ADVANCED MATERIALS
www.advmat.de

Biomembrane-Functionalized Micromotors: Biocompatible Active Devices for Diverse Biomedical Applications

Fangyu Zhang, Rodolfo Mundaca-Uribe, Nelly Askarinam, Zhengxing Li, Weiwei Gao, Liangfang Zhang, and Joseph Wang**

There has been considerable interest in developing synthetic micromotors with biofunctional, versatile, and adaptive capabilities for biomedical applications. In this perspective, cell membrane-functionalized micromotors emerge as an attractive platform. This new class of micromotors demonstrates enhanced propulsion and compelling performance in complex biological environments, making them suitable for various in vivo applications, including drug delivery, detoxification, immune modulation, and phototherapy. This article reviews various proof-of-concept studies based on different micromotor designs and cell membrane coatings in these areas. The review focuses on the motor structure and performance relationship and highlights how cell membrane functionalization overcomes the obstacles faced by traditional synthetic micromotors while imparting them with unique capabilities. Overall, the cell membrane-functionalized micromotors are expected to advance micromotor research and facilitate its translation towards practical uses.

1. Introduction

Tremendous progress in developing synthetic micromotors based on different propulsion mechanisms and designs has been achieved in the last decade.[1–4] Powered by local fuels or external forces, artificial micromotors have been shown to navigate in biological fluids while performing diverse tasks connected to critical biomedical applications ranging from targeted drug delivery to precision surgery. This impressive progress has placed synthetic micromotors at the forefront of biomedical research.[5,6] While several initial successful in vivo animal tests have been reported,[7–9] key challenges need to be addressed before micromotors can be safely and efficiently applied in living systems and translated to practical applications. The performance and effectiveness of these micromotors rely largely on synthetic materials, which are susceptible to immune response and biofouling process in complex biological systems. Practical in vivo applications of synthetic micromotors thus require biocompatible and biomimetic designs, capable of prolonged and efficient operation in the physiological environment without producing any unintended harmful consequences.

Combining the advantages of the dynamic movement of synthetic motors with the versatility and unique biological functions of natural cells leads to cell-like micromotors that enable new opportunities for overcoming many obstacles that synthetic motors currently face in numerous biomedical operations.[10,11] By taking inspiration from nature, essential biological functions of natural cells, such as immune stealth, faithful antigen presentation, cell- or tissue-specific targeting, and selective binding with bacterial toxins or pathogens, can thus be harnessed and imparted to mobile synthetic microsystems. Cell membrane coating represents a powerful top-down approach for replicating complex protein profiles and biological functions of host cell membrane that are otherwise impractical to achieve with bottom-up synthetic approaches. The cell membrane-synthetic motor coupling results in novel active biocompatible devices, offering synergistic functionalities and new capabilities for a broad range of applications. In particular, recent attention has been given to cell membrane-functionalized micromotors.[12,13]

In this review, we discuss the preparation, unique capabilities, and advantages of biomimetic micromotors, leveraging the attractive properties of cell membrane-derived biomaterials and dynamic synthetic micromotors. Cellular membranes play crucial roles in the interface of cells with their complex surrounding biological environment.[14] The use of natural cell membranes to functionalize micromotors has been shown recently to address major barriers (e.g., biofouling) that hinder in vivo operations of synthetic motors while rendering them with a wide range of new properties and unique capabilities that greatly enhance their performance in biological systems. For instance, the cell membrane-functionalized micromotors can achieve prolonged propulsion in complex biofluids and efficient neutralization of harmful agents through the cell membrane receptors. This new class of biomimetic microscale motors thus combines the merits of synthetic motors with those of natural cell membranes. The diversity of different types of cell membranes and their associated biological functionalities enables the development of numerous biomimetic micromotor platforms with broad applicability. The judicious coupling of these different types of cell membranes with various types of

F. Zhang, R. Mundaca-Uribe, N. Askarinam, Z. Li, W. Gao, L. Zhang, J. Wang
Department of Nanoengineering
University of California San Diego
La Jolla, CA 92093, USA
E-mail: zhang@ucsd.edu; josephwang@ucsd.edu
The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adma.202107177.

DOI: 10.1002/adma.202107177

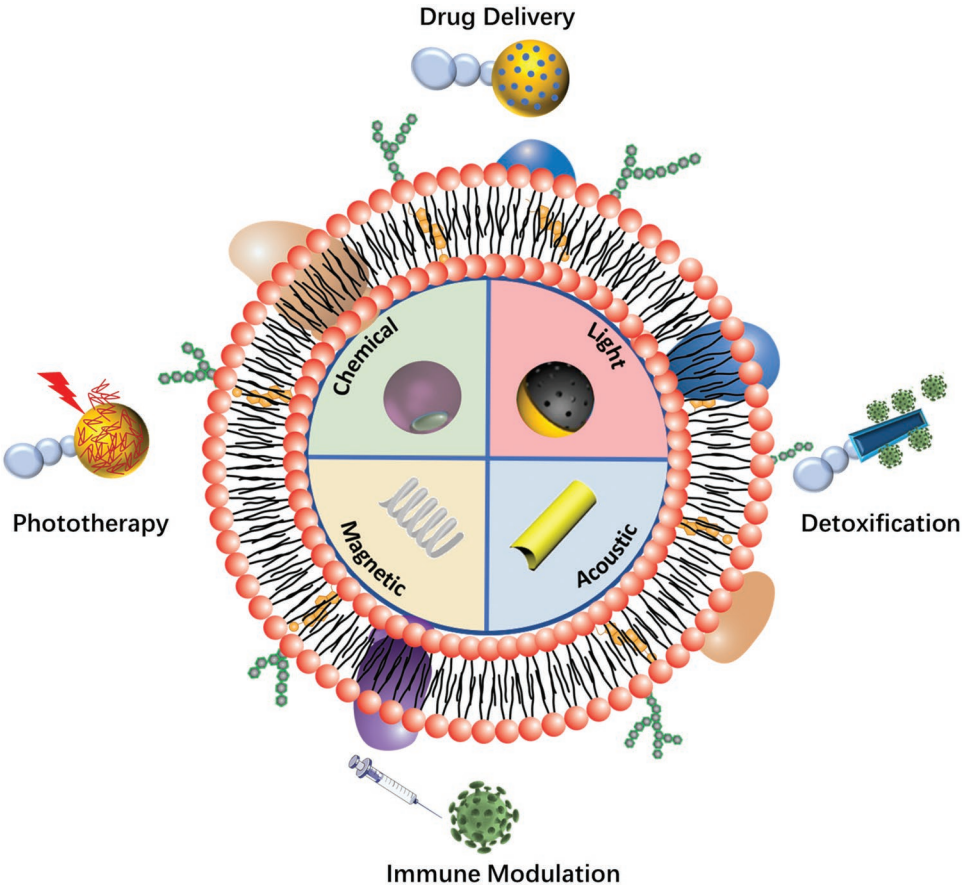


Figure 1. Cell membrane-functionalized micromotors for biomedical applications. Schematic illustration of a wide range of synthetic micromotors based on different propulsion mechanisms (inner) that are functionalized with various types of cell membranes (middle) for a variety of biomedical applications, including drug delivery, detoxification, immune modulation, and phototherapy (outer).

synthetic micromotors has shown robust utility, including active and targeted drug delivery, biodetoxification, immune modulation, and photothermal therapy (**Figure 1**). As a result, the cell membrane functionalization bestows artificial motors with superb biocompatibility that enables the advancement of micromotor research from laboratory test-tubes to whole living systems. These developments, unique capabilities, and representative applications of cell membrane-functionalized micromotors are reviewed in the following sections, along with the discussion on prospects and new opportunities.

2. Cell Membrane Nanomaterials

Researchers have made cell membrane vesicles to harness the biological functions of cell membranes.[15] These vesicles feature a closed bilayer structure and are natural analogs of synthetic liposomes but with asymmetric constituents across the lipid bilayer (**Figure 2**A). They can be fabricated from isolated subcellular membranes through well-known processes such as homogenization, extrusion, sonication, or gas cavitation.[16] Cell membrane vesicles also form naturally as endogenous

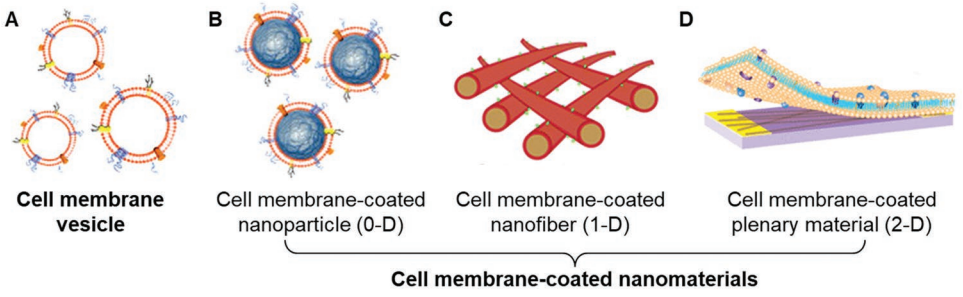


Figure 2. Major cell membrane-based nanomaterials, including A) cell membrane vesicle and B–D) cell membrane-coated nanomaterials. The latter includes B) 0D cell membrane-coated nanoparticle, C) 1D cell membrane-coated nanofiber, and D) 2D cell membrane-coated plenary material.

carriers responsible for transporting proteins and nucleic acids between cells.[17] All domains of life were found to produce membrane vesicles.[18] A few mechanisms have been identified in eukaryotes to form distinct membrane vesicles. For example, exosomes originate from multivesicular bodies, which are intraluminal vesicles that bud inward into the endosomal lumen.[19] Exosomes are released when the multivesicular bodies fuse with the cell surface. Contrary to exosomes, shedding vesicles are produced directly from the budding of the plasma membrane.[20] In addition, apoptotic cells release "apoptotic bodies" during the disassembly stage as a distinct class of membrane vesicles.[21] Regardless of their source cell type, origin, preparation method, or biological state, cell membrane vesicles are all inherently adept at performing certain biological functions. As a result, they have become attractive nanomaterials for biomedical applications, including targeted delivery, immune modulation, and biosensing.[22–24]

For better control over material properties, researchers recently used cell membranes to coat synthetic nanoparticle substrates, creating cell membrane-coated nanoparticles as a unique nanomedicine platform (Figure 2B).[14,25] The coating process relies on the interactions between the inner face of the cell membrane and the outer face of the substrate. The coating occurs when the fusion of the two surfaces reduces the total surface energy.[26] In this strategy, the substrate cores enhance nanoparticle stability by immobilizing the membrane shell and preventing membrane-membrane fusion. They also serve as a template, dictating the size and geometry of the coated nanoparticles. Besides, the cores can act as reservoirs for payload encapsulation and controlled release.[27] The development of cell membrane-coated nanoparticles started with using red blood cell (RBC) membrane, resulting in nanoparticles that mimicked the long-circulation feature of the natural RBCs attractive for drug delivery.[25] Soon after this development, these nanoparticles were applied as decoys of susceptible RBCs to intercept and neutralize toxic agents, including bacterial toxins, pathological antibodies, and chemical toxicants.[28–31] Meanwhile, RBC membrane-coated nanoparticles detained and neutralized bacterial toxins without compromising their structural integrity. These "nanotoxoid" vaccines elicited strong protective immunity against bacterial infections.[32] Following the initial development, membranes of other cell types, including platelets, white blood cells, cancer cells, stem cells, bacteria, and intracellular organelles, were also derived for nanoparticle coating.[14,33,34] The substrate cores were also extended from initial biodegradable polymers to gold, iron oxide, hydrogel, and oil nanodroplets.[31,35–37]

Built upon the success of cell membrane-coated nanoparticles, researchers also made cell membrane-coated nanofibers (Figure 2C). This class of nanomaterials differs drastically from nanoparticles in terms of dimensional and mechanophysical characteristics. For example, polycaprolactone nanofibers coated with the membrane of pancreatic beta cells possessed an antigenic exterior closely resembling that of the source beta cells, therefore recapitulating the characteristics of intercellular interaction among beta cells found in the pancreas.[38] When such nanofiber scaffolds were used to culture beta cells, both cell proliferation rate and function were significantly enhanced. Membranes from human fibroblasts and keratinocytes were also coated onto polycaprolactone nanofibers.[39] The coated nanofibers improved the growth of human keratinocytes as compared to RBC membrane-coated or uncoated scaffolds. These studies show how cell membrane-coated nanofibers can harness cell membrane functions by adding a new dimension of flexibility and controllability.

More recently, cell membrane-coating was extended to two-dimensional plenary substrates to further leverage natural cell functions (Figure 2D). In this development, small membrane vesicles were first made from RBC membrane using sonication and then allowed for spontaneous fusion onto carbon nanotube-based field-effect transistors (FETs). Such a fusion process led to a uniform bilayer membrane coating.[40] This biomimetic biosensor design distinguishes itself by selectively interacting with and absorbing broad-spectrum hemolytic toxins regardless of the toxin molecular structures. The detection mechanism is based on the toxin-membrane interactions that alter the local charge distribution at the FET surface. The device response is ultrasensitive with a detection limit of femtomolar range and concentration-dependent. As plasma membranes can be derived from various cell types, similar biosensors can therefore be constructed with diverse membrane functions. Following a similar work mechanism, they are expected to detect and measure various biological functions and events specific to the corresponding cell types. Indeed, researchers recently coated FET sensors with an outer mitochondrial membrane.[34] These sensors successfully detected and distinguished a group of B-cell lymphoma-2 agonists, including antibodies and small molecules.

Through the development of cell membrane vesicles and cell membrane-coated nanomaterials, researchers have unlocked the unique abilities of cell membranes for biomimicry and biointerfacing. As the technology progresses, the application of these cell membrane-based nanomaterials has been drastically broadened as additional functions beyond those derived from the natural cell membranes are integrated.[41] For example, through lipid insertion, functional ligands can be incorporated onto natural cell membranes through a lipid anchor.[42] Furthermore, mixing multiple cell membranes or natural membranes with synthetic liposomes has led to hybrid membranes that can boost the functional characteristics of coated nanoparticles.[43,44] Additionally, through metabolic engineering, non-natural ligands hijack natural biosynthesis pathways, participate in the relevant cellular metabolic processes, and subsequently anchor to the cell surfaces for additional functionalities.[45,46] Lastly, through selective gene editing, genetically modified membranes with altered protein expression on the cell surfaces can be made and coated onto nanomaterials for functionalization.[47,48]

Overall, the advancement of the cell membrane-based nanomaterials demonstrates the versatility and adaptivity of cell membranes as novel biomaterials, especially when combining with the merits of synthetic counterparts.

3. Cell Membrane-Functionalized Micromotors

The process of fabricating cell membrane-functionalized micromotors typically involves three steps: synthesis of the active micromotors, preparation of cell membrane vesicles, and fusion of the cellular nanovesicles with the micromotors. Specific examples based on the coupling of different micromotor

designs with different cell membrane coatings are discussed in this section.

3.1. RBC Membrane-Functionalized Micromotors

RBC membrane as a coating material has attracted considerable attention to functionalize synthetic structures for broad applications, including drug delivery,[27] imaging,[49] photothermal therapy,[50] and immune modulation.[32] By mimicking host RBCs, RBC membrane coating offers superior immune stealth and functions as a decoy to absorb hemolytic toxins.[28,31] Recently, the micromotor technology showed fast mobility and enhanced interaction and collision with analytes in diverse media matrices.[51] The ability of RBC membrane to neutralize toxins can thus be further improved in combination with micromotor technology. Wu et al. described an acoustic-propelled RBC membrane-coated micromotor for accelerated neutralization of hemolytic toxins.[52] Such acoustic nanomotors rely on gold nanowires (AuNWs) fabricated by template-assisted electrodeposition followed by motor release via membrane dissolution. A negative charge was added to the gold surface by overnight incubating the AuNWs with citric acid before membrane coating. The resulting AuNWs were agitated with RBC vesicles by an ultrasonication process, which spontaneously fused onto the motor surfaces, leading to scalable production of membrane-coated nanomotors (**Figure 3**A). The fusion mechanism is based on the high surface tension and semistable characteristics of the vesicles which are prone to fuse onto the solid gold surface to minimize the free energy of the system. Specifically, the asymmetric charge between exoplasmic and cytoplasmic sides of RBC membranes enabled the fusion of the less negatively charged inner surface of RBC vesicles onto negatively charged micromotors and led to a right-side-out membrane orientation.[26] Such membrane coating resulted in a full surface coverage while preserving the concave structure on one end of AuNWs, essential for the acoustic propulsion (Figure 3B). The retention of the original concave end of the AuNWs ensures maintaining the efficient ultrasound-powered movement. The resulting RBC membrane-coated micromotor displayed an efficient motion in various biological fluids (Figure 3C). An evaluation on the stability of the micromotor after 1 h propulsion under acoustic field was performed. The negligible change of fluorescence intensity of membrane coating reflects the high stability and integrity of membrane-coated motor (Figure 3D). The nanomotor propulsion was not affected by biofouling effects even after 48 h incubation in whole blood (Figure 3E), indicating considerable promise for future in vivo applications.

In addition, the RBC membrane was also modified to many other substrates, such as magnesium microparticle,[12,53] magnetic hemoglobin,[54] perfluorocarbon emulsion,[55] and chitosan-heparin layer-by-layer assembly capsules,[56] to impart diverse functionalities from rapid detoxification, photodynamic therapy, oxygen delivery to thrombus ablation.

3.2. Platelet Membrane-Functionalized Micromotors

Platelets display distinct surface moieties responsible for modulating their adhesion to various disease-relevant substrates involving vascular damage, immune evasion, and pathogen interactions.[57] They are also essential players in interacting with many types of cells for modulating the immune response, maintaining hemostasis, and engaging in wound healing.[58] Such broad biointerfacing capabilities of platelets have inspired the use of their membrane to develop platelet membrane-coated micromotors. Early studies with PL membrane-coated nanoparticles indicate several essential capabilities, including reduced cellular uptake by immune cells,[59,60] subendothelial adhesion,[61] improved tumor targeting,[62,63] and enhanced affinity towards pathogens.[61,64]

Recently, platelet-membrane-derived vesicles (PL-vesicles) have been fused to the surface of helical nanomotors to form PL-nanomotors.[13] **Figure 4**A illustrates the preparation of such nanomotors by template-assisted electrodeposition.[65] First, the helical structures were fabricated by the Pd/Cu co-electrodeposition in the 400 nm pores of a polycarbonate membrane, followed by the Cu dissolution, release of the Pd nanostructures, and subsequent deposition of a Ni/Au bilayer to confer them with magnetic capabilities. After collecting the synthesized magnetic helical nanostructures, their surfaces were modified with 3-mercaptopropionic acid (MPA) to provide negative charges onto the Au surface, thus allowing effective coating of the helical motor surface with the PL-vesicles following incubation under ultrasonication. Figure 4B displays scanning electron microscopy (SEM) images of bare helical nanomotors (top) and PL-nanomotors (bottom). Both images show the characteristic periodic helical structure, demonstrating that the platelet coating does not affect the PL-nanomotor structure.

Since the coating with platelet membrane does not affect the helical structure, their magnetic propulsion is not affected by the presence of the biomembrane. The propulsion and antibiofouling capability of PL-nanomotors were evaluated in whole blood. Figure 4C displays the 10 s tracking trajectories of a bare helical nanomotor (top) and PL-nanomotor (bottom) after 1 h of actuation in whole blood. These trajectories illustrate that the efficient propulsion of the PL-motors compared with bare nanomotors. The propulsion of the bare nanomotors has been hampered by severe biofouling, while PL-nanomotors displayed an efficient magnetic actuation. Such phenomenon further validates that the platelet membrane coating can protect the helical nanomotors from biofouling effects in complex biological matrices and have potential for in vivo studies.

3.3. Cancer Cell Membrane-Functionalized Micromotors

Cancer cells offer homotypic targeting capability through cell membrane antigens.[66] Meanwhile, the antigenic components are advantageous for modulating anticancer immunity.[33] In addition, cancer cells can be easily cultured for membrane derivation.[14] These advantages have made cancer cell membrane coating attractive for cancer drug targeting and imaging. Polymeric nanoparticles have been functionalized with cancer cell membrane to mimic the antigenic makeup like the source cancer cells. Such nanoparticle design has opened the avenue for two types of anticancer therapies. First, cancer cell membrane-coated nanoparticles (CCNPs) have successfully been shown to deliver tumor-associated antigens along with

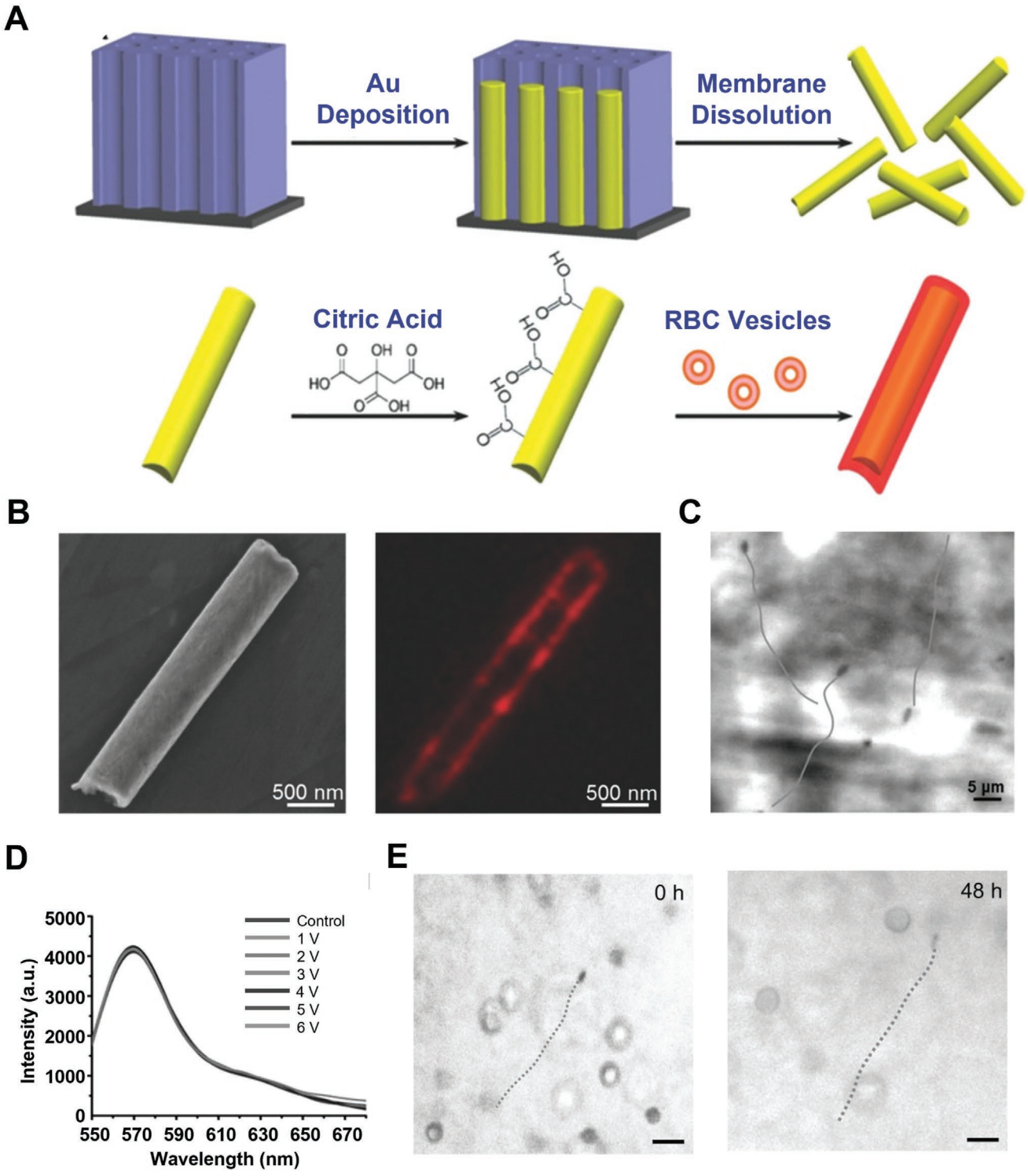


Figure 3. RBC membrane-functionalized micromotors for effective biodetoxification. A) Schematic fabrication of acoustic-propelled micromotor consisting of RBC membrane-functionalized gold nanowire. B) SEM (left) and fluorescent (right) images of RBC membrane-functionalized micromotor. C) Tracking trajectories of RBC membrane-functionalized micromotor in deionized water. D) Fluorescence spectra illustrating the stability of RBC membrane coating on the motors during 1 h acoustic propulsion under ultrasound transducer voltage over the range 0–6 V. E) Time-lapse images showing the propulsion of the motors in whole blood before (left) and after (right) 48 h incubation in the whole blood. Scale bars, 10 µm. Ultrasound field conditions: 5 V and 2.83 MHz. Reproduced with permission.[52] Copyright 2015, Wiley-VCH.

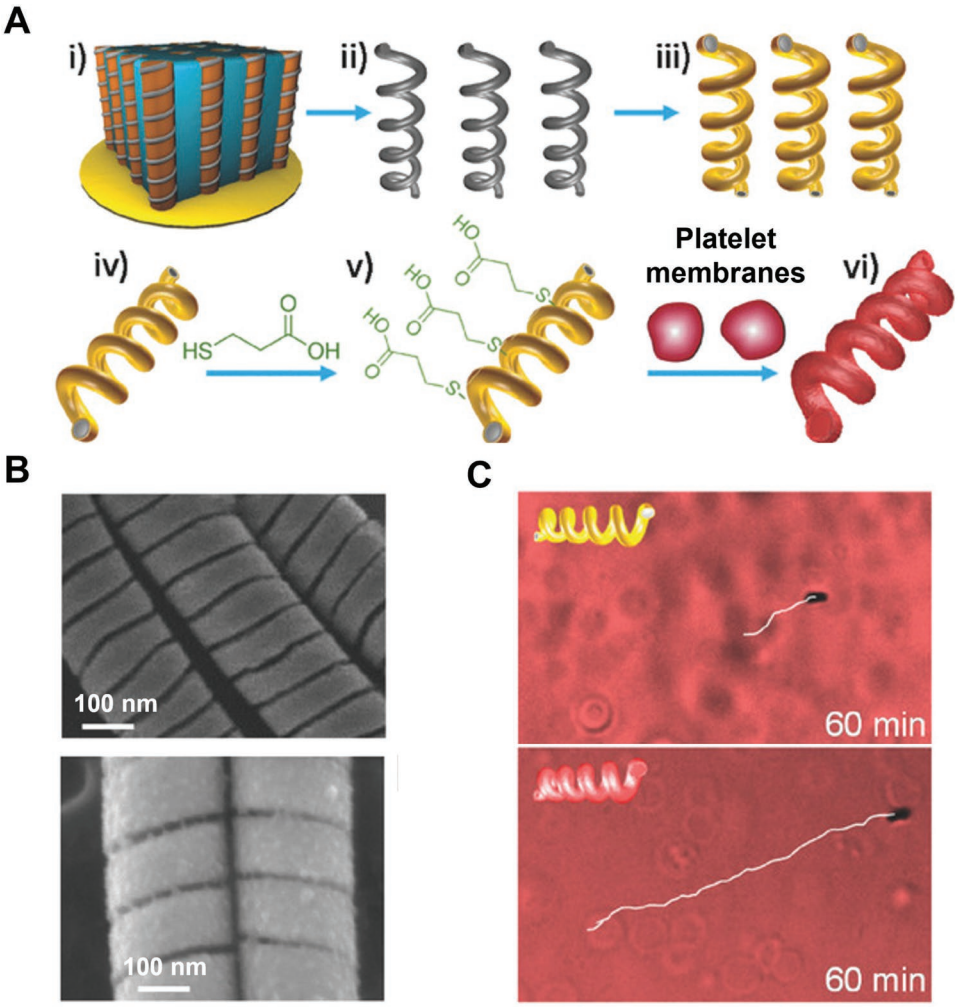


Figure 4. Platelet membrane-functionalized micromotors for binding and isolation of biological threats. A) Schematic preparation of magnetic-driven micromotor consisting of platelet membrane-functionalized helical Ni/Au/Pd nanostructure. B) SEM image of bare micromotor without platelet membrane coating (top) and platelet membrane-functionalized micromotor (bottom). C) Comparison of the tracking trajectories between platelet membrane-functionalized micromotor and bare micromotor after 60 min propulsion in whole blood. Reproduced with permission.[13] Copyright 2018, Wiley-VCH.

immunological adjuvants to antigen-presenting cells, eliciting anticancer immune responses.[66] Second, CCNPs contain cell adhesion molecules as the source cancer cells that enable them to engage in a phenomenon known as homotypic binding, observed in cancer cells adhering to one another and resulting in the growth of a tumor mass.[33] This homotypic binding property allows CCNPs to engage in cell-specific targeting of cancer cells, an essential component for directed, localized cancer therapy.

Zhang et al. fabricated gold nanoshell-covered $CaCO_3$ micromotors coated with the membrane sourced from G422 murine cancer cells, which can be detected by antigen-presenting cells and thus produce cellular immunity against corresponding cancer cells.[67] The cancer cell membrane coating imparted the micromotors with new functionality for homotypic binding, providing them the unique ability to target corresponding cancer cells. In the study, spindle-shaped $CaCO_3$ microparticles were first prepared using a gelatin-stabilized coprecipitation method, followed by deposition of a gold layer, forming a gold-functionalized nanoshell microparticle (**Figure 5**A). G422 membrane was prepared into membrane vesicles and incubated with the microparticles for attachment. Figure 5B displays the corresponding SEM and Energy Dispersive X-ray Spectroscopy mapping analysis, demonstrating the elemental composition of the motor, including the deposited gold layer and the presence of phosphorus and sulfur, associated with the phospholipid and protein component of the G422 cell membrane. The cancer cell membrane-coated gold nanoshell-functionalized $CaCO_3$ motor displayed efficient motion under external acoustic actuation (frequency = 1.4 MHz) in a rotating fashion around a narrow axis in a reservoir of water (Figure 5C) as well as in PBS, serum, and blood matrices.

3.4. Leukocyte Membrane-Functionalized Micromotors

Leukocytes are a major category of blood cells that consist of macrophages, neutrophils, dendritic cells, T cells, and B

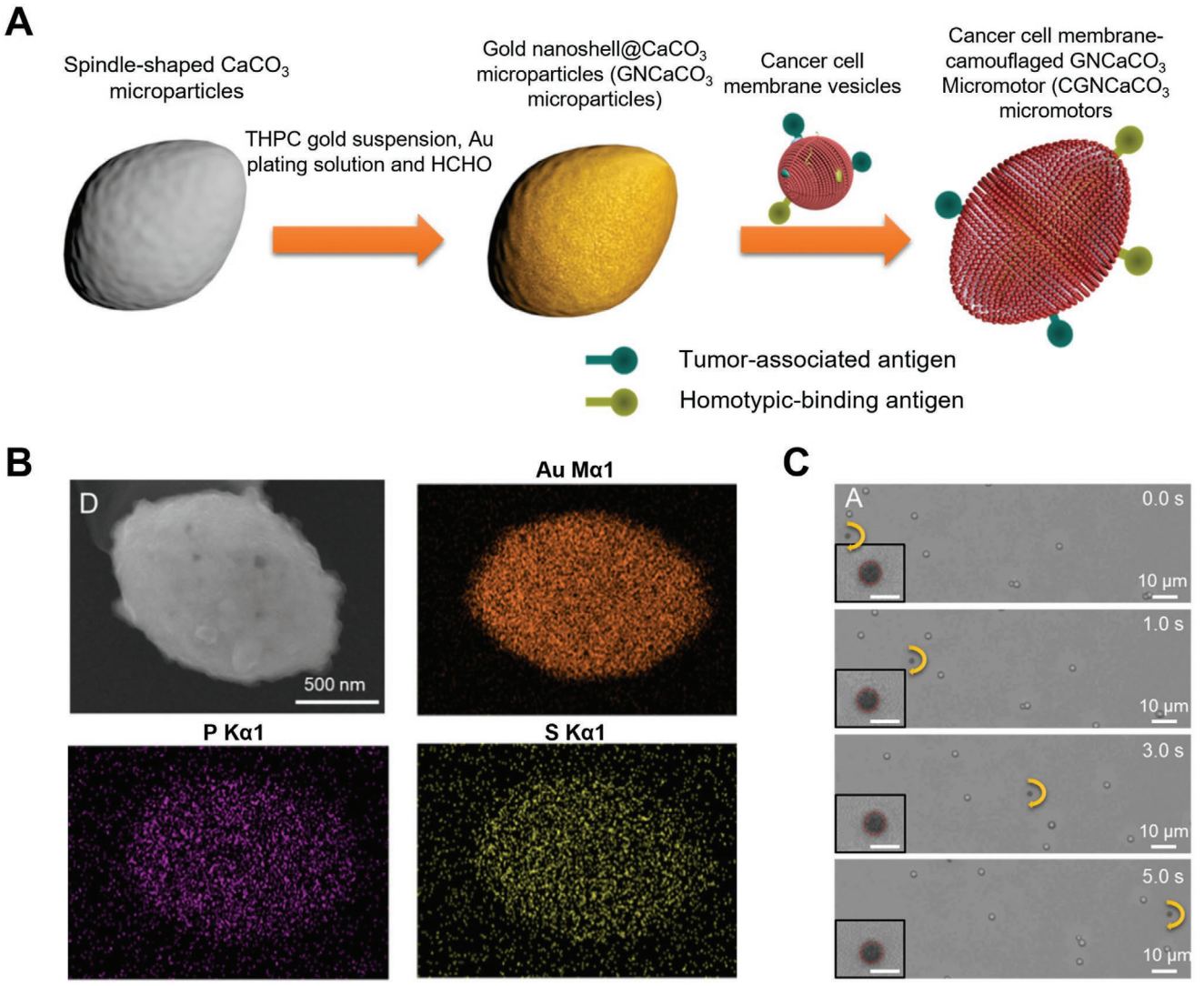


Figure 5. Cancer cell membrane-functionalized micromotors with homotypic targeting ability. A) Schematic fabrication of acoustic-propelled micromotor based on cancer cell membrane-coated gold nanoshell@$CaCO_3$ microparticle. B) Scanning electron microscopy and energy-dispersive X-ray spectroscopy images of cancer cell membrane-coated micromotor. C) Time-lapse images showing the movement of the micromotor under an applied acoustic field at a frequency of 1.4 MHz. Reproduced with permission.[67] Copyright 2020, Wiley-VCH.

cells. Coating with the leukocyte membrane offers the cellular self-recognition mechanisms for evading phagocytosis by the source cells. Leucocyte coating also transfers surface ligands of the source cells for binding preferentially to receptors at disease sites.[68] These two properties together make them attractive carriers for drug delivery. Additionally, leucocyte membrane coating provides receptors from source cells dedicated to sensing and responding to pathogens and immune signals, therefore suitable for neutralizing bacterial toxins, viruses, and inflammatory cytokines.[69] Leucocyte coating can also allow for binding with circulating cancer cells (CTCs) but remains homologous to source leucocytes, a valuable feature for sensitive circulating tumor cell detection and isolation.[70] Furthermore, leucocyte coating can mimic the leucocyte-cancer interactions and thus boost the body's anticancer immunity.[71] Alternatively, coated leucocyte membrane may detain bacterial toxins for immune presentation and elicit protective immunity.[72] Overall, these properties make leucocyte membrane highly attractive for coating synthetic nanomotors.[73]

Recently, Wang et al. made a gallium-based shape-transformable rodlike liquid metal nanomotor for active cell drilling under an acoustic field.[74] To fabricate liquid metal-based nanomotors, bulk liquid metal gallium was shaped into the polycarbonate membrane coated filters, followed by 6 h filtration under a pressure of 105 Pa at 35 °C. Subsequently, the liquid metal nanomotors were released by dissolving the templates. The leukocyte membrane was coated onto the liquid metal nanomotor as a "camouflage layer" that enabled the nanomotor to actively recognize cancer cells in a neutrophil-like way (**Figure 6**A).[75] Confocal laser scanning microscopy (CLSM) image clearly shows the colocalization of DiD-labeled cell membrane and liquid metal with green fluorescence, demonstrating that the cell membrane successfully fused onto the liquid metal surface (Figure 6B,C). To achieve

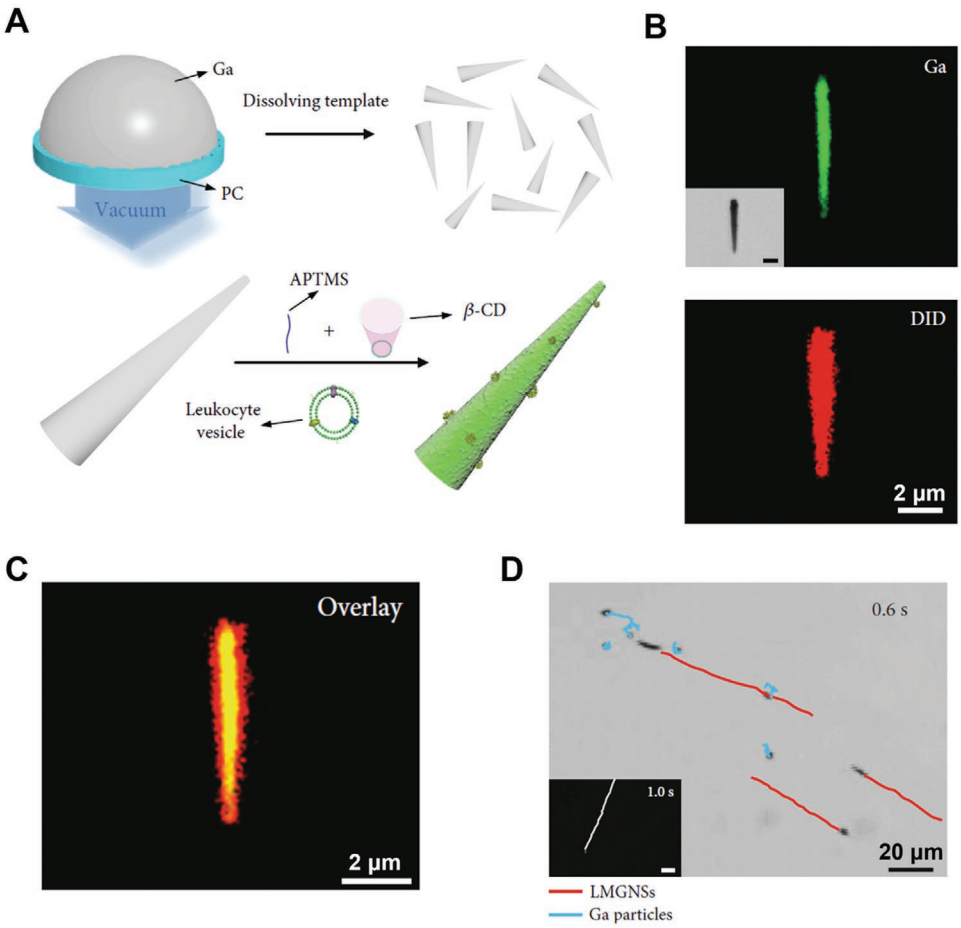


Figure 6. Leukocyte membrane-functionalized micromotors for actively targeted delivery and synergistic chemophotothermal therapy. A) Schematic preparation of acoustic-driven micromotor established on leukocyte membrane-coated gallium needle-like microstructure. B) Confocal laser scanning microscopy images of gallium micromotor and leukocyte membrane coating. C) Overlay of gallium with green fluorescence and DiD-labeled leukocyte membrane from (C). D) Time-lapse image of motor movement under an applied voltage of 10 V at a frequency of 420 kHz. Reproduced with permission.[75] Copyright 2020, AAAS.

an anticancer efficacy, aminopropyltrimethoxysilane (APTMS), carbonylated β-cyclodextrin (β-CD), and doxorubicin were chosen to modify onto the shell of the liquid metal for anticancer drug delivery. The as-synthesized leukocyte membrane-coated liquid metal nanomotor also displayed a longer motion lifetime in biological medium and significantly higher speed compared to the bare gallium nanomotor, reflecting the efficient anti-biofouling protection imparted by the cell membrane coating (Figure 6D).

In addition to liquid metal-based nanomotors, Janus mesoporous silica nanoparticles (JMSNs) were also cloaked by macrophage membrane to form a hybrid nanomotor.[76] The JMSNs were fabricated by the "sol-gel" method followed by chemical vapor deposition with a thin layer of gold. The macrophage membrane was then wrapped onto the silica core through a sonication-based approach.[29] The structure of macrophage membrane-coated Janus nanoparticles was confirmed by the transmission electron microscope, CLSM, and zeta potential measurements. Owing to the macrophage membrane coating, the nanomotors showed enhanced motion capability in versatile biological media compared to the bare JMSNs.

4. Applications of Cell Membrane-Functionalized Micromotors

A summary of the biofunctions of various cell membrane types has been listed in **Table 1**. Combining the efficient movement of synthetic micromotors with the biofunctionality of natural cell membranes imparts these micromotors with unique capabilities that greatly enhance their performance towards improving diverse biomedical operations, including drug delivery, toxin neutralization, immune modulation, and phototherapy. Such new capabilities are discussed in the following sections.

4.1. Drug Delivery

Intracellular delivery has attracted tremendous attention in many fields, including gene transfection, drug delivery, imaging, and cell-based therapy.[77] Extensive research efforts currently focus on the development of various functional particles for efficient cellular uptake.[78] However, passive nanoparticles rely on endocytosis for intracellular delivery, which

Table 1. Cell types and their biofunctions.

Cell type	Biofunction	Ref.
RBC	Superior immune stealth; absorption and neutralization of hemolytic toxins	[28,31]
Platelet	Reduced cellular uptake by immune cells; improved tumor targeting; subendothelial adhesion; enhanced affinity towards pathogens	[59–64]
Cancer cell	Modulation of anticancer immunity; cell-specific targeting of cancer cells, allowing for localized cancer therapy	[33,66]
Leukocytes	Cellular self-recognition mechanisms for evading phagocytosis; binding to receptors at disease sites and CTCs	[68–70]

faces the challenge of low efficiency and limited endosomal escape ability.

Nanomotors have recently been developed as new active delivery platforms, offering distinct advantages of fast cytosolic delivery of biological payloads (siRNA, protein) bypassing endocytosis.[79–81] Among the applications, oxygen delivery to cells is essential for maintaining oxygen availability and improving longevity for patients with blood loss. Based on the capacity to restore and transport oxygen, RBCs are widely used in surgical procedures for blood transfusion.[82] However, donated RBCs shows limitation during acute surgical situations, limited by the short shelf life and low oxygen delivery efficiency.[83] RBC membrane-coated perfluorocarbons nanoemulsions (RBC-PFCs) offer considerable improvement in oxygen-carrying abilities based on the relatively high hydrophobic and low reactive capacity of PFC.[84] For further application, Zhang et al. made AuNW motor that modified the gold surface with RBC-PFC nanoemulsions with electrostatic interactions.[55] The AuNWs were fabricated through a template-assisted electrodeposition method with a 400 nm diameter porous PC membrane. Then, with the stepwise surface modification, the AuNWs were functionalized with a negative charge of the self-assembled 3-mercaptopropionic acid (MPA) monolayer, followed by a positively charged poly-L-lysine (PLL) layer. RBC-PFCs were thus attached onto AuNW nanomotors (denoted as "Motor-PFC") based on the negative charge of the RBC membrane surface and the positive charge of the PLL layer showing in **Figure 7**A. For intracellular oxygen delivery, the Motor-PFC rapidly propelled under the ultrasound field, which could save the hypoxia-induced J774 macrophage cells and protect the cells from anoxic environments (Figure 7B). To confirm oxygen delivery by RBC-PFC functionalized nanomotor, image-iT Green hypoxia reagents were introduced to examine cell viability. After 72 h incubation, the Motor-PFC treated cells remained nonfluorescent (Figure 7C left) compared with the untreated group, which displayed a bright fluorescence from the anoxic cells (Figure 7C right). Under the time-dependent cell viability study, the active Motor-PFC resulted in 85% cell recovery even after long periods of hypoxia induction. In contrast, the control groups, including bare motor and bare RBC-PFC emulsion, only had 30–40% cell recovery (Figure 7D). In particular, only a small portion was attached to the cells under the ultrasound field treatment for the RBC-PFC group, generating a slight improvement in cell viability. The study also demonstrated the potential value of the Motor-PFC-based intracellular oxygen delivery for local hypoxic tissue sites such as tumor cells for therapeutic purposes and cardiac muscle cells for myocardial oxygen consumption. Although this proof-of-concept work demonstrates in vitro the potential advantages of the nanomotor-based system for intracellular oxygen delivery, future research needs to evaluate its

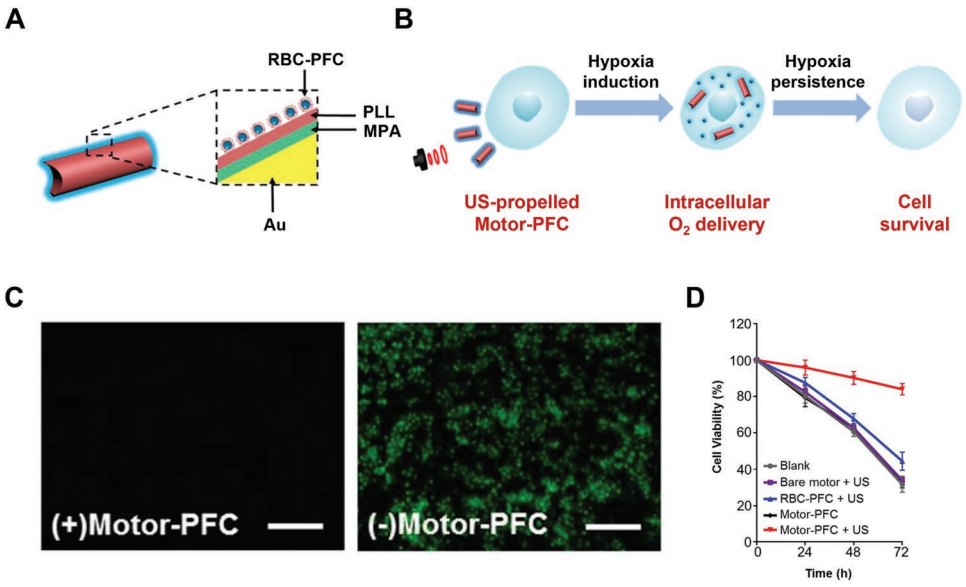


Figure 7. Acoustic-propelled micromotor carrying RBC membrane-coated perfluorocarbons (Motor-PFC) for intracellular oxygen delivery in vitro. A) Schematic illustration of the structure of Motor-PFC. B) Schematic depicting an intracellular delivery of Motor-PFC to J774 macrophages. C) Representative fluorescence images showing the hypoxic stress of the cells within (left) and without (right) Motor-PFC treatment. D) Viability of J774 macrophages with different treatment conditions. Reproduced with permission.[55] Copyright 2019, American Chemical Society.

potential in vivo therapeutic applications and leverage such delivery strategy into clinical settings.

While acoustic propulsion and fast cell internalization systems have illustrated valuable applications for various intracellular processes, future efforts are expected to combine cell membrane technology with other types of nano/micromotors to realize distinct advantages for diverse intracellular operations. For instance, magnetically propelled micromotors have demonstrated controlled maneuverability inside the cell with no adverse effect on cell viability.[85] NIR light-propelled micromotors have also shown payload delivery to the cell vicinity.[86] Besides tuning the motion behavior, other cell membranes that can be easily taken up by immune cells, such as bacterial membrane, can assist the micromotor-based cell penetration for further payload delivery.[87,88] Overall, the development of new cell membrane-coated motors and their cellular operation could endow new opportunities for future therapeutic applications in more practical scenarios.

4.2. Detoxification

Toxins pose a severe threat to the healthcare worldwide. It is urgent to explore safe and effective methods for detoxification. Conventionally, detoxification platforms, such as monoclonal antibodies and small-molecule inhibitors, have been designed to recognize toxins based on their molecular structures. Cell membrane-coated nanomaterials have recently been shown to offer efficient binding and neutralization of different types of harmful agents relying on cell membrane surface receptors to recognize and capture toxins.[89] Similarly, micromotors can be designed to act as broad-spectrum toxin decoys, offering new possibilities for treating toxin-mediated diseases.

Among various cell types, RBC membrane is attractive to make toxin nanodecoys due to its capability to absorb various types of pore-forming toxins (PFTs).[28] The coupling of such toxin binding capability of RBC cell membrane with the fast motion of water-powered Mg micromotors greatly enhanced the efficiency of detoxification compared with static counterparts based solely on Brownian motion.[12] Moreover, acoustic-driven nanomotors based on RBC membrane-coated gold nanowires were able to effectively neutralize PFTs.[52] However, from a therapeutic standpoint, it is highly demanding to remove both hemolytic toxins and toxin-produced bacteria that lead to desirable efficacy. To achieve these goals, Esteban-Fernández de Ávila et al. fabricated RBC-platelet hybrid membrane-coated gold nanowire microrobots (RBC-PL-motors) by using a template-assisted AuNWs electrodeposition as well as a dual-membrane coating method.[90] The resulting RBC-PL-motors propelled under acoustic actuation, simultaneously neutralizing the toxins and removing the toxin-produced bacteria (**Figure 8**A). In a bacteria binding study, RBC-PL-motors were able to target 4′,6-diamidino-2-phenylindole (DAPI)-labeled MRSA as a model PL-adhering pathogen (Figure 8B). A dramatic increase of fluorescence intensity was observed during the incubation of DAPI-labeled MASA with acoustic-propelled RBC-PL-motors or PL-motors compared to the negative controls, indicating the importance of combining the acoustic propulsion of micromotors with the PL membrane coating (Figure 8C). To further examine the potential of RBC-PL-motors for neutralizing PFTs, α-toxin as a model PFT was incubated with the RBC-PL-motors for 5 min under acoustic field, followed by RBC hemolysis characterization. The sample treated with the RBC-PL-motors displayed substantially lower hemolysis (5.5%) compared with negative control groups, reflecting the effective binding and neutralization of toxins due to the assistance of the fast motion of RBC-PL-motors (Figure 8D,E).

A variety of toxic agents present in different sites in the body can damage crucial enzymes necessary for maintaining normal physiological functions. For example, vacuolating cytotoxin secreted from *Helicobacter pylori* (*H. pylori*) has major effects when interacting with gastric epithelial cells, resulting in apoptotic cell death.[91] It is critical to find an effective way to neutralize and remove this toxin from the body. Cell membrane-coated micromotors show high toxin removal efficiency. Therefore, applying such functionalized micromotors to in vivo studies would be useful for fast and efficient toxin neutralization. Furthermore, different classes of toxin-removing cell membranes can be derived for coating various nanomotors to enable broad biomedical applications.

4.3. Immune Modulation

During the past decade, one of the significant challenges has been developing particulate delivery systems for the loading and encapsulating of antigenic and immunostimulatory agents. These platforms have shown enhanced loading capacity, sustained-release capabilities, targeted delivery, and improved vaccination efficacy when orally administered.[92,93]

The cell membrane coating technology serves as an efficient strategy to immobilize and neutralize toxins onto the carrier surface. Combining this technology with micromotor platform can lead to improved cargo delivery and enhanced tissue penetration. Recently, a unique biomimetic micromotor toxoid strategy has been developed for oral vaccination.[53] In this approach, micromotor toxoids were prepared by a sequential process in which micromotors were coated with a toxin-inserted RBC membrane to confer antigenic activity. **Figure 9**A illustrates the composition of a motor toxoid and its oral delivery. Here, the motor toxoid was orally administered to a mouse to reach the final destination of the intestine. Upon reaching the intestine, micromotors were activated and propelled in the surrounding fluid, enabling enhanced retention and penetration of the antigenic payload. The use of pH-responsive enteric coating protected these motor toxoids from activation and degradation in the low pH environment of the stomach before reaching the intestine (Figure 9B).[94] In this approach, the motor toxoids' ability to induce an immune response against staphylococcal α-toxin was evaluated by administering the motor toxoids and static microparticle toxoids (serving as the passive control group). As indicated from the absorbance data of the ELISA assay of Figure 9C, the motor toxoids produced more IgA antibodies against α-toxin when compared with the static microparticle toxoid counterparts, confirming the benefits of active delivery. This difference was more evident in Figure 9D, where the titer data showed that the motor toxoid platform enhanced the IgA production in around one order of magnitude.

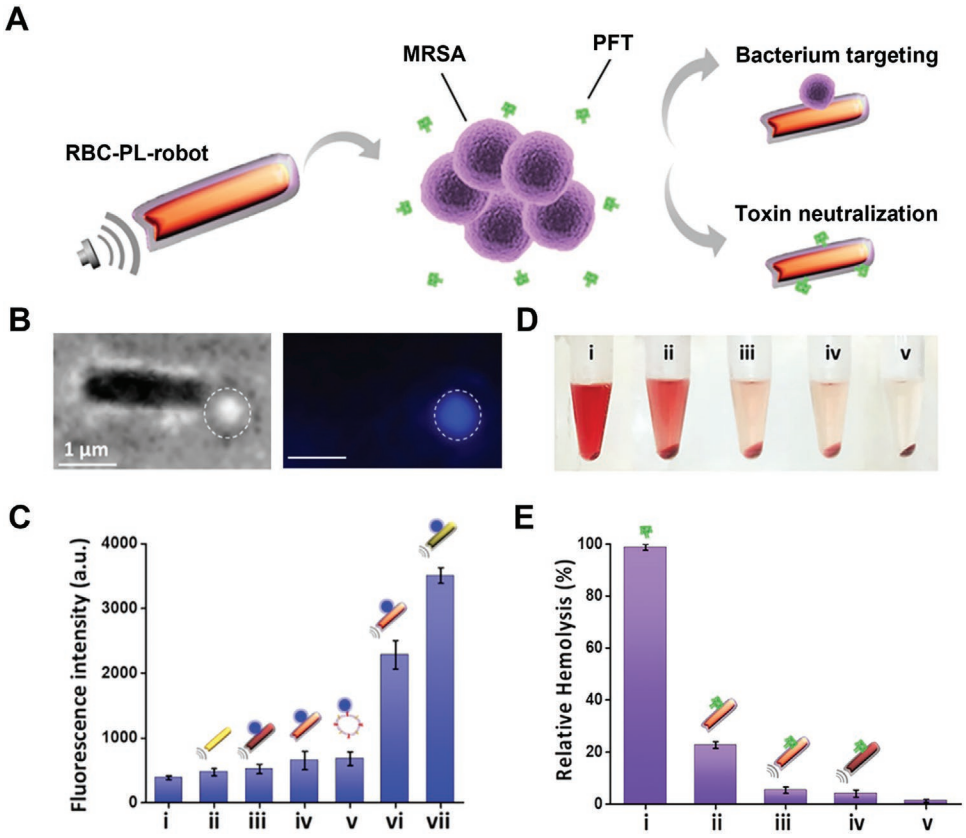


Figure 8. RBC-platelet hybrid membrane-coated micromotor (RBC-PL-motor) for detoxification. A) Schematic illustration of RBC-PL-motor for bacteria targeting and PFT neutralization. B) Microscopic and fluorescent images showing the binding of MRSA bacterium to an RBC-PL-motor. C) Fluorescence intensity of DAPI-stained MRSA bacteria retained on vi) RBC-PL-motor versus controls of i) PBS, ii) bare robots, iii) RBC-robots (without PL membranes), iv) RBC-PL-robots under a static condition, v) RBC-PL-vesicles, and vii) PL-robots (without RBC membranes). D) Images showing hemolysis of RBC solution after incubation with α-toxin in iv) acoustic-propelled RBC-robots compared with controls in i) PBS, ii) static RBC-PL-robots, iii) ultrasound-propelled RBC-PL-robots, and v) PBS without α-toxin. E) Hemolysis quantification of the samples shown in (D). Reproduced with permission.[90] Copyright 2018, AAAS.

Considering that the cell membrane-based toxin detainment platform can be extended to the safe delivery of a wide range of toxic antigenic cargoes and the efficient active delivery capabilities provided by the micromotor technology, combining these two technologies into one system is expected to pave the way in developing effective immunotherapeutic formulations that are safe, potent and easy to administer.

4.4. Photothermal Therapy

Currently, drug resistance has been a primary obstacle in disease treatment, especially for cancer therapy. To overcome this limitation, biomimetic nanoparticles coated with cancer cell membrane that inherits surface properties of source cancer cells have been combined with photothermal therapy towards enhanced targeting and adhesion with tumor cells or tissues.[95–97] Compared to passive drug carriers, the biologically interfaced dynamic vehicles combine rapid drug transport with targeted functions.

While cell membrane coating has enabled numerous added functionalities to micromotors, the efficient propulsion enabled by these synthetic motors was recently demonstrated in overcoming chemoresistance and improving cancer therapeutic efficacy. Zhou et al. demonstrated how cell membrane coating, sourced from MCF-7 cancer cells, promoted the self-thermophoretic motion of NIR light-driven semi-yolk@spiky shell carbon@silica nanomotors loaded with DOX to treat cancers (**Figure 10**A).[98] Such MC@SiO2@DOX motors were assessed in their photothermal and chemotherapeutic therapy of breast cancer (Figure 10B). The cell membrane camouflaged the motors, reduced bio-adhesion, and thus lowered their resistance to propel in the viscous cell culture media. The cellular uptake efficiency of motors increased significantly in the presence of NIR light propulsion, demonstrating that effective motor propulsion can enhance cellular uptake efficiency. The fluorescent images of Figure 10C illustrate the effectiveness of this treatment strategy, where the live cells are shown in green fluorescence before treatment while dead cells stained with red fluorescence are shown after treatment. From the treatment of controls, immobile MC@SiO2@DOX motors were found to destroy 48.2% of MCF-7 cells in a 30-min duration, whereas cell death rose to 65.6% under NIR radiation, demonstrating that the added propulsion promoted cell adhesion of the motors loaded with DOX, leading to higher cell death. Nevertheless, the most effective treatment strategy was utilizing the

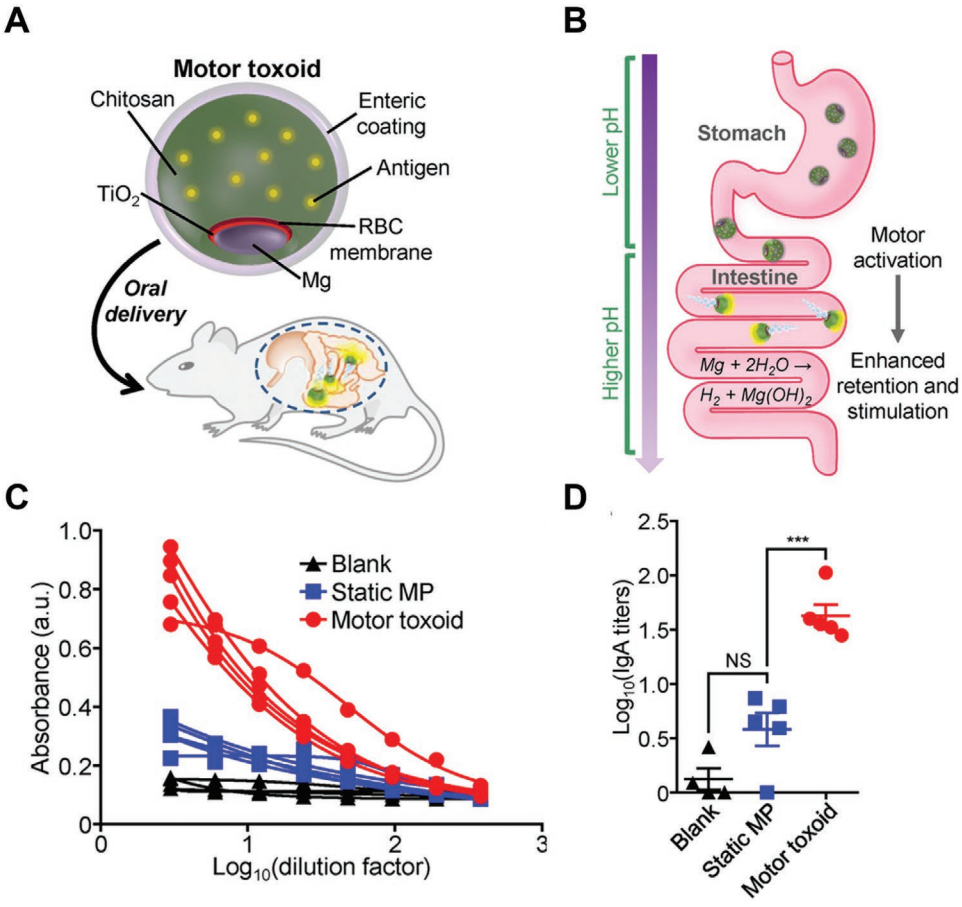


Figure 9. Toxin binding RBC membrane-coated Mg micromotor (micromotor toxoid) for oral vaccination. A) Schematic illustration of the composition of micromotor toxoid. B) Schematic of oral administration of micromotor toxoid. The active propulsion of micromotor toxoid enables enhanced motor retention and promoted immune modulation. C) The effect of enhanced retention of motor toxoid to induce immune responses against α-toxin by accessing the absorbance for IgA antibody production. D) IgA titers production against α-toxin as plotted using the data from (C). Reproduced with permission.[53] Copyright 2019, American Chemical Society.

combination of photothermal and chemotherapeutic therapy, in which MC@SiO2@DOX motors were incubated with MCF-7 cells for 30 min at low power NIR laser (980 nm, 0.8 W cm^{-2}) and 10 min at high power NIR laser (980 nm, 2 W cm^{-2}), presenting only 9.2% in cell viability, indicating enhanced treatment by combining photothermal therapy and chemotherapy (Figure 10D).

Overall, the homotypic targeting effect of cancer cell membrane-coated micromotors makes them suited for chemo/phototherapies in local tumor sites. Like cancer cell membrane, the ability of other cell membranes for specific targeting, such as platelet or white blood cells, could be utilized for chemo/photothermal therapies. Combined with the fast motion ability of micromotors, cell membrane-coated micromotors can act as powerful therapeutic vehicles with considerable promise for future cancer treatment applications.

5. Future Prospects

In this review, we discuss the preparation, characterization, and unique functions of biomembrane-modified micromotors, leveraging the attractive properties of synthetic micromotors and cell membrane-derived natural biomaterials. Such use of cell membranes to functionalize micromotors offers considerable promise for addressing major barriers that hinder in vivo operations of micromotors in complex biological environments while imparting unique capabilities that greatly enhance such operations. These attractive capabilities of cell membrane-functionalized micromotors have positioned these motors as highly promising biomimetic dynamic tools for diverse in vivo applications. Combining such intrinsic biofunctionality and adaptability of cell membranes with the dynamic propulsion of micromotors results in active biomimetic devices that enable unique synergistic effects towards a wide range of biomedical applications.

Our initial discussion describes the formation of cell membrane vesicles in nature and identifies the main fabrication processes of these cell membrane vesicles, such as homogenization, extrusion, sonication, and gas cavitation, along with coverage of early studies of passive cell membrane-coated nanoparticles. Then, we describe how micromotors based on the most common propulsion mechanisms—chemical, light, magnetic, and acoustic—have been combined with different types of cell

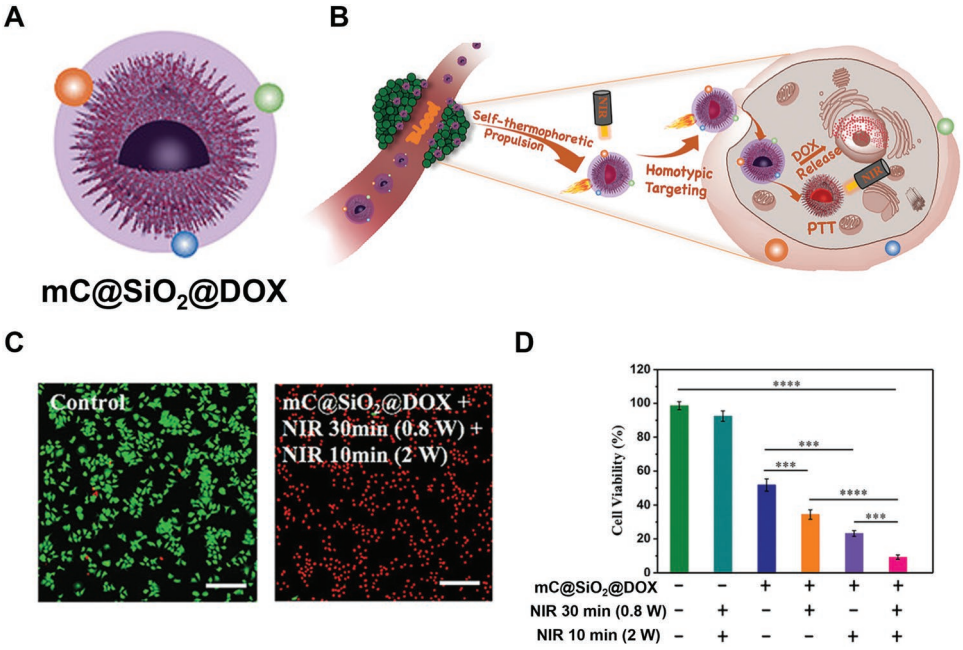


Figure 10. Self-thermophoretic induced cancer cell membrane-clocked nanomotor for photothermal therapy. A) Schematic illustration of the structure and composition of carbon@silica nanomotor. B) Schematic presenting the self-thermophoretic propulsion of nanomotor into tumor cells for photothermal and chemotherapy. C) CLSM images of MCF-7 cancer cells without and with nanomotor treatment. Calcein-AM and PI are used for live (green) and dead (red) cell staining, separately. D) Cell viabilities of MCF-7 cancer cells with different treatments. Reproduced with permission.[98] Copyright 2020, Wiley-VCH.

membranes to leverage the functions of natural cell membranes to enable different biomedical operations across a wide range of applications, including drug delivery, decontamination, immunotherapy phototherapy, and so on.

Since the initial development of cell membrane coating technology, various methods have been used to functionalize cell membrane for coatings, such as lipid insertion, membrane hybridization, metabolic engineering, and genetic modification, adding diverse functions in a non-disruptive fashion to natural cell membranes.[41] The modified membranes are expected to further enhance the multifunctional and multitasking ability of cell membrane-coated micromotors, making them more adaptive to complex biological environments. Considering the wide range of membrane-derived biomaterials based on different biological cells that provide new distinct properties (**Table 2**)[48,99–105] and the rapid advances in the field of micromotors, we expect continued future development of powerful and innovative biomimetic micromotors, offering unique capabilities and opportunities for biomedical research. For example, plasma membranes of gastric epithelial cells could be used

Table 2. Cell membranes with great promise for creating useful biomimetic micromotors.

Cell type	Genetic Engineering	Biofunction	Application	Ref.
T cell	No	Long blood circulation time; ability to recruit and localize at tumor sites; ability to detect inflammation and diseased tissues	Enhance drug targeting in gastric cancer	[99]
Stem cell	No	Secretion of paracrine factors that promote endogenous repair; triggering intracellular protective and regenerative pathways in the host	"Synthetic stem cells" for cardiac regeneration	[100]
Gastric epithelial cell	No	Surface receptors (i.e., Integrin β1, CD29) allowing for pathogen-host adhesion capability	Targeted antibiotic delivery against *H. pylori* infection	[101]
Lung epithelial cell	No	Surface receptors that pathogens depend on for cellular entry	SARS-CoV-2 neutralization	[102]
Human umbilical vascular endothelial cell	No	Release of vesicles for biocamouflaging capabilities	MRI, therapeutic application	[103]
Mosquito Aedes albopictus cell	No	Long systemic circulation; tumor-targeting ability; pathogen-binding capability	Zika virus trap to prevent viral infection	[104]
Leukemia cell	Yes C1498-VLA/VCAM	Targeting sites of inflammation; express high levels of integrin β1	Targeted drug delivery to inflamed lungs	[48]
Hybrid cell	Yes 293T-ACE	Enhanced competition with host cells for pathogen binding; neutralization of viruses and inflammatory cytokines	SARS-CoV-2 and cytokine neutralization	[105]

for improved operational capabilities of micromotors in the stomach.[101]

Despite the distinct advantages of these biomembrane-functionalized micromotors, key challenges, such as improvement of the propulsion in complex biofluid, collective actuation for targeted drug delivery, and realization of fuel-free movement, need to be addressed further towards their practical in vivo operations. Nature has provided us with many examples of realizing collective motion behavior. For example, living microorganisms can efficiently propel in biofluid and complete versatile tasks in a collective mode. Learning from nature, biohybrid micromotors—coupling natural microorganisms (e.g., sperm, bacteria, and microalgae) with artificial substrates—were fabricated in recent years to produce biofunctional devices with new and improved capabilities.[106–110] Among them, magnetic field-driven sperm can be controlled to swim toward an egg for assisted fertilization.[106] Magneto-aerotactic bacteria carrying drug-loaded liposomes has been delivered to tumor hypoxic regions.[108] Phototactic algae were steered under visible light to collectively self-propel for on-demand cargo delivery.[110] Looking forward, the integration of multifunctionality, versatility, and adaptivity of cell membranes with the smart behavior of natural micromotors and the efficient propulsion of synthetic micromotors, will create powerful biohybrid systems with expanded capabilities towards diverse in-vitro and in-vivo operations. Such future developments of biomimetic micromotors require close collaborative efforts among researchers from different disciplines. The new capabilities of cell membrane-functionalized micromotors are expected to advance the fields of micromotors and nanomedicine.

Acknowledgements

This work is supported by the Defense Threat Reduction Agency Joint Science and Technology Office for Chemical and Biological Defense under Grant Number HDTRA1-18-1-0014 and the National Science Foundation Grant DMR-1904702.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Keywords

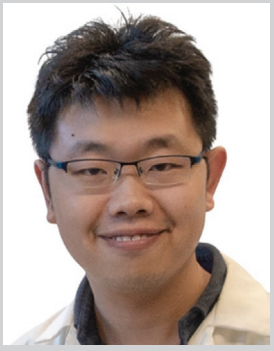
cell membranes, detoxification, drug delivery, immunotherapy, micromotors, phototherapy

Received: September 9, 2021
Revised: October 14, 2021
Published online: December 18, 2021

[1] J. Wang, *Nanomachines: Fundamentals and Applications*, Wiley-VCH, Weinheim, Germany **2013**.
[2] Q. Wang, L. Zhang, *ACS Nano* **2021**, *15*, 149.
[3] H. Wang, M. Pumera, *Chem. Rev.* **2015**, *115*, 8704.
[4] J. Wang, W. Gao, *ACS Nano* **2012**, *6*, 5745.
[5] J. Li, B. E.-F. de Ávila, W. Gao, L. Zhang, J. Wang, *Sci. Robot.* **2017**, *2*, eaam6431.
[6] S. Tottori, L. Zhang, F. Qiu, K. K. Krawczyk, A. Franco-Obregón, B. J. Nelson, *Adv. Mater.* **2012**, *24*, 811.
[7] B. E.-F. de Ávila, P. Angsantikul, J. Li, W. Gao, L. Zhang, J. Wang, *Adv. Funct. Mater.* **2018**, *28*, 1705640.
[8] B. E.-F. de Ávila, P. Angsantikul, J. Li, M. Angel Lopez-Ramirez, D. E. Ramírez-Herrera, S. Thamphiwatana, C. Chen, J. Delezuk, R. Samakapiruk, V. Ramez, L. Zhang, J. Wang, *Nat. Commun.* **2017**, *8*, 272.
[9] W. Gao, R. Dong, S. Thamphiwatana, J. Li, W. Gao, L. Zhang, J. Wang, *ACS Nano* **2015**, *9*, 117.
[10] B. E.-F. de Ávila, W. Gao, E. Karshalev, L. Zhang, J. Wang, *Acc. Chem. Res.* **2018**, *51*, 1901.
[11] C. Gao, Z. Lin, X. Lin, Q. He, *Adv. Therap.* **2018**, *1*, 1800056.
[12] Z. Wu, J. Li, B. E. F. de Ávila, T. Li, W. Gao, Q. He, L. Zhang, J. Wang, *Adv. Funct. Mater.* **2015**, *25*, 7497.
[13] J. Li, P. Angsantikul, W. Liu, B. E.-F. de Ávila, X. Chang, E. Sandraz, Y. Liang, S. Zhu, Y. Zhang, C. Chen, W. Gao, L. Zhang, J. Wang, *Adv. Mater.* **2018**, *30*, 1704800.
[14] R. H. Fang, A. V. Kroll, W. Gao, L. Zhang, *Adv. Mater.* **2018**, *30*, 1706759.
[15] Q.-V. Le, J. Lee, H. Lee, G. Shim, Y.-K. Oh, *Acta Pharm. Sin. B* **2021**, *11*, 2096.
[16] J. Gao, D. F. Chu, Z. J. Wang, *J. Controlled Release* **2016**, *224*, 208.
[17] G. van Niel, G. D'Angelo, G. Raposo, *Nat. Rev. Mol. Cell Biol.* **2018**, *19*, 213.
[18] S. Gill, R. Catchpole, P. Forterre, *FEMS Microbiol. Rev.* **2019**, *43*, 273.
[19] D. M. Pegtel, S. J. Gould, *Annu. Rev. Biochem.* **2019**, *88*, 487.
[20] I. M. Bjorge, S. Y. Kim, J. F. Mano, B. Kalionis, W. Chrzanowski, *Biomater. Sci.* **2017**, *6*, 60.
[21] T. K. Phan, D. C. Ozkocak, I. K. H. Poon, *Biochem. Soc. Trans.* **2020**, *48*, 2079.
[22] M. Saenz-Cuesta, M. Mittelbrunn, D. Otaegui, *Front. Immunol.* **2015**, *6*, 381.
[23] S. Stremersch, S. C. De Smedt, K. Raemdonck, *J. Controlled Release* **2016**, *244*, 167.
[24] O. P. B. Wiklander, M. A. Brennan, J. Lotval, X. O. Breakefield, S. El Andaloussi, *Sci. Transl. Med.* **2019**, *11*, eaav8521.
[25] C. M. J. Hu, L. Zhang, S. Aryal, C. Cheung, R. H. Fang, L. Zhang, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 10980.
[26] B. T. Luk, C. M. J. Hu, R. H. Fang, D. Dehaini, C. Carpenter, W. Gao, L. Zhang, *Nanoscale* **2014**, *6*, 2730.
[27] S. Aryal, C. M. J. Hu, R. H. Fang, D. Dehaini, C. Carpenter, D. E. Zhang, L. Zhang, *Nanomedicine* **2013**, *8*, 1271.
[28] C. M. J. Hu, R. H. Fang, J. Copp, B. T. Luk, L. Zhang, *Nat. Nanotechnol.* **2013**, *8*, 336.
[29] J. A. Copp, R. H. Fang, B. T. Luk, C. M. J. Hu, W. Gao, K. Zhang, L. Zhang, *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 13481.
[30] Z. Q. Pang, C. M. J. Hu, R. H. Fang, B. T. Luk, W. Gao, F. Wang, E. Chuluun, P. Angsantikul, S. Thamphiwatana, W. Y. Lu, X. G. Jiang, L. Zhang, *ACS Nano* **2015**, *9*, 6450.
[31] Y. Chen, Z. Jia, J. Zhuang, J. H. Lee, L. Wang, R. H. Fang, W. Gao, L. Zhang, *ACS Nano* **2019**, *13*, 7209.
[32] C. M. J. Hu, R. H. Fang, B. T. Luk, L. Zhang, *Nat. Nanotechnol.* **2013**, *8*, 933.
[33] A. V. Kroll, R. H. Fang, L. Zhang, *Bioconjugate Chem.* **2017**, *28*, 23.
[34] H. Gong, Q. Zhang, A. Komarla, S. Wang, Y. Duan, Z. Zhou, F. Chen, R. H. Fang, S. Xu, W. Gao, L. Zhang, *Nano Lett.* **2021**, *21*, 2603.

[35] W. Gao, C. M. J. Hu, R. H. Fang, B. T. Luk, J. Su, L. Zhang, *Adv. Mater.* **2013**, *25*, 3549.
[36] Y. Zhang, J. H. Zhang, W. S. Chen, P. Angsantikul, K. A. Spiekermann, R. H. Fang, W. Gao, L. Zhang, *J. Controlled Release* **2017**, *263*, 185.
[37] J. Sherwood, J. Sowell, N. Beyer, J. Irvin, C. Stephen, A. J. Antone, Y. P. Bao, L. M. Ciesla, *Nanoscale* **2019**, *11*, 6352.
[38] W. Chen, Q. Zhang, B. T. Luk, R. H. Fang, Y. Liu, W. Gao, L. Zhang, *Nanoscale* **2016**, *8*, 10364.
[39] W. H. Chooi, Q. Dong, J. Z. Y. Low, C. Yuen, J. S. Chin, J. Lin, W. Ong, Q. Liu, S. Y. Chew, *ACS Appl. Bio Mater.* **2021**, *4*, 4079.
[40] H. Gong, F. Chen, Z. Huang, Y. Gu, Q. Zhang, Y. Chen, Y. Zhang, J. Zhuang, Y. K. Cho, R. H. Fang, W. Gao, S. Xu, L. Zhang, *ACS Nano* **2019**, *13*, 3714.
[41] X. Ai, S. Wang, Y. Duan, Q. Zhang, M. Chen, W. Gao, L. Zhang, *Biochemistry* **2021**, *60*, 941.
[42] R. H. Fang, C. M. J. Hu, K. N. H. Chen, B. T. Luk, C. W. Carpenter, W. Gao, S. Li, D.-E. Zhang, W. Lu, L. Zhang, *Nanoscale* **2013**, *5*, 8884.
[43] D. Dehaini, X. Wei, R. H. Fang, S. Masson, P. Angsantikul, B. T. Luk, Y. Zhang, M. Ying, Y. Jiang, A. V. Kroll, W. Gao, L. Zhang, *Adv. Mater.* **2017**, *29*, 1606209.
[44] W.-L. Liu, M.-Z. Zou, T. Liu, J.-Y. Zeng, X. Li, W.-Y. Yu, C.-X. Li, J. Ye, W. Song, J. Feng, X.-Z. Zhang, *Nat. Commun.* **2019**, *10*, 3199.
[45] Y. T. Han, H. Pan, W. J. Li, Z. Chen, A. Q. Ma, T. Yin, R. J. Liang, F. M. Chen, N. Ma, Y. Jin, M. B. Zheng, B. H. Li, L. T. Cai, *Adv. Sci.* **2019**, *6*, 1900251.
[46] F. Zhang, L. J. Zhao, S. M. Wang, J. Yang, G. H. Lu, N. N. Luo, X. Y. Gao, G. H. Ma, H. Y. Xie, W. Wei, *Adv. Funct. Mater.* **2018**, *28*, 1703326.
[47] Y. Jiang, N. Krishnan, J. Zhou, S. Chekuri, X. Wei, A. V. Kroll, C. L. Yu, Y. Duan, W. Gao, R. H. Fang, L. Zhang, *Adv. Mater.* **2020**, *32*, 2001808.
[48] J. H. Park, Y. Jiang, J. R. Zhou, H. Gong, A. Mohapatra, J. Y. Heo, W. Gao, R. H. Fang, L. Zhang, *Sci. Adv.* **2021**, *7*, eabf7820.
[49] L. Rao, Q.-F. Meng, L.-L. Bu, B. Cai, Q. Huang, Z.-J. Sun, W.-F. Zhang, A. Li, S.-S. Guo, W. Liu, *ACS Appl. Mater. Interfaces* **2017**, *9*, 2159.
[50] J.-G. Piao, L. Wang, F. Gao, Y.-Z. You, Y. Xiong, L. Yang, *ACS Nano* **2014**, *8*, 10414.
[51] J. Parmar, D. Vilela, K. Villa, J. Wang, S. Sanchez, *J. Am. Chem. Soc.* **2018**, *140*, 9317.
[52] Z. Wu, T. Li, W. Gao, T. Xu, B. Jurado-Sánchez, J. Li, W. Gao, Q. He, L. Zhang, J. Wang, *Adv. Funct. Mater.* **2015**, *25*, 3881.
[53] X. Wei, M. Beltrán-Gastélum, E. Karshalev, B. E.-F. de Ávila, J. Zhou, D. Ran, P. Angsantikul, R. H. Fang, J. Wang, L. Zhang, *Nano Lett.* **2019**, *19*, 1914.
[54] C. Gao, Z. Lin, D. Wang, Z. Wu, H. Xie, Q. He, *ACS Appl. Mater. Interfaces* **2019**, *11*, 23392.
[55] F. Zhang, J. Zhuang, B. E.-F. de Ávila, S. Tang, Q. Zhang, R. H. Fang, L. Zhang, J. Wang, *ACS Nano* **2019**, *13*, 11996.
[56] J. Shao, M. Abdelghani, G. Shen, S. Cao, D. S. Williams, J. C. Van Hest, *ACS Nano* **2018**, *12*, 4877.
[57] S. Wang, Y. Duan, Q. Zhang, A. Komarla, H. Gong, W. Gao, L. Zhang, *Small Struct.* **2020**, *1*, 2000018.
[58] J. Chen, J. A. Lopez, *Microcirculation* **2005**, *12*, 235.
[59] M. Olsson, P. Bruhns, W. A. Frazier, J. V. Ravetch, P.-A. Oldenborg, *Blood* **2005**, *105*, 3577.
[60] S. S. Kunde, S. Wairkar, *Int. J. Pharm.* **2021**, *598*, 120395.
[61] C.-M. J. Hu, R. H. Fang, K.-C. Wang, B. T. Luk, S. Thamphiwatana, D. Dehaini, P. Nguyen, P. Angsantikul, C. H. Wen, A. V. Kroll, C. Carpenter, M. Ramesh, V. Qu, S. H. Patel, J. Zhu, W. Shi, F. M. Hofman, T. C. Chen, W. Gao, K. Zhang, S. Chien, L. Zhang, *Nature* **2015**, *526*, 118.
[62] Q. Hu, W. Sun, C. Qian, C. Wang, H. N. Bomba, Z. Gu, *Adv. Mater.* **2015**, *27*, 7043.
[63] J. Zhuang, H. Gong, J. Zhou, Q. Zhang, W. Gao, R. H. Fang, L. Zhang, *Sci. Adv.* **2020**, *6*, eaaz6108.
[64] S. Tang, F. Zhang, H. Gong, F. Wei, J. Zhuang, E. Karshalev, B. E.-F. de Ávila, C. Huang, Z. Zhou, Z. Li, L. Yin, H. Dong, R. H. Fang, X. Zhang, L. Zhang, J. Wang, *Sci. Rob.* **2020**, *5*, eaba6137.
[65] J. Li, S. Sattayasamitsathit, R. Dong, W. Gao, R. Tam, X. Feng, S. Ai, J. Wang, *Nanoscale* **2014**, *6*, 9415.
[66] R. H. Fang, C.-M. J. Hu, B. T. Luk, W. Gao, J. A. Copp, Y. Tai, D. E. O'Connor, L. Zhang, *Nano Lett.* **2014**, *14*, 2181.
[67] H. Zhang, Z. Li, Z. Wu, Q. He, *Adv. Therap.* **2019**, *2*, 1900096.
[68] H. Harjunpaa, M. L. Asens, C. Guenther, S. C. Fagerholm, *Front. Immunol.* **2019**, *10*, 1078.
[69] S. Thamphiwatana, P. Angsantikul, T. Escajadillo, Q. Zhang, J. Olsan, B. T. Luk, S, Z. , R. H. Fang, W. Gao, V. Nizet, L. Zhang, *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 11488.
[70] A. J. Rushton, G. Nteliopoulos, J. A. Shaw, R. C. Coombes, *Cancers* **2021**, *13*, 970.
[71] J. Winkler, A. Abisoye-Ogunniyan, K. J. Metcalf, Z. Werb, *Nat. Commun.* **2020**, *11*, 5120.
[72] X. Wei, D. Ran, A. Campeau, C. Xiao, J. Zhou, D. Dehaini, Y. Jiang, A. V. Kroll, Q. Zhang, W. Gao, D. J. Gonzalez, R. H. Fang, L. Zhang, *Nano Lett.* **2019**, *19*, 4760.
[73] A. Parodi, N. Quattrocchi, A. L. Van De Ven, C. Chiappini, M. Evangelopoulos, J. O. Martinez, B. S. Brown, S. Z. Khaled, I. K. Yazdi, M. V. Enzo, L. Isenhart, M. Ferrari, E. Tasciotti, *Nat. Nanotechnol.* **2013**, *8*, 61.
[74] D. Wang, C. Gao, W. Wang, M. Sun, B. Guo, H. Xie, Q. He, *ACS Nano* **2018**, *12*, 10212.
[75] D. Wang, C. Gao, C. Zhou, Z. Lin, Q. He, *Research* **2020**, *2020*, 3676954.
[76] M. Xuan, J. Shao, C. Gao, W. Wang, L. Dai, Q. He, *Angew. Chem., Int. Ed.* **2018**, *57*, 12463.
[77] L. Y. Chou, K. Ming, W. C. Chan, *Chem. Soc. Rev.* **2011**, *40*, 233.
[78] F. Zhao, Y. Zhao, Y. Liu, X. Chang, C. Chen, Y. Zhao, *Small* **2011**, *7*, 1322.
[79] B. E.-F. de Ávila, A. Martín, F. Soto, M. A. Lopez-Ramirez, S. Campuzano, G. M. Vásquez-Machado, W. Gao, L. Zhang, J. Wang, *ACS Nano* **2015**, *9*, 6756.
[80] B. E.-F. de Ávila, C. Angell, F. Soto, M. A. Lopez-Ramirez, D. F. Báez, S. Xie, J. Wang, Y. Chen, *ACS Nano* **2016**, *10*, 4997.
[81] P. L. Venugopalan, B. Esteban-Fernández de Ávila, M. Pal, A. Ghosh, J. Wang, *ACS Nano* **2020**, *14*, 9423.
[82] P. L. Giangrande, *Br. J. Haematol.* **2000**, *110*, 758.
[83] L. M. Napolitano, S. Kurek, F. A. Luchette, H. L. Corwin, P. S. Barie, S. A. Tisherman, P. C. Hebert, G. L. Anderson, M. R. Bard, W. Bromberg, W. C. Chiu, M. D. Cipolle, K. D. Clancy, L. Diebel, W. S. Hoff, K. M. Hughes, I. Munshi, D. Nayduch, R. Sandhu, *J. Trauma Acute Care Surg.* **2009**, *67*, 1439.
[84] J. Zhuang, M. Ying, K. Spiekermann, M. Holay, Y. Zhang, F. Chen, H. Gong, J. H. Lee, W. Gao, R. H. Fang, L. Zhang, *Adv. Mater.* **2018**, *30*, 1804693.
[85] M. Pal, N. Somalwar, A. Singh, R. Bhat, S. M. Eswarappa, D. K. Saini, A. Ghosh, *Adv. Mater.* **2018**, *30*, 1800429.
[86] Z. Wu, X. Lin, Y. Wu, T. Si, J. Sun, Q. He, *ACS Nano* **2014**, *8*, 6097.
[87] J. Shao, M. Xuan, H. Zhang, X. Lin, Z. Wu, Q. He, *Angew. Chem., Int. Ed.* **2017**, *129*, 13115.
[88] H. Zhang, Z. Li, C. Gao, X. Fan, Y. Pang, T. Li, Z. Wu, H. Xie, Q. He, *Sci. Rob.* **2021**, *6*, eaaz9519.
[89] R. H. Fang, B. T. Luk, C.-M. J. Hu, L. Zhang, *Adv. Drug Delivery Rev.* **2015**, *90*, 69.

[90] B. E.-F. de Ávila, P. Angsantikul, D. E. Ramírez-Herrera, F. Soto, H. Teymourian, D. Dehaini, Y. Chen, L. Zhang, J. Wang, *Sci. Rob.* **2018**, *3*, eaat0485.
[91] T. L. Cover, U. S. Krishna, D. A. Israel, R. M. Peek, *Cancer Res.* **2003**, *63*, 951.
[92] R. H. Fang, L. Zhang, *Annu. Rev. Chem. Biomol. Eng.* **2016**, *7*, 305.
[93] J. Zhou, A. V. Kroll, M. Holay, R. H. Fang, L. Zhang, *Adv. Mater.* **2020**, *32*, 1901255.
[94] S. Zhang, A. M. Bellinger, D. L. Glettig, R. Barman, Y.-A. L. Lee, J. Zhu, C. Cleveland, V. A. Montgomery, L. Gu, L. D. Nash, D. J. Maitland, R. Langer, G. Traverso, *Nat. Mater.* **2015**, *14*, 1065.
[95] H. Sun, J. Su, Q. Meng, Q. Yin, L. Chen, W. Gu, P. Zhang, Z. Zhang, H. Yu, S. Wang, *Adv. Mater.* **2016**, *28*, 9581.
[96] Z. Chen, P. Zhao, Z. Luo, M. Zheng, H. Tian, P. Gong, G. Gao, H. Pan, L. Liu, A. Ma, *ACS Nano* **2016**, *10*, 10049.
[97] S.-Y. Li, B.-R. Xie, H. Cheng, C.-X. Li, M.-K. Zhang, W.-X. Qiu, W.-L. Liu, X.-S. Wang, X.-Z. Zhang, *Biomaterials* **2018**, *151*, 1.
[98] M. Zhou, Y. Xing, X. Li, X. Du, T. Xu, X. Zhang, *Small* **2020**, *16*, 2003834.
[99] L. Zhang, R. Li, H. Chen, J. Wei, H. Qian, S. Su, J. Shao, L. Wang, X. Qian, B. Liu, *Int. J. Nanomed.* **2017**, *12*, 2129.
[100] J. Tang, D. Shen, T. G. Caranasos, Z. Wang, A. C. Vandergriff, T. A. Allen, M. T. Hensley, P.-U. Dinh, J. Cores, T.-S. Li, J. Zhang, Q. Kan, K. Cheng, *Nat. Commun.* **2017**, *8*, 13724.
[101] P. Angsantikul, S. Thamphiwatana, Q. Zhang, K. Spiekermann, J. Zhuang, R. H. Fang, W. Gao, M. Obonyo, L. Zhang, *Adv. Ther.* **2018**, *1*, 1800016.
[102] Q. Zhang, A. Honko, J. Zhou, H. Gong, S. N. Downs, J. H. Vasquez, R. H. Fang, W. Gao, A. Griffiths, L. Zhang, *Nano Lett.* **2020**, *20*, 5570.
[103] A. K. A. Silva, R. Di Corato, T. Pellegrino, S. Chat, G. Pugliese, N. Luciani, F. Gazeau, C. Wilhelm, *Nanoscale* **2013**, *5*, 11374.
[104] L. Rao, W. Wang, Q.-F. Meng, M. Tian, B. Cai, Y. Wang, A. Li, M. Zan, F. Xiao, L.-L. Bu, *Nano Lett.* **2019**, *19*, 2215.
[105] L. Rao, S. Xia, W. Xu, R. Tian, G. Yu, C. Gu, P. Pan, Q.-F. Meng, X. Cai, D. Qu, *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 27141.
[106] M. Medina-Sanchez, L. Schwarz, A. K. Meyer, F. Hebenstreit, O. G. Schmidt, *Nano Lett.* **2016**, *16*, 555.
[107] A. V. Singh, Z. Hosseinidoust, B. W. Park, O. Yasa, M. Sitti, *ACS Nano* **2017**, *11*, 9759.
[108] O. Felfoul, M. Mohammadi, S. Taherkhani, D. De Lauauze, Y. Z. Xu, D. Loghin, S. Essa, S. Jancik, D. Houle, M. Lafleur, L. Gaboury, M. Tabrizian, N. Kaou, M. Atkin, T. Vuong, G. Batist, N. Beauchemin, D. Radzioch, S. Martel, *Nat. Nanotechnol.* **2016**, *11*, 941.
[109] D. B. Weibel, P. Garstecki, D. Ryan, W. R. Diluzio, M. Mayer, J. E. Seto, G. M. Whitesides, *Proc. Natl. Acad. Sci. USA* **2005**, *12*, 11963.
[110] M. B. Akolpoglu, N. O. Dogan, U. Bozuyuk, H. Ceylan, S. Kizilel, M. Sitti, *Adv. Sci.* **2020**, *7*, 2001256.



Fangyu Zhang is a Ph.D. candidate in nanoengineering at the University of California San Diego under the supervision of Prof. Joseph Wang. His research focused on developing novel biohybrid micro/nanorobots—coupling versatile modes of propulsion with unique cell/cell membrane functionalities—for applications including drug delivery and detoxification. He received his B.S. in materials science and engineering at Shanghai Jiao Tong University and M.S. in biological and environmental engineering at Cornell University.

Rodolfo Mundaca-Uribe is a Ph.D. candidate in nanoengineering at the University of California San Diego. He received his B.S. degree in pharmacy and M.S. degree in pharmaceutical sciences from the University of Concepcion, Chile. His research interests are focused on the development of novel platforms towards active drug delivery, microrobotics, and pharmaceutical analytical chemistry.

Nelly Askarinam is a Ph.D. student at the University of California, San Diego in the Department of Chemistry. She received her B.S. in psychobiology from the University of California, Los Angeles and subsequently received her M.S. in chemistry from the University of California, San Diego. Her research interests include fabricating micromotors and smart materials for drug delivery applications.

Zhengxing Li is a Ph.D. candidate at the materials science and engineering program at the University of California, San Diego. His research focuses on developing bio-micromotor and targeting in vivo applications. He holds his B.S. degree in biomedical engineering from the Beihang University of China and M.S. degree in materials science and engineering from UCSD.

Weiwei Gao is an associate project scientist in the Department of NanoEngineering at the University of California San Diego. He received his Ph.D. in chemical engineering at Yale University. His research is focused on developing biomimetic nanoparticles for drug delivery and biodetoxification applications.

Liangfang Zhang is a professor in the Department of NanoEngineering and Moores Cancer Center at the University of California San Diego. He received his Ph.D. in chemical and biomolecular engineering at the University of Illinois at Urbana–Champaign. His research aims to create cutting-edge biomimetic nanotechnologies and exploit them for various biomedical applications with a particular focus on drug delivery, biodetoxification, and vaccination. Prof. Zhang is a Thomson Reuters Highly Cited Researcher.

Joseph Wang is distinguished professor, SAIC Endowed Chair, and former chair of the Department of Nanoengineering at the University of California, San Diego. He is also the director of the UCSD Center of Wearable Sensors. His scientific interests are concentrated in the areas of bioelectronics, wearable biosensors, and microrobots. Prof. Wang has been the founding editor of *Electroanalysis* (Wiley), is RSC, ECS and AIMBE Fellow and a Thomson Reuters Highly Cited Researcher. He received two American Chemical Society Awards in 1999 (Instrumentation) and 2006 (Electrochemistry).