Colloidal chemistry method | Urease/PT/Fe$_3$O$_4$ nanomotor hollow mSiO$_2$ nanomotor | 300 | Urea/H$_2$O$_2$/magnetic field | – | | [50] |
| Enzyme (catalase, urease, glucose oxidase)-coated liposome nanomotor | 100 | H$_2$O$_2$/urea/glucose | – | | | [51] |
| NO-driven nanomotor | 170 | L-Arginine | Tumor diagnosis and therapy | | | [52] |
| Urease-powered liposomal vesicles nanomotor | 100 | Urea | – | | | [53] |
| Fabrication techniques | Nanomotors                                                                 | Structure | Size (nm) | Fuel or energy source | Application scenarios                          | Advantages and limitations | References |
|------------------------|---------------------------------------------------------------------------|-----------|-----------|-----------------------|-----------------------------------------------|----------------------------|------------|
|                        | Dual enzyme-functionalized-powered metal-organic framework nanomotor      |           | 200       | H₂O₂/glucose          | Photodynamic and starvation therapy           |                            | [54]       |
|                        | Urease-powered liquid metal (LM) nanomotors                               |           | 350       | Urea                  | Imaging and targeted therapy                  |                            | [55]       |
|                        | Janus Au nanomotor                                                        | Janus     | 13        | Fe(CN)₆³⁻, S₂O₃²⁻    | –                                              |                            | [56]       |
|                        | GOx-powered Janus Au nanomotor                                            |           | 60–90     | Glucose              | –                                              |                            | [57]       |
|                        | Janus Pt-mSiO₂ nanomotor                                                 |           | 100       | H₂O₂                 | –                                              |                            | [58]       |
|                        | DNase functionalized Janus nanomotor                                      |           | 150       | DNA gradient         | –                                              |                            | [59]       |
|                        | Au-BP/SP Janus nanomotor                                                 |           | 130       | Light                | –                                              |                            | [60]       |
|                        | Bowl-shaped stomatocyte nanomotors                                        | Hollow    | 25        | H₂O₂/urea/glucose, etc.| Tumor therapy                                |                            | [61,62]   |
|                        | Enzyme (glucose oxidase or catalase)-powered polymersome nanomotor        |           | 80        | Glucose/H₂O₂         | Penetrate blood-brain barrier                  |                            | [63]       |
|                        | Flask bottle-like nanomotor                                              |           | 350       | H₂O₂                 | –                                              |                            | [64]       |
|                        | Tadpole-like mSiO₂ nanomotor                                              |           | 500       | H₂O₂                 | –                                              |                            | [65]       |
|                        | Au/Pt-egg-in-nest nanomotors                                              |           | 80        | H₂O₂                 | –                                              |                            | [66]       |
substrate followed by slow evaporation. To form a uniform monolayer, it is necessary to create a suitable temperature and stable airflow environment to eliminate the evaporation accumulation of suspension, so as to ensure that there is no airflow interference to form the superposition between particles during the formation of a monolayer. The surface of the substrate forming a monolayer structure needs to be smooth and clean. Glass slides are usually selected as the carrier and plasma cleaner is adopted to ensure its cleanliness. Furthermore, before the formation of the monolayer, the particles should be dissolved in a solvent with good hydrophilicity (such as ethanol) and in an appropriate concentration as the limited surface of the substrate cannot carry too many particles. The suspension containing particles should be transferred to the substrate surface at once, multiple drops. When a uniform monolayer is formed, either catalytic materials or inert materials for blocking reactions are then deposited on the top of the monolayer to form hemispherical caps on the surface of the nanoparticles. After fabrication, the Janus nanoparticles are detached from the substrate via sonication. The size of the fabricated nanomotors can be regulated by tuning the size of templated particles.

The most common catalytic Janus nanomotors are the Pt-catalyzed Janus nanoparticle.\cite{35,36} A pioneering work was reported by Peer Fischer’s group.\cite{35} They fabricated a kind of 30 nm ellipsoidal Pt–Au Janus nanomotor by using glancing angle deposition of Au under fast substrate rotation onto an array of Pt nanoparticles (PtNPs) produced by block copolymer micelle lithography (Figure 1A). These bimetallic Janus nanomotors can catalyze the decomposition of \( \text{H}_2\text{O}_2 \) to \( \text{H}_2\text{O} \) and \( \text{O}_2 \), and thus can actively move by self-electrophoresis mechanism. Another type of spherical Janus nanomotor was reported by Sánchez’s group.\cite{36} They fabricated Pt–mesoporous silica (mSiO\(_2\)) Janus nanomotors by deposition of a very thin Pt layer on an mSiO\(_2\) nanosphere. By tuning the size of mSiO\(_2\) nanosphere templates, they obtained nanomotors with sizes ranging from 40 to 90 nm. In addition, Prof. Sánchez’s group also reported an enzyme-powered Janus nanomotor which was prepared by the physical vapor deposition technique.\cite{39,41} The enzyme-powered mSiO\(_2\) nanomotor was prepared by the physical vapor deposition technique.

**FIGURE 1** Representative nanomotors prepared by the physical vapor deposition. (A) Preparation of 30 nm ellipsoidal Pt–Au Janus nanomotors by the glancing angle deposition. Reproduced with permission.\cite{35} Copyright 2014, American Chemical Society. (B) Preparation of cap-like Au/TiO\(_2\) nanomotors with the self-assembled 200 nm polystyrene sphere (PS) monolayer as the template. Reproduced with permission.\cite{37} Copyright 2018, Wiley-VCH. (C) The near-infrared (NIR)-driven Janus mSiO\(_2\)–Au nanomotors (MSNMs) prepared by sputtering Au layer on one side of the monolayer of mSiO\(_2\) nanoparticles. Reproduced with permission.\cite{38} Copyright 2016, American Chemical Society.
Janus nanomotors were fabricated by half-capping the hollow SiO2 nanospheres (modified with an amine group on the surface) with a 10 nm SiO2 layer using electron beam deposition. The enzymes were covalently conjugated onto the noncoated side of the Janus nanoparticles via glutaraldehyde linker molecules. Each enzyme can catalyze the decomposition of the corresponding fuel, which provides the self-propulsion for the nanomotors. On the basis of spherical templates, nanomotors with other morphologies can also be fabricated by physical vapor deposition. For instance, Sánchez and coworkers demonstrated the fabrication of 175 nm cap-like Au/TiO2 nanomotors by combining plasma etching and electron beam deposition (Figure 1B). The cap-shaped nanomotors displayed enhanced diffusion in the presence of broad-spectrum visible light depending on a mechanism called the plasmonic photocatalytic effect in the field of photocatalysis. In addition to catalytic nanomotors, the nanomotors driven by external physical fields also can be prepared by the physical vapor deposition technique. For instance, He and coworkers reported a near-infrared (NIR)-driven Janus mSiO2–Au nanomotor by vacuum sputtering of a 10 nm Au layer on one side of mSiO2 nanospheres (Figure 1C). Upon exposure to the NIR laser, the nanomotors can actively be driven by the self-thermophoresis mechanism. Fischer and coworkers prepared helical magnetic nanopropellers (approximately 70 nm in diameter and 400 nm in length) by using the shadow-growth technique on nanolithographically patterned substrates. The Ni layer-coated SiO2 helices were grown at room temperature using glancing angle deposition on top of uniform arrays of Au nanodots produced via micellar nanolithography with spacings. The helical nanopropellers can be propelled by a rotating magnetic field (H) and move through high viscosity solutions and gels. Physical vapor deposition techniques have been successfully used to fabricate Janus and helical nanomotors with sizes ranging from tens to hundreds of nanometers. However, the techniques face several limitations for the preparation of nanomotors. First, it is difficult to regulate the shapes, sizes, and components of the nanomotors. Meanwhile, the thickness and uniformity of film deposited on the template are also hard to control. Second, they always depend on expensive or complicated equipment. Third, the preparation process is laborious and time-consuming.

2.2 Colloidal chemistry methods

Colloidal chemistry methods play an important role in nanofabrication, where different components are combined to form the desired nanostructure via building blocks, including atoms, molecules, and even nanostructures of various compositions. Compared with physical vapor deposition, colloidal chemistry methods can greatly increase the yield of nanomotors and enrich the functionality of nanomotors due to the components of different properties. In this subsection, experimentally realized nanomotors are highlighted in terms of three categories: defect-dominated, Janus, and hollow geometries.

2.2.1 Defect-dominated nanomotors

A defect-dominated nanomotor typically consists of core material and a catalyst modified on its surface or encapsulated on its body. The self-propulsion of this category of defect-dominated nanomotors is achieved by an asymmetric generation of forces caused by an inherent slight asymmetry in catalyst distribution on nanoparticles. The SiO2 nanoparticles are the most widely used core materials for the fabrication of defect-dominated nanomotors by functionalized catalysts on their surface. Sánchez et al. reported a urease-powered mSiO2 nanomotor by using mSiO2 nanoparticles as a core. The surface of mSiO2 was modified with 3-aminopropyltriethoxysilane (APTES) to obtain nanoparticles with free amine groups on the surface, which were used to covalently modify urease using glutaraldehyde as a linker molecule, thus yielding urease-powered nanomotors. In the presence of urea, the urease modified on the surface of the nanomotors catalyzed the decomposition of urea into ammonia and carbon dioxide (Figure 2A). The same group demonstrated a lipase-modified mSiO2 nanomotor using a similar method by replacing urease with lipase. The resulting nanomotors can display enhanced Brownian motion through a biocatalytic reaction between lipase and its corresponding water-soluble oil substrate (triacetin) as fuel. Apart from mSiO2 nanoparticles, a variety of materials, including liposome, metal-organic framework (Figure 2B), and liquid metal nanoparticle (Figure 2C) have been explored as core materials to prepare defect-dominated nanomotors. In addition to the covalent coupling of catalysts, Wan et al. developed a nitric oxide (NO)-driven nanomotor by encapsulating the fuel (l-arginine) into the body of the nanomotor (Figure 2D). The L-arginine can be decomposed by ROS (e.g., H2O2) for the production of NO as a driving force. The preparation process of defect-dominated nanomotors is relatively simple, whereas the driving force of these category nanomotors is inferior to their asymmetrical counterparts.
2.2.2 Janus nanomotors

Most reported nanomotors have Janus structures and in this case are Janus nanomotors. They include nanosphere dimers with a big difference in the connected particle sizes and passive nanoparticles with one part of the surface activated. In comparison to defect-dominated nanomotors, this type of nanomotors displays a stronger driving force due to morphological asymmetry. Apart from physical vapor deposition techniques, various colloidal chemistry methods have also been utilized to prepare Janus nanomotors so far. It is a most common strategy that large-sized nanoparticles are employed to adsorb small nanoparticles in solution and thus build asymmetric nanostructures, similar to the abovementioned methods based on physical vapor deposition techniques. Qin et al. synthesized Janus Au nanoparticles (AuNPs) nanomotors by using a top-selective surface modification strategy (Figure 3A). The bis (p-sulfonatophenyl) phenylphosphine (BSPP)-modified AuNPs were first adsorbed on amine-functionalized SiO₂ particles, and then the exposed surface of AuNPs was modified with short thiolated oligonucleotides to recover catalytic activity. The resulting nanomotors were driven by a self-thermophoresis mechanism in solutions. He and coworkers utilized the same strategy to prepare a glucose oxidase (GOx)-powered Janus Au nanomotor. Díez et al. prepared a Janus Pt–mSiO₂ nanomotor by using a Pickering emulsion template with paraffin wax as a basal surface. The mSiO₂ nanoparticles

![Diagram](image_url)
were first partially embedded at the interface of the Pickering emulsion, formed by paraffin wax (oily phase) and water−ethanol (aqueous phase). The unmasked mSiO2 surface was decorated with reactive thiol groups, on which PtNPs were subsequently attached. After removing the paraffin with chloroform, Janus Pt−mSiO2 nanomotors were obtained (Figure 3B). These Janus-type nanomotors presented an ultrafast self-propelled motion due to the catalytic decomposition of low concentrations of H2O2. In addition to relying on the interface, the Janus nanomotors can also be grown in-situ by a colloidal chemistry method. Tu and coworkers proposed a DNase functionalized Au-polyacrylicacid (PAA) Janus nanomotor. The PAA was used to wrap one-half of the AuNPs (60 nm in diameter) to form Au-PAA Janus nanoparticles in the presence of isopropyl alcohol due to the interfacial energy difference (Figure 3C). Upon the fabrication of Janus nanostructures, DNase was coupled to the PAA side through the reaction between carboxylic groups of PAA and amino moieties of DNase via EDC/NHS chemistry. The as-obtained nanomotors can be powered by the decomposition of ultralow concentration of DNA.

2.2.3 Hollow nanomotors

Hollow nanoparticles with a concave cavity loaded by catalysts, called hollow nanomotors here, are another type of extensively studied nanomotors. Owing to the concave cavity, hollow nanomotors catalytically generate the products in a confined space, of which the diffusion is seriously inhibited and the local concentration is thus increased. This always makes them display strong driving forces. In addition, the concave cavity can also act as space cargo for delivery.

Wilson et al. reported a series of bowl-shaped stomatocyte nanomotors. The bowl-shaped stomatocytes were derived from spherical polymersomes via dialysis, and the preformed active catalysts PtNPs were selectively entrapped within the nanocavities.
of the stomatocytes. The entrapped PtNPs catalyzed the decomposition of H₂O₂ into O₂ and H₂O to generate autonomous movement (Figure 4A). The method required large amounts of organic solvent, and cannot apply for the encapsulation of proteins, because the long contact time between the protein and the organic solvent, generally led to protein denaturation. To solve this problem, they reported a strategy for enzyme entrapment and nanomotor assembly via controlled and reversible folding of polymersomes into stomatocytes under mild conditions, allowing the encapsulation of the proteins inside the stomach and retention of activity. The resulting enzyme-driven nanomotors can propel these structures with low fuel concentrations (H₂O₂ or glucose) via a one-enzyme or two-enzyme system. Although the size of as-prepared stomatocyte motors is at the nanoscale, they are still larger than 200 nm, which is not ideal for biomedical applications at the cellular level. Then, they fabricated a 150 nm stomatocyte polymersome through the addition of polyethylene glycol (PEG) additive, which allowed for both shape transformation of small polymersomes into stomatocyte and encapsulation of catalase. Joseph et al. reported another enzyme-powered asymmetric polymersome nanomotor. The asymmetric polymersomes with two separate domains were formed by the self-assembly of two different amphiphilic copolymers in water. Enzymes (GOx alone or in combination with catalase) were encapsulated into asymmetric polymersomes by using a technique based on electroporation (Figure 4B). As the enzymes reacted with their respective substrates, the confined reactions could produce a flux of products that were preferentially expelled out of the polymersomes from the most permeable patch. This in turn generated a localized gradient of the products that should set up the conditions for self-propulsion.

In addition to the organic stomatocyte structure, hollow SiO₂ nanomotors with catalysts loaded in the nanocavities have been synthesized. Yi et al. reported a flask bottle-like nanomotor. The chemically asymmetric SiO₂ nanobottles with a diameter of ~350 nm and an opening of ~100 nm were first synthesized by an
anisotropic sol–gel growth in a water/pentanol emulsion. Citrate-capped PtNPs were selectively loaded into the hydrophilic cavity of nanobottles by hydrogen bonding between the PtNPs and the interior surface of the nanobottles (Figure 4C). The PtNPs@nanobottle nanomotors can be self-propelled by the catalytic decomposition of H₂O₂.[64] Ma et al. reported tadpole-like mSiO₂ nanomotors with a big streamlined head and a slender tail, which exhibited large inner cavities (75–170 nm) and the tail length can also be regulated from 30 to 650 nm. The streamlined hollow mSiO₂ nanoparticles with controllable surface curvature were synthesized via an interfacial dynamic migration strategy.[66] By selectively loading the Fe₃O₄ catalyst in the cavity of the streamlined SiO₂ nanotadpoles, the H₂O₂-driven mesoporous nanomotors were designed. The Fe₃O₄ catalyzed the decomposition of H₂O₂ fuel, producing a large local dissolved-oxygen concentration gradient for efficient self-diffusiophoretic propulsion with directionality.

Kwon et al. prepared a noble metal-based hollow nanomotor (Au/Pt-egg-in-nest nanomotors) by using a dynamic-casting approach. A large Au-seed was fixed in a SiO₂-yolk nanoreactor, which provides an anisotropically confined concave hollow nanospace to grow curved Pt-dendritic networks (Figure 4D).[65] Owing to the intimately interfaced Au and Pt catalytic sites integrated into a unique anisotropic nestlike morphology, Au/Pt-egg-in-nest nanomotors exhibited high diffusion rates and displacements as the result of a glucose-converted O₂ concentration gradient. The nanomotors showed enhanced motion as a result of dual enzyme-relay catalytic cascade in physiological biomaedia.

With rapidly developed nanotechnology, colloidal chemistry methods are able to finely tune the shapes, sizes, and components of the nanostructures. They, together with appropriate surface modification technology, can be used to fabricate multifunctional nanomotors, thus enriching their application scenarios.

3 | MOTION CHARACTERIZATION FOR NANOMOTORS

Common techniques for the characterization of the movement of motors do not work when the size of motors is reduced to the nanoscale. In fact, it is somewhat difficult to track the motion trajectory of nanomotors. It is general to use the motion speed and diffusion coefficient obtained to evaluate the motion behaviors of nanomotors. Here, we summarize the characterization techniques used for evaluating the motion behaviors of nanomotors, which can be divided into statistical and microscopic methods based on whether they can characterize a single nanomotor or not.

3.1 | Statistical characterization techniques

Owing to the serious influence of Brownian motion, most of the nanomotors display enhanced diffusion in the presence of fuels or external fields. In this subsection, we discuss statistical characterization techniques for evaluating the motion behaviors of nanomotors, including dynamic light scattering (DLS), fluorescence correlation spectroscopy (FCS), and nanoimpact voltammetry. They all can provide the diffusion coefficient of a swarm of active nanomotors.

As the most widely used statistical characterization technique for the motion behaviors of nanomotors,[62,62,83] DLS is based on detecting the fluctuations in scattered light of the nanomotors, as shown in Figure 5A. Assumed that the intensity of scattered light independent of points in a time defined as delay time (τ), and the correlation coefficient is 1, the autocorrelation function (ACF) can be obtained as below:[84]

\[ G(\tau) = 1 + b \cdot e^{-2D_c q^2 \tau} \]  \hspace{1cm} (1)

where \( b \) is the constant dependent on the instrument and settings, \( D_c \) is the translational diffusion coefficient, and \( q \) is the scattering vector, which can be expressed by the following equation:

\[ |q| = \frac{4\pi n_0}{\lambda_0 \sin \frac{\theta}{2}} \]  \hspace{1cm} (2)

where \( n_0 \) is the refractive index of the solvent, \( \lambda_0 \) is the wavelength in vacuum, and \( \theta \) is the scattering angle. It provides the \( D_c \) of nanomotors in solution, and thus the diameter by Stokes–Einstein equation. DLS is suitable for monodisperse particles with a size range of 1 nm to 10 μm.[85] Lee et al. verified the enhanced diffusion of the ellipsoidal Janus Au-Pt nanomotors in the presence of H₂O₂.[35] It is worth mentioning that nanomotors with the shape or optical anisotropy can cause intensity fluctuations during the flipping process, which is related to the rotational diffusion coefficient (\( D_r \)). In the presence of H₂O₂ fuel, \( D_r \) of Pt–Au nanomotors with catalytic activity increased by about 20% and \( D_r \) decreased by about 40% compared with that of Au–Au nanoparticles without catalytic activity.

FCS is an optical method that can be used to detect the motion behaviors of fluorescent nanomotors (Figure 5B).[87] By detecting the fluctuations in fluorescence signal of nanomotors, the ACF is calculated by
Equation (3), which always has a great approximate with 3D Gaussian profile:  
\[ G(\tau) = \frac{\langle \delta F(t) \delta F(t + \tau) \rangle}{\langle F(t) \rangle^2} = \frac{1}{N} \left( 1 + \frac{\tau}{\tau_D} \right)^{-1} \left( 1 + \frac{\tau}{S^2} \right)^{-\frac{1}{2}}, \]  
where \( F(t) \) is calculated by \( \langle F(t) \rangle = \frac{1}{T} \int_0^T T(t) dt \), which represents the fluorescence intensity at time \( t \), \( N \) is the average number of nanomotors in the effective detection volume. The diffusion time \( \tau_D \) can be used to calculate \( D_t \), 
\[ \tau_D = \frac{w_0^2}{4D_t}. \]  

This approach is appropriate for the fluorescent dye-labeled nanomotor in the <300 nm range. It can only detect the motion of fluorescent particles but not of unlabeled impurities, showing an advantage in selectivity. In addition, FCS only requires very low sample concentrations (pM–nM), avoiding the interference caused by the aggregation of particles and high concentrations of products. For reliable FCS measurements, it is essential to guarantee that only a single kind of fluorescent reagent is present in the solution. By using this method, several enzymes were found to display enhanced diffusion at solution containing the corresponding substrates.

Nanoimpact voltammetry, also called particle-electrode impact voltammetry, can be used to measure the motion behaviors of nanomotors of metallic nanoparticles and proteins with a size ranging from 1.5 to 100 nm. As shown in Figure 5C, the nanomotors randomly collide on the surface of the microelectrode and generate a characteristic current peak. Ignoring convection in a small volume of a sample, we can describe the progress of mass transport by the following equation:  
\[ \partial_t c(\vec{r}, t) = \sum_i \sum_j \partial x_i D_{ij} \partial x_j c(\vec{r}, t) = D_t \Delta c(\vec{r}, t), \]  
where \( c \) is the concentration of nanomotor at the time \( t \) and the position \( \vec{r} \), and \( D_{ij} \) is the tensor of the \( D_t \), agglomeration, and related information can be obtained from Equation (5) by analytical, computational, and Monte Carlo methods. It allows the measurement of a single particle in its native state without molecular modifications using cost-effective experimental setups.

### 3.2 | Microscopic characterization techniques

Unlike statistical characterization techniques, microscopic characterization techniques can provide the motion information of a single nanomotor, such as direction.
and trajectory. In this subsection, optical microscopy and nanoparticle tracking analysis (NTA) are summarized below.

Optical microscopy is most widely used for the characterization of the motion behaviors of nanomotors.\cite{63,72,74,84} The motion behaviors of a single nanomotor can be clearly imaged on the screen of a computer. By tracking the trajectory of a nanomotor with commercial software, its coordinates with time are obtained for calculating the mean square displacement (MSD), $D_t$, and speed. Considering the optical diffraction effect, white-light optical microscopy (Figure 6A)\cite{96} only...
applies for nanomotors of larger than 200 nm.\textsuperscript{[57]} This size limitation may be overcome with confocal laser scanning microscopy (CLSM, Figure 6B) when a small pinhole is set near the object to restrict the radiation field.\textsuperscript{[97]} He et al. studied the motion behaviors of the fluorescein isothiocyanate (FITC)-labeled NIR-driven Janus mSiO$_2$ nanomotors with a size of 50 nm by two-photon CLSM.\textsuperscript{[38]}

Dark-field microscopy (Figure 6C) has been used to observe the motion behaviors of noble metal-based nanomotors.\textsuperscript{[35,99,100]} Upon the illumination of light with a matching frequency, the free electrons in noble metals collectively oscillate in resonance with the light (known as localized surface plasmon resonance [LSPR]), leading to enhanced scattering and absorption spectra, which rely on Mie theory\textsuperscript{[98]}:

$$E(\lambda) = \frac{24\pi^2N\lambda^2\varepsilon_{\text{out}}^2}{\lambda \ln(10)} \left[ \frac{\varepsilon_i(\lambda)}{\left(\varepsilon_i(\lambda) + \chi \varepsilon_{\text{out}}^2 \omega^2 + \varepsilon_i(\lambda)^2\right)} \right],$$

(6)

where $N$ is the number of nanoparticles, $a$ is the radius of the nanoparticles, $\varepsilon_i$ and $\varepsilon_r$ are the real and imaginary components of the metal-dielectric function, respectively, $\varepsilon_{\text{out}}$ is the dielectric constant of the medium surrounding the nanoparticle, and $\chi$ is the correction factor. This LSPR effect makes it easy to observe the motion of noble metal-based nanomotors in dark-field microscopy. Ji et al. recorded the movement trajectory of a GOx-powered Janus nanomotor with a 20 nm Au core by dark-field microscopy, concluding that the motion of polymer brush nanomotors increased more than that of nanomotors without polymer brush with the same increase of glucose concentration.\textsuperscript{[59]}

NTA (Figure 6D) combines the laser light-scattering technique with a charge-coupled device (CCD) camera. It is typically used to track particles between 30 and 1000 nm in real-time as they move through a solution.\textsuperscript{[57,58,63,83,101,102]} In a quite short time interval $t$, the movement of particles is recorded and calculated as below:

$$D_{tx} = \frac{\langle x^2 \rangle}{2t},$$

(7)

$$D_{ty} = \frac{\langle y^2 \rangle}{4t},$$

(8)

$$D_{tz} = \frac{\langle z^2 \rangle}{6t}.$$  

(9)

Depending on the dimensions of data recorded by NTA, Equations (7–9) can be used to calculate the $D_t$ of the one, two, and three dimensions, respectively. Using NTA to observe the trajectories and the calculated MSDs of bowl-shaped stomatocyte nanomotors of 152 ± 50 nm in diameter, Wilson et al. indicated that the stomatocyte nanomotors showed a fuel concentration-dependent directional movement.\textsuperscript{[61]}

Besides, emerging new characterization technologies for nanoscale particles are also worthy of being explored to characterize the motion behaviors of nanomotors. For example, the newest model of ZEISS’s ultrahigh resolution living cell imaging system can be used to observe the nanostructures as small as 60 nm at a speed of up to 255 frames/s, and collect the 3D images of them.

### 4 Motion Behaviors of Nanomotors

Compared with micromotors, nanomotors are strongly affected by the Brownian forces due to the nanometer size. Thus, most of them exhibit enhanced diffusion or ballistic motion, while some nanomotors with special nanostructure or under the guidance of external fields or the chemical gradients show directional motion.

#### 4.1 Enhanced diffusion and ballistic motion

When the size of motors decreases to the nanoscale, the random Brownian forces become dominant. This makes it difficult for small-sized nanomotors to display ballistic motion, which their micro-scaled counterparts generally perform. The motion behaviors of nanomotors are mainly determined by the structure. Most defect-dominated and Janus spherical nanomotors exhibit enhanced diffusion.\textsuperscript{[35–37,39,41,43]} For instance, the urease-symmetrically modified mSiO$_2$ nanomotors (344 nm in diameter) presented by Sánchez et al. displayed enhanced diffusion in urea aqueous solutions (100 mM urea) with an increase in the diffusion coefficient of about 35% (Figure 7A).\textsuperscript{[43]} For the urease-powered Janus nanomotors (390 nm in diameter), the apparent diffusion coefficient of the nanomotors was found to be increased by 52% at 25 mM urea compared to without fuel.\textsuperscript{[39]} The results indicated that the nanomotor with a Janus structure showed a stronger driving force than those with defect-dominated with a similar size. Apart from enhanced diffusion, a small number of Janus nanomotors exhibit ballistic motion. Diez et al. reported a Janus Pt–mSiO$_2$ nanomotor with a directional movement and an average speed of 19.4 μm/s in a phosphate-buffered saline (PBS) buffer solution containing 0.35% H$_2$O$_2$. 

The significantly improved propulsion of the nanomotor was attributed to the major roughness and active catalytic area of the dendrites-like structure of Pt segment. The hollow nanomotor with a concave cavity always showed ballistic motion owing to the confined space structure. The bowl-shaped stomatocytes nanomotors prepared by Wilson et al. exhibited ballistic motion in the fuel solution. When the PtNPs were encapsulated in the cavity of the stomatocyte, the nanomotors showed obvious directional movement with an average speed of 23 µm/s in 100 mM H₂O₂ aqueous solution. When the catalysts were replaced by catalase molecules, the nanomotors ran at a remarkably high speed of 60 µm/s, three times higher than that of Pt-driven counterparts. The high efficiency was most probably attributed to both the high catalytic activity of the catalase molecules and the excellent encapsulation efficiency compared with the catalytically active PtNPs. When the catalase-encapsulated stomatocyte nanomotors were reduced to 150 nm, they could still move with a speed of 20 µm/s in a 20 mM H₂O₂ aqueous solution, which was quite fast when compared to other motors of similar size (Figure 7C). Except for hollow nanomotors, most recently reported nanomotors suffered from weak driving forces. It was worth noting that the motion behaviors of nanomotors were mostly evaluated in water medium with negligible ionic strength. As body fluids or biological media always contained various components (e.g., ions and proteins), the motion performance of the nanomotors in them would be greatly affected. To achieve the practical applications of nanomotors in complicated biological environments, the motion behaviors should be systematically evaluated in different biological media, while the propulsion...
mechanisms should be clarified for enhanced motion performances.

4.2 | Motion manipulation

To achieve the biomedical application in a complicated environment, nanomotors must have the ability to reach a specified position,[103] though the strong random Brownian forces make them difficult to perform an on-demand movement.[31]

Like micromotors, nanomotors with magnetic- or light-responsive components incorporated may also be guided by external fields, such as $H$ and light.[38,49,74,104] As a demonstration, Wilson et al. reported the $H$-regulating motion direction of a magnetically actuated stomatocyte nanomotor by encapsulating Ni–Pt nanoparticles inside the nanocavity of stomatocyte (Figure 8A).[74] Qiu et al. reported a bottle-like mSiO$_2$ nanomotor with Fe$_3$O$_4$ nanoparticles uniformly assembled on its inner and outer surfaces, which endowed them with the guidance by $H$.[104] Xuan et al. demonstrated the movement of a NIR-driven Janus Au–mSiO$_2$ nanomotor toward lower light intensities in an inhomogeneous laser field (Figure 8B).[38] Upon illumination of an NIR laser, the Au half-shell of the nanomotor could be heated by a photothermal effect and result in thermophoretic slip flows, which allowed the nanomotors to align under the phoretic aligning torque and escape from regions of high light intensity, exhibiting negative phototaxis. The strategies could precisely control the direction, speed, and start/stop of nanomotors by tuning the parameters of the external fields.

**FIGURE 8** Representative manipulation techniques for controlling the movement direction of nanomotors. (A) The movement direction of a Ni–Pt nanoparticles loaded stomatocyte nanomotor actuated by the magnetic field. Reproduced with permission.[74] Copyright 2017, Wiley-VCH. (B) The movement direction of a Janus Au–mSiO$_2$ nanomotor controlled by NIR light. Reproduced with permission.[38] Copyright 2016, American Chemical Society. (C) Enzyme-coated liposome nanomotors exhibit both positive and negative chemotaxis. Reproduced with permission.[54] Copyright 2019, Nature Publishing Group
Taking the advantage of ubiquitous chemical gradients in biological scenarios, chemotactic nanomotors are attractive in biomedical applications.\[103\] When motors swim in solutions with fuel concentration gradients, asymmetric phoretic slip flows will induce around them, generating torques to align and exhibit chemotaxis.\[105\] It has been reported that catalytical nanomotors are capable of responding to the overexpressed chemicals related to tumors, such as $\text{H}_2\text{O}_2$, glucose, and acid.\[55,63,76,77\] Somasundar et al. demonstrated that the liposome modified with enzymes would exhibit chemotaxis (Figure 8C).\[54\] Catalase-coated liposomes undergo positive chemotaxis in a gradient of $\text{H}_2\text{O}_2$, while urease-modified liposomes display negative chemotaxis in a gradient of urea. Joseph et al. reported that the glucose oxidase and catalase-encapsulated asymmetric polymersome nanomotors displayed positive chemotactic motion along the concentration gradient near a glucose resource by inducing a slip velocity on their surface.\[63\] In combination with low-density lipoprotein receptors, they were capable of a fourfold increase in penetration to the brain compared to nonchemotactic systems. Wilson and coworkers fabricated nanomotors by growing in situ CaCO$_3$ nanoparticles inside supramolecular architectures, which under slightly acidic pH conditions could autonomously migrate toward HeLa cells using pH taxis.\[62\] Tu et al. prepared a DNase functionalized Janus nanomotor that could sense the subtle DNA gradient generated by apoptotic tumor cells and showed directional movement toward tumor cells.\[58\] The chemotactic nanomotors are able to implement intelligent self-navigation and self-targeting in complex environments, which allow them to achieve in vivo active cargo delivery.

Although the motion direction of nanomotors can be maneuvered by both external fields and chemical concentration gradient, it is still a great challenge to employ them in practical environments. The reported external field-based methods are difficult to control the small-sized nanomotors. Besides, the recently developed chemotactic nanomotors can only sense a concentration of chemical signals much bigger than that in biological environments. It is necessary to significantly improve the sensing sensitivity of chemotactic nanomotors.

## 5 BIOMEDICAL APPLICATIONS OF NANOMOTORS

Complex biological environment and physiological obstacles bring about the difficulty for conventional passive nanocarriers to accumulate and infiltrate in an effective efficiency in targeted tissues or cells. In the case of cancer treatment, for example, more than 95% of passive nanocarriers present serious side effects to other organs.\[7\] With autonomous locomotion properties, MNMs have shown considerable promise to revolutionize the diagnosis and treatment of diseases by actively targeting the lesion location. For the treatment of many major diseases (e.g., tumors), the drug carriers need to enter cells, which requires motors in nanoscale. In this section, we summarize the recent developments of in vitro and in vivo active drug delivery by nanomotors in detail.

### 5.1 Cardiovascular disease therapy

Cardiovascular diseases, such as hyperlipidemia, blood stickiness, atherosclerosis, and hypertension, seriously threaten human life and health.\[106\] Owing to the poor penetration, the passive drug delivery systems for the treatment of cardiovascular disease always suffer from low drug utilization rates and unsatisfactory therapeutic effects.\[49,107–109\] The emergence of nanomotors technology may offer new perspectives.

Sánchez et al. reported lipase-powered nanomotors with stochastic binding of lipase on mSiO$_2$ nanoparticles, able to swim in triglyceride-containing PBS solutions.\[46\] Compared to free lipase, the lipase-powered nanomotors showed an enhanced degradation efficiency of slightly dissolvable triglycerides (tributyrin drops) with a very high degree (−98% with 50 min), as shown in Figure 9A. The results suggest that the nanomotors have applications in remedying high-triglyceride-related diseases. Atherosclerosis is one of the most important cardiovascular diseases that greatly threatens human health. Mao et al. demonstrated paclitaxel-loaded platelet membrane bionic Janus mSiO$_2$ nanomotors for the treatment of atherosclerosis, as shown in Figure 9B.\[108\] Upon the NIR irradiation, the nanomotors can not only penetrate into the plaque but also be effectively taken up by activated endothelial cells and inflammatory macrophages. The cell viability decreases to 12.6% after incubation with the nanomotors for 48 h, indicating that the nanomotors can effectively complete the ablation of the macrophages. In vivo results show that the nanomotors can promote drug retention in the plaque area and effectively decrease the vascular proliferation area through the combination treatment of photothermal and drug therapy. In their latest work, the dual-mode propulsion nanomotors that were sensitive to high reactive oxygen species (ROS) and NIR laser were applied to regulate the microenvironment of atherosclerosis in multiple ways. The amount of nanomotors with dual-mode propulsion in the aorta of mice is about 3.3 times more than that without the illumination of the NIR laser. After the 2 months of treatment by
dual-mode propulsion nanomotors, the aortic plaque areas of mice are dropped from 28.4% to 5.2%. Meanwhile, the Au content in the aorta of mice is up to 0.2470 mg/g, much higher than that in other organs (not exceeding 0.0037 mg/g), indicating that the nanomotors have a good targeting ability.[109] In another field, Mao’s group fabricated platelet-derived porous nanomotors for thrombus therapy (Figure 9C).[49] The self-driven
nanomotors that were coated with platelet membrane, which contain GPIIb/IIIa complex could target the thrombus site and realize the effective aggregation. Under the irradiation of the NIR laser, the nanomotors infiltrated into the thrombus, accompanied by the rupture of the platelet membrane caused by the photothermal effect. Without the protection of the platelet membrane, the urokinase located in the outer macro pores of the nanomotors could release rapidly in 3 h to dissolve the thrombus. Then the nanomotors loading with Hep penetrated into blood vessels and slowly released the anticoagulant drug for at least 20 days to prevent thrombus recurrence. More recently, Zhang and coworkers reported a magnetic field-propelled microswarm constitue of Fe3O4 nanoparticles for the dissolution of thrombus.110 Guided by ultrasound imaging and adjusted by an oscillating H, the microswarm could be navigated toward clot regions and deformed to adapt to different widths of blood clots. Experimental results showed that the three-dimensional (3D) flow generated by the microswarm could enhance the fluid convection and shear stress around the blood clots. On the basis above, microswarm collaborated with tissue plasminogen activator (tPA) was able to achieve a 3.13-fold lysis rate of dissolve thrombus compared with that using tPA drug only. The abovementioned examples have already indicated that using self-driven nanomotors as drug carriers can improve the depth of drug penetration in diseased sites, which will bring effective ideas for cardiovascular disease therapy in the near future.

5.2 Tumor therapy

Due to the autonomous movement ability, nanomotors have a great potential to serve as active drug or drug delivery carriers to improve the treatment of cancer.7 Recent studies focused on the two-dimensional (2D) cellular models.43,44,60,79,111,112 Sánchez et al. presented urease-powered mSiO2 nanomotors for doxorubicin (DOX) anticancer drug loading, release, and efficient delivery to cells.43 A fourfold increase in drug release was achieved by nanomotors after 6 h compared to their passive counterparts. Higher content of DOX inside HeLa cells was detected after incubation with active nanomotors compared to passive DOX-loaded nanoparticles. The improvement in drug delivery efficiency could be attributed to a faster release of drugs to the media, increased transport near or inside the cell and increased cell uptake of the nanomotors. Following this study, they introduced pH-responsive supramolecular nanovalves on the surface of mSiO2 nanomotors for stimuli-responsive antitumor drug release, as shown in Figure 10A.44 The encapsulated DOX can only be released after nanomotor internalization in cells due to the pH-triggered de-threading of the nanovalve. Studies with HeLa cells indicate that the presence of urea enhances nanomotors’ internalization (2.4 times larger than their static counterparts) and drug intracellular release due to the acidity of lysosomal compartments. Nanocarriers with a size of about 20–200 nm are more beneficial to overcome cell barriers and accumulate around tumors through the EPR effect than those of other sizes. This is also a common strategy for enhancing passive targeting capabilities. Based on it, Wilson et al. demonstrated a bowl-shaped stomatocyte nanomotor of about 150 nm which encapsulated biocatalyst catalase molecules in its nanocavity.79 With a small size and self-propulsion, the nanomotor is able to efficiently penetrate a confluent monolayer of pulmonary artery endothelial cells and be internalized into HeLa cells in the presence of H2O2 or not. It is approved by 2D cellular models that the self-propelled nanomotors have the ability to greatly improve cellular uptake efficiency and enhance the permeability of the vascular wall.

To better mimic real tumor environments in vitro, a 3D multicellular tumor spheroid was used as a model to evaluate the penetration ability of nanomotors.45,48,102,113,114 Sánchez et al. demonstrated a urease-powered mSiO2 nanomotor modified with a specific bladder cancer antibody on its surface for the active targeting of bladder cancer cells in 3D tumor spheroids (Figure 10B).45 The nanomotors improved the chances of the antibody to contact with the antigen, thus enhancing the penetration into the spheroid. In combination with the targeting and motion capabilities, its internalization efficiency in 3D tumor spheroids was improved almost 14 times higher than that of passive particles without antibodies. Compared with the bare one, the targeted nanomotor presented stronger inhibitory effects on spheroid proliferation, suggesting that the antibody-modified nanomotor possessed huge potential as a tool for targeting bladder cancer treatment.

Owing to the good performance in vitro evaluation, the proof-of-concept studies on the nanomotor-based active delivery systems have also been done by testing the utility and performance in animals.148,60,113–115 Mao et al. developed an NIR-driven mesoporous-macroporous SiO2–Pt nanomotor for studying permeability of nanomotors in 3D multicellular tumor spheroid and in vivo models (Figure 10C).46 In the 3D multicellular tumor spheroid model, the nanomotor under NIR irradiation showed a penetration depth of about 110 μm, much larger than that of passive
nanoparticles of about 60 μm. In in vivo model, the fluorescence signals were found to distribute in the whole tumor tissue when treated with the nanomotors under NIR irradiation. Both of them indicated that the movement of the nanomotor can greatly enhance the permeability of loaded drugs in tumor tissue. In another example shown in Figure 10D, Mao et al. reported that the penetration distance of nanomotors was 150 μm which was longer than that of non-nanomotors (50 μm), indicating the effective intracellular drug distribution by nanomotors.\[113]\n
They observed good performances of nanomotors by detecting the biological distribution, tumor enrichment effect, as well as the therapeutic effect in vivo. These prior in vivo studies have obviously cleared a path toward direct evaluation of disease-oriented therapeutic efficacy associated with nanomotor-enabled active drug delivery. More recently, Wei et al. developed NO-driven nanomotors to promote the degradation of tumor blood vessels and ECM, significantly improving the ability of immune cells to infiltrate the tumor in vivo. They evaluated the stability of nanomotors during blood circulation, which followed a typical one-compartment model. Both the subcutaneous and abdominal tumor models confirmed that the nanomotors showed good antitumor activity.\[115]\n
In general, all the experiment animals mentioned above carried out no obvious abnormalities in body weight, major organs or blood tests, demonstrating good biocompatibility of nanomotors.

Above all, the autonomous movement of up-to-date nanomotors can increase their cell uptake efficiency and tissue penetration ability to a certain extent. There is some evidence to confirm that compared with passive nanocarriers, nanomotors can enhance the therapeutic effect of the treatment of cardiovascular and tumor diseases, performing a good targeting ability. Nevertheless, more relevant statistical results are necessary to show the targeting efficiency of nanomotors in tumor sites. However, as most of the reported nanomotors can only drive in a disease area and lack the ability to actively target disease sites, they have not fundamentally solved the problem faced by passive nanocarriers. Subsequently, the research topic should focus on how to realize the motion control of nanomotors in complex biological environments.

6 CONCLUDING REMARKS AND FUTURE OUTLOOK

In the last decade, remarkable progress has been made in the fabrication, locomotion characterization, and manipulation, as well as biomedical applications of nanomotors. A large number of nanomotors with various sizes, shapes, and components have been fabricated by physical vapor deposition techniques and colloidal chemical methods. They are able to perform enhanced diffusion or ballistic movement depending on their structure. The directional movement of nanomotors is to some extent realized with the assistance of external fields and chemical gradients. Encouragingly, several proof-of-concept studies of both in vitro and in vivo environments have demonstrated that the nanomotor-based active drug delivery systems are able to remarkably improve the therapeutic effect of tumor and cardiovascular disease therapy compared to their static counterparts. Despite great achievements, nanomotors are still in their infancy. There are at least several fundamental scientific issues that need to be understood before nanomotors can be put into practical biomedical applications, as illustrated in the following.

6.1 How to clarify the propulsion mechanisms of nanomotors?

Most of the recently developed nanomotors display enhanced diffusion, while a few nanomotors with special structures show ballistic motion. The bowl-shaped stomatacyte nanomotors are considered to be propelled by a bubble recoil mechanism, but no visible bubbles are observed in the system. So far, there are few studies on the propulsion mechanisms of nanomotors due to the restriction of motion characterization techniques. In addition, the motion performance of nanomotors will be remarkably suppressed in biological environments, which was considered to be caused by the existence of a high concentration of ions and high viscosity. Apart from different ions, there are various components in biological media. For instance, the blood contains a large amount of proteins and red blood cells. It is necessary to figure out

**FIGURE 10** Representative nanomotors for cancer therapy. (A) Urease-powered mSiO2 nanomotors for pH-responsive antitumor drug release. Reproduced with permission.\[44\] Copyright 2019, American Chemical Society. (B) Urease-powered mSiO2 nanomotors for the enhancement of the penetration ability on three-dimensional (3D) multicellular tumor spheroid. Reproduced with permission.\[45\] Copyright 2019, American Chemical Society. (C) NIR-driven mesoporous-macroporous SiO2–Pt nanomotors for in vitro and in vivo tumor permeation efficiency research. Reproduced with permission.\[48\] Copyright 2020, Wiley-VCH. (D) Zwitterionic polymer-based H2S-driven nanomotors for the evaluation of in vivo penetration depth and biodistribution of self-propelled nanomotors. Reproduced with permission.\[113\] Copyright 2021, Wiley-VCH
the relation between movement behaviors of nanomotors and these components parameters. Understanding the physicochemical mechanisms behind these problems will help to find the strategies to improve the driving force of nanomotors. Several examples have demonstrated that the driving force of nanomotors can be dramatically improved by designing nanostructures with a confined space.\cite{61,63-65} In addition, the methods used to improve the catalytic efficiency of nanoparticles in the field of catalysis might be an alternative solution.\cite{70}

### 6.2 How to achieve motion manipulation of nanomotors in complicated biological environments?

As summarized in Section 4, external fields can be used to precisely regulate the speed, direction, and on/stop of the nanomotors over a long distance, while the chemotaxis can be utilized to control the movement direction of nanomotors in complicated environments over a short distance.\cite{106} Therefore, the combination of external fields and chemotaxis on one nanomotor might be beneficial for motion manipulation in complicated biological environments. The nanomotor can migrate to the position near the diseased area by regulating with external fields, and then actively seek for the diseased area by sensing the chemical signals released by the lesions. To achieve this goal, two issues need to be resolved: First, it is necessary to build a system that integrates the clinically noninvasive imaging, feedback, and manipulation functions for external field motion manipulation. Second, the chemotactic ability of nanomotors should be improved to match the actual application requirements.

### 6.3 Systematic research of the performance of nanomotors in vivo

Most of the current studies utilize in vitro models and focus primarily on the cellular uptake efficiency and penetration ability of self-propelled nanomotors. Different from in vitro applications, in vivo applications, especially for those related to the blood circulation system, are more complicated. Like passive nanostructures, nanomotors will certainly encounter various biological barriers upon entering the body. To reduce the clearance by the immune system, the surface of nanomotors is required to be modified with appropriate functional groups (e.g., PEG or cell membrane). In addition, the nanomotors should be propelled by biocompatible energy and fabricated by biodegradable materials. After finishing their task, the nanomotors can be self-destructed under certain conditions and then degraded to nontoxic substances. Thus, more systematic research is required to be done in vivo models to address a number of issues, including the avoidance or suppression of immune responses, and the selectivity and efficiency in terms of targeting, biodistribution, biodegradation, clearance, and toxicity.

In summary, a clear understanding of the propulsion mechanism of nano-sized motors is a precondition for designing high-efficient nanomotors. Intelligence and multifunction are the ultimate research goals of nano-sized motors. Although there is a long way to go to translate robust minimized motors from bench to bedside, considerable progress is being made bringing fantasy closer to reality.

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**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

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