Nano/Microscale Motors: Biomedical Opportunities and Challenges

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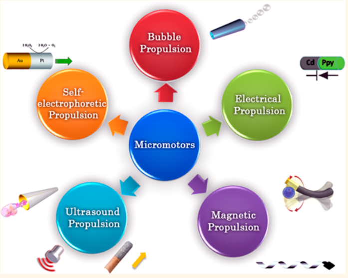
ABSTRACT Artificial nano/microscale machines hold great promise for diverse future biomedical applications. This Perspective summarizes recent advances in microscale motors, as exemplified by Hoyos and Mallouk in this issue of *ACS Nano*, and highlights the challenges and opportunities in translating this remarkable progress toward practical biomedical applications. Various areas of medicine, including targeted drug delivery, precision nanosurgery, biopsy, cell sorting, or diagnostic assays, would benefit from recent developments of efficient fuel-free and fuel-driven nano/microscale machines. Newly introduced ultrasound-driven propulsion mechanisms greatly enhance the prospects for these biomedical applications. With continuous innovation and attention to key challenges, we expect that man-made nano/microscale motors will have profound impact upon different medical areas.



The 1966 movie *Fantastic Voyage* captured the world's imagination, portraying a tiny submarine navigating through the human bloodstream and treating life-threatening medical conditions. Nearly five decades later, science is starting to catch up to the fiction of Hollywood. Recent advances in synthetic nano/microscale machines may help to realize the *Fantastic Voyage* vision of delivering therapeutic and diagnostic agents to previously inaccessible areas of the body.

A variety of fuel-driven and fuel-free microscale motors, developed during the past decade (Figure 1),[1−5] offer great promise for diverse biomedical applications. The sophistication of these tiny man-made machines has been increasing rapidly over the past five years and provides unlimited opportunities. As new capabilities are developed and proper attention is given to key challenges, these nanovehicles could realistically be used for a broad range of important biomedical applications, ranging from directed drug delivery to biopsy and from cleaning clogged arteries to precision nanosurgery or transport of radioactive seeds to tumor locations. In this Perspective, we summarize recent progress toward biomedical applications of microscale motors and highlight key challenges for realizing these opportunities.

Considerable efforts have been devoted to chemically powered micro/nanoscale motors based on surface catalytic decomposition of a solution-borne fuel, usually hydrogen peroxide.[6−14] Particular attention has been given to catalytic nanowire motors[6−8] and microtubular engines[11−14] (Figure 1, top). The latter rely on an oxygen-bubble thrust and possess the relatively high power that is essential for performing different biomedical tasks (*e.g.*, cargo towing and biomaterial drilling), as reflected by their remarkable speed, which can exceed 1000 body-lengths/s.[15] Motion control, which is another important requirement for diverse biomedical applications of catalytic nanomotors, has been accomplished by magnetically guiding their directionality and regulating their speed using different stimuli.[16] Unfortunately, the self-electrophoretic mechanism of catalytic nanowires is not compatible with high-ionic-strength biological fluids. In addition, due to the requirement for the hydrogen peroxide fuel, *in vivo* applications of current catalytic nanowire and microtubular motors face significant challenges.

To enhance biocompatibility, several groups have also explored fuel-free micro/nanomachine propulsion mechanisms based on externally applied magnetic or electric fields.[17−21] Magnetically driven micromotors, which swim under externally applied magnetic fields, are particularly attractive for a variety of biomedical applications because they can perform complex maneuvers and demanding tasks while obviating fuel requirements. These micromotors include magnetically driven helical (cork-screw) microstructures,[17,18] and flexible[19] or tumbling[20] nanowires (Figure 1, bottom right). In the following sections,

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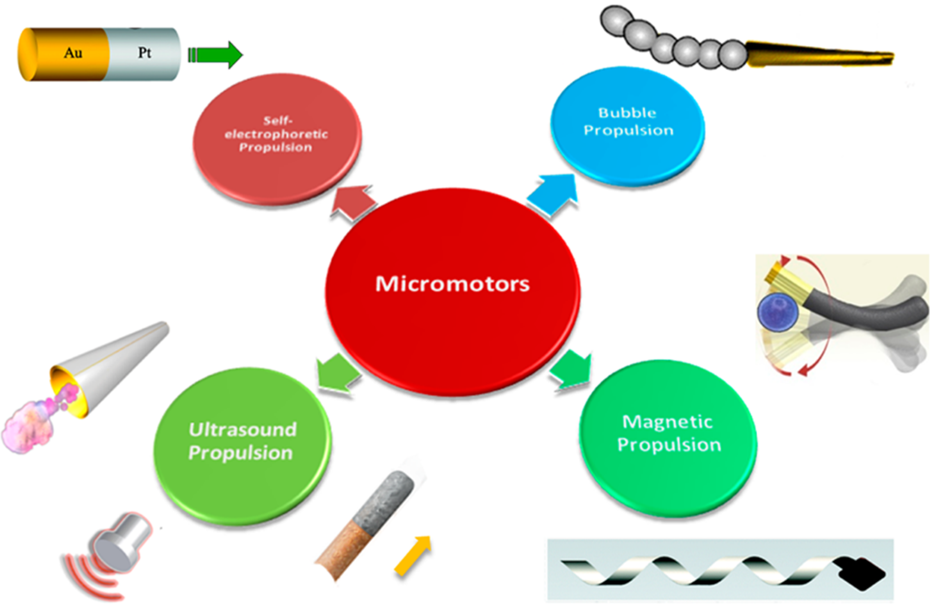

Figure 1. Micromotors powered by different mechanisms.

we explore the outlook for recently developed nano/microscale motors in medicine and the challenges that lie ahead.

The Arrival of Ultrasound-Driven Locomotion. Despite recent advances in fuel-free microscale motors, there continues to be a need for a biocompatible energy transduction mechanism that can power micromotors. In this issue of *ACS Nano*, Hoyos and Mallouk describe exciting experiments in which ultrasonic acoustic waves can propel template-grown metallic nanowires in fast (~200 μm/s) axial directional motion and in-plane rotation.[22] In particular, their article illustrates that MHz frequency acoustic waves can propel, align, rotate, and assemble metallic nanowires in aqueous media (Figure 2A). Such propulsion has been attributed primarily to a locally induced pressure gradient associated with the concave end of the nanowires (Figure 2A,e), which leads to directional motion by a self-acoustophoresis mechanism. The significance of these findings lies in the possibility of using ultrasound for driving and controlling micromachines in biologically relevant environments.

Parallel efforts by Esener and Wang at UCSD have illustrated powerful ultrasound-driven "microbullets", possessing sufficient force to penetrate, to cleave, and to deform cellular tissue (Figure 2B).[23] These microbullets utilize the rapid expansion and vaporization of perfluorocarbon emulsion droplets—confined to the microtubular machine interior—triggered by an ultrasound pulse (analogous to the externally triggered explosion experienced within a gun barrel). Such acoustic droplet vaporization of an on-board biocompatible fuel accelerates the conical microtube like a bullet and leads to a remarkable speed of over 6 m/s (*i.e.*, approximately 1000 times faster than previous micromachines). This propulsive power is sufficient to penetrate tissue and to overcome cellular barriers (Figure 2B,c). An embedded magnetic layer permits externally guided magnetic alignment for precision steering. Overall, these parallel pioneering proof-of-principle studies indicate exciting possibilities for ultrasound-driven motors in medicine.

Ultrasound applications in medicine are extensive.[24] In particular, ultrasound is the most widely used clinical cross-sectional imaging technique for viewing internal body organs.[25] It has also played a growing role in the delivery of therapeutic agents.[26] Ultrasound is an acoustic (sound) energy in the form of waves having a frequency above the human hearing range (*i.e.*, at frequencies above 20 kHz). Such high-frequency sound waves have minimal deleterious effects on biological systems.

Toward Drug Delivery. A bottleneck in nanoparticle-mediated drug delivery is the poor tissue penetration of the nanoparticle carrier and its therapeutic cargo. To combine active targeting with precise guidance and control, future generation drug-delivery vehicles will require powerful propulsion and navigation capabilities in order to deliver payloads to predetermined body locations. Major research efforts have thus been devoted to searching for the magic bullets to target and to treat cancer. Nanoshuttle carriers, transporting their drug payloads directly to diseased tissues, hold considerable promise for improving the therapeutic efficacy and reducing the side effects of toxic drugs. Such nanoshuttles can be functionalized to carry large payloads of drugs, along with imaging moieties and targeting ligands to confer tissue specificity.

Several initial proof-of-concept studies of nanoshuttle drug carriers have been carried out over the past three years.[27−32] Early work illustrated

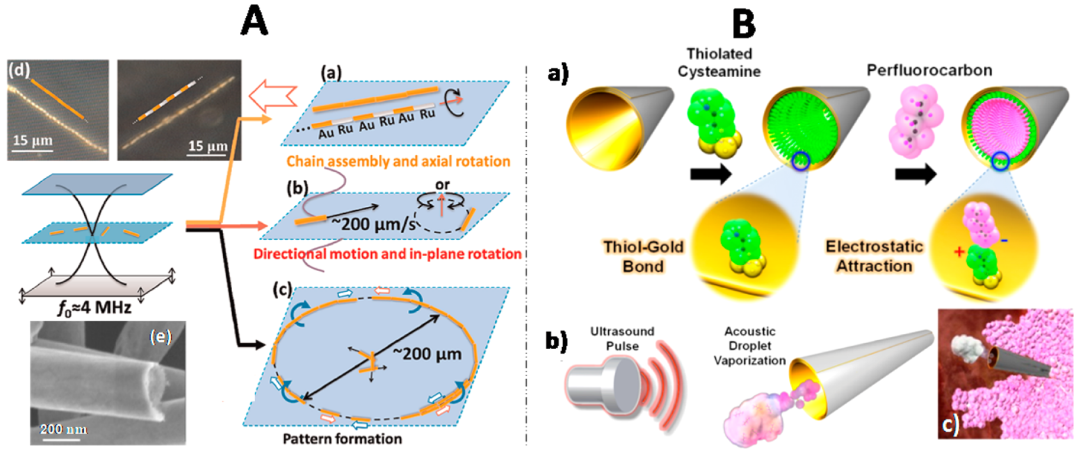

Figure 2. Ultrasound powered (A) nanowire and (B) microtube motors. (A): (a–c) Illustration of different kinds of motion (axial directional motion, in-plane rotation, chain assembly, axial spinning, and pattern formation) of metal nanowires in acoustic field. (d) Dark-field images of typical chain structures and ring patterns formed by Au wires. (e) Scanning electron micrograph of Au–Ru nanowire used in the ultrasonic propulsion experiments, demonstrating the concave end essential for the directional motion. Reprinted from ref 22. Copyright 2012 American Chemical Society. (B): (a) Preparation of the perfluorocarbon emulsion-loaded microbullets. (b) Schematic illustration of "microbullet" propulsion through acoustic droplet vaporization of the bound emulsion triggered by an ultrasound pulse. (c) Schematic of a "microbullet" penetrating into tissue for drug delivery. Reprinted with permission from ref 23. Copyright 2012 Wiley-VCH.

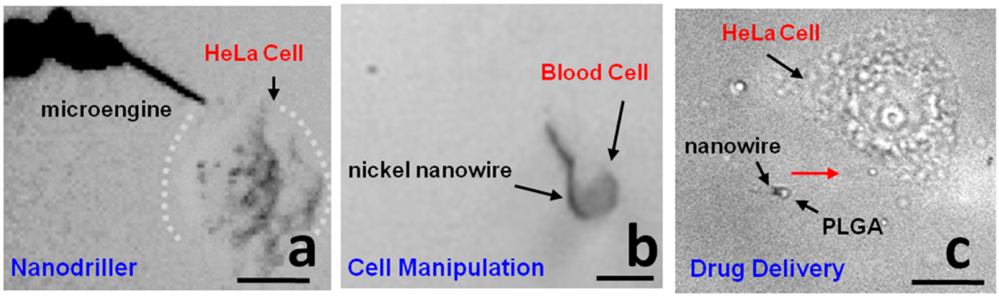

Figure 3. (a) Active nanotool drilling into a cross-linked biomaterial—a *p*-formaldehyde-fixed HeLa cell. Reprinted from ref 29. Copyright 2012 American Chemical Society. (b) Manipulation of flagellated microorganism by a magnetically driven tumbling nickel nanowire. Reprinted with permission from ref 31. Copyright 2012 Elsevier. (c) Delivery of drug-loaded PLGA nanoparticle to HeLa cancer cell by a flexible magnetic nanowire swimmer. Reprinted with permission from ref 32. Copyright 2012 Wiley-VCH. Scale bar, 10 μm.

that the catalytic nanowire shuttles can readily pick up drug-loaded poly(D,L-lactic-*co*-glycolic acid) (PLGA) particles and liposomes and transport them over predefined routes toward predetermined target destinations.[27] Powerful alloy and carbon nanotube (CNT)-based nanowire motors have thus been used to provide the high force necessary to transport "heavy" therapeutic cargo. In comparison to the PLGA particles, the liposome transport has been relatively slower due to its large size. Catalytic microtube engines have also been shown to be useful for transporting heavy cargo.[28] Imparting asymmetry into rolled-up InGaAs/GaAs/(Cr)Pt microtubular structures was shown to be useful in providing a corkscrew-like motion that was employed for drilling and embedding into fixed cells (Figure 3a),[29] suggesting potential use of these catalytic nanostructures as microtools. The extent of asymmetry of the shape of these rolled-up microtube drillers has a profound effect upon their trajectory.

The cargo-towing capabilities of fuel-free magnetically driven nanomotors in biological environments make them attractive target-specific nanoshuttle drug carriers. For example, the localized fluid flow of rotating (tumbling) nickel nanowires—actuated by weak rotating magnetic fields—was shown to be useful for noncontact cargo manipulations (*e.g.*, pushing, pulling), including trapping and transport of individual microorganisms (Figure 3b).[30,31] Flexible nanowire swimmers were shown to be useful for the pick-up and transport of variously sized polymeric drug carriers through a predefined route under external magnetic field, including directed delivery of doxorubicin-loaded PLGA microparticles to HeLa cancer cells in cell-culture media (Figure 3c).[32]

Despite this recent progress in nanoshuttle drug carriers, tremendous challenges remain for translating these initial proof-of-concept studies into practical drug delivery for *in vivo* applications. These challenges include limited tissue penetration, autonomous release of the therapeutic payload, swimming against the dynamic blood flow, and use of biocompatible materials. The use of cleavable linkers that are responsive to tumor microenvironments (*e.g.*, protease enzyme and acidic pH) should enable autonomous release of the therapeutic payloads at the target site. The remarkable force of newly introduced ultrasound-triggered microbullets[23] makes them particularly promising for transporting therapeutic payloads directly to diseased tissues, overcoming cellular barriers, or moving against blood flow. Eventually, such externally driven nanoshuttles will provide an attractive new approach for delivering drug payloads directly to predetermined destinations in a target-specific manner.

Isolation of Biological Targets. Artificial nano/microscale motors hold considerable promise for diverse medical diagnostic applications.[33,34] Particularly attractive for such bioanalytical applications are new receptor-functionalized artificial nanomotors, which are capable of capturing and isolating biological targets from unprocessed biological media.[35−39] Such capture and transport of biological targets offer an attractive alternative to current (time-consuming and laborious) sample-processing protocols. Selective on-the-fly isolation of biological targets—ranging from nucleic acids to circulating tumor cells—from raw biological fluids has thus been realized through the rational functionalization of catalytic tubular microengines with different bioreceptors (Figure 4). Such motion-based isolation routes enable direct visualization of the binding events based on the movement of the microtransporters.

Receptor-functionalized synthetic nanomotors are particularly promising for enhancing bioanalytical microchip systems. Functionalized nanomotors could be guided through the microchip channels, picking up and transporting target biomolecules to isolation compartments for subsequent analysis and quantification. By transporting captured analytes without bulk fluid flow, such microscale motors can eliminate the need for external pumps or power sources common in lab-on-chip systems. This application represents a major step toward designing integrated biomedical microsystems that perform a series of tasks for diverse diagnostic and therapeutic applications.

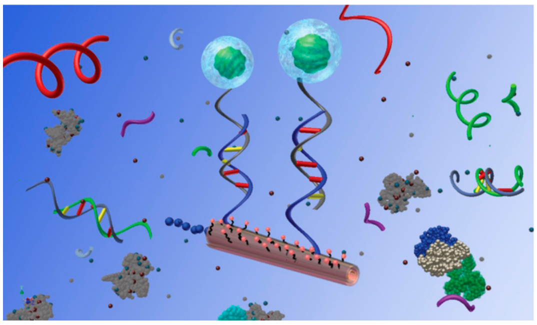

Figure 4. "On-the-fly" DNA hybridization. Scheme depicting (a) the selective pickup of target nucleic acid from a raw biological sample using an oligonucleotide-modified microtube engine. Reprinted from ref 37. Copyright 2012 American Chemical Society.

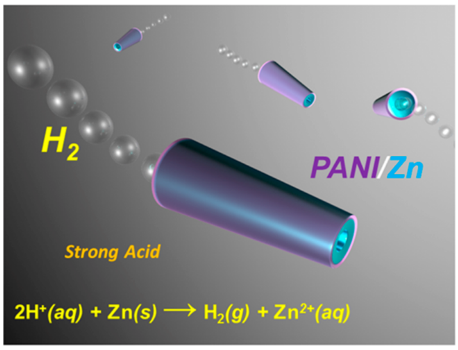

Figure 5. Schematic of hydrogen-propelled acid-driven PANI-Zn tubular microengine. Reprinted from ref 40. Copyright 2012 American Chemical Society.

Toward *In Situ* Fuels: Using the Sample as Fuel Source. The requirement of the common hydrogen peroxide fuel hinders some practical biomedical applications of catalytically propelled micro/nanomotors. A wide range of such applications, particularly *in vivo* applications, thus require other fuel sources. Extending the scope of chemically powered nanomotors to diverse biomedical operations and different biological fluids would require the identification of new *in situ* fuels in connection with newcatalytic materials and reactions. Ultimately, it would be beneficial to explore the sample matrix itself as the fuel source, thus obviating the need for adding external fuels and not compromising the viability of the biological target.

Recent efforts have thus been directed at exploring the use of the sample matrix (media or constituents) as the fuel. For example, Gao *et al.* described[40] a biocompatible polyaniline/Zn tubular microengine that propels itself autonomously and efficiently in extreme acidic environments without an additional fuel (Figure 5). The effective propulsion of these acid-powered microengines reflects the continuous thrust of hydrogen bubbles generated by the spontaneous redox reaction at the inner Zn surface. These acid-powered microrockets could expand the scope of applications of micromotors toward diverse applications in extreme environments, such as the human stomach, including targeted drug delivery and motion-based pH sensing.

TABLE 1. Summary of Microscale Motors, Based on Different Propulsion Mechanisms, and Their Potential for Biomedical Applications

propulsion mechanism	micro/nanostructures	promise/challenge for biomedical applications	group/ref
catalytic	bisegment metallic nanowires	autonomous motion/rely on hydrogen peroxide fuel; incompatible with high ionic strength media	Sen, Mallouk *et al.*[6] Ozin *et al.*[7]
	Janus microspheres	autonomous motion/rely on hydrogen peroxide fuel; limited speed and power	Zhao *et al.*[9]
	multilayer microtubes	high speed and power; cargo-towing and tissue-drilling abilities; efficient propulsion in biological fluids/commonly rely on hydrogen peroxide fuel	Mei, Schmidt[11,12] Wang *et al.*[13,14]
magnetic	helical microstructure	fuel-free biocompatible propulsion; movement in biological fluids without requiring chemical fuel/effective towing performance	Nelson *et al.*[17] Fischer *et al.*[18]
	flexible nanowires		Wang *et al.*[19]
	tumbling nanowires		Nelson *et al.*[20]
electric	diode nanowires	incompatible with high ionic media	Wang *et al.*[21]
light	AgCl microparticles	limited efficiency/toxicity	Mallouk, Sen *et al.*[43]
ultrasound	metallic nanowires	remarkable speed and power; tissue penetration ability/movement in biological fluids/biocompatible	Mallouk *et al.*[22]
	mutilayer microtubes		Wang, Esener *et al.*[23]

Biocatalytic propulsion, powered by ensembles of multiple enzymes, has shown promise for moving microobjects in the presence of glucose fuel.[41,42] The abundant presence of glucose in body fluids makes it an attractive biocompatible fuel. For example, Feringa's group[41] described autonomously moving carbon nanotubes, functionalized with a dual-enzyme (glucose-oxidase/catalase) assembly, which relied on glucose fuel to generate hydrogen peroxide and oxygen gas for their propulsion. Mano and Heller[42] demonstrated rapid propulsion at the water–oxygen interface of carbon fibers containing (on their opposite ends) a redox-polymer wired glucose oxidase and an oxygen-reducing bilirubin oxidase. Such a terminal glucose-oxidizing microanode and an oxygen-reducing microcathode resulted in a power-generating glucose–oxygen reaction and efficient bioelectrochemical locomotion. Other biocompatible fuels are *via* different biocatalytic reactions.

OUTLOOK AND FUTURE CHALLENGES

These are exciting times for research on nano/microscale machines. These miniature man-made machines have arisen from the fictional world of the *Fantastic Voyage* and are approaching initial proof-of-concept biomedical studies. This Perspective has highlighted opportunities and challenges in translating recent advances in microscale motors toward practical biomedical applications.

While impressive progress has been made over the past decade toward developing a wide range of synthetic fuel-driven and fuel-free nano/microscale machines (outlined in Table 1), the realization of practical biomedical applications requires further improvement in their efficiency, power, performance, functionalization, versatility, sophistication, and biocompatibility. Proper attention should also be given to control issues; integration of electronics, communication, software, and mechanics; and related scaling-down and packaging issues. Performing demanding biomedical tasks may also require an autonomous self-adaptive operation with machines cooperating and communicating with each other. For example, such collective action holds particular promise toward multiple-motor-driven transport of "heavy" therapeutic payloads. Improved understanding of the physical limitations of such nanomotor-towing ability is desired for effective drug-delivery applications.

As new capabilities are further developed and future nanomachines become more functional, these tiny devices are expected to perform more diverse and demanding tasks and benefit different important medical areas. These miniature machines are likely to have profound impact upon diverse biomedical applications, including directed drug delivery, nanosurgery, biopsy, cell sorting, artery cleaning, or microchip bioassays. Micro/nanoscale machines thus offer considerable promise to change various aspects of medicine by navigating through bodily fluids, cleaning clogged arteries, and performing targeted therapy and localized diagnosis in hard-to-reach places. The recent introduction of tiny, yet highly powerful, acoustically driven machines opens up the possibility of driving and controlling micromotors using deeply penetrative yet medically safe ultrasound.

The sophistication of man-made nano/microscale machines has been increasing at a fast pace to provide unlimited biomedical opportunities. Although significant progress over the past 10 years has greatly advanced the capabilities of these tiny man-made machines, much more work is required before real biomedical benefits are realized. Artificial nanomotors are thus expected to advance from current initial proof-of-concept studies into practical *in vitro* and *in vivo* biomedical applications for further evaluation. Given the enormous interest in this cutting-edge research field, we anticipate exciting new ideas and applications in the future. With such innovations and developments, along with careful attention to key challenges and requirements, nano/microscale motors are expected to have tremendous impact on diverse biomedical applications, providing unlimited opportunities limited only by one's imagination. These remarkable developments will eventually revolutionize disease treatment and diagnosis, lead to major improvements in the quality of our life, and facilitate the realization of the *Fantastic Voyage* vision.

Conflict of Interest: The authors declare no competing financial interest.

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