

Recent Advances in Membrane-Coated Micro/Nanomotors in Biological Applications

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Abstract: The integration of synthetic micro/nanomotors (MNM) with natural biomaterials derived from cell membranes has emerged as a highly promising strategy for advancing biological applications. The membrane-coated MNM offers distinct advantages over earlier MNMs dependent on chemical fuels such as hydrogen peroxide, which were prone to poor biocompatibility and harmful byproducts. These include enhanced biocompatibility, immune evasion via natural membrane surfaces, multifunctionality for drug delivery, self-propulsion in complex environments, self-degradation to reduce residual toxicity and inherent imaging capabilities enabling real-time tracking. This review provides a comprehensive overview of the integration of various types of micromotors with natural cell membranes commonly present in the circulatory system. Additionally, it summarizes the methodologies for the preparation, characterization and functional evaluation of biofilm-modified micromotors. The present article also critically examines current developments in biofilm-modified micromotors, addressing their challenges and limitations in enhancing clinical efficacy and facilitating transition to clinical trials in humans.

Keywords: micro/nanomotors, nanodrugs, membrane-coated, self-propulsion, drug delivery

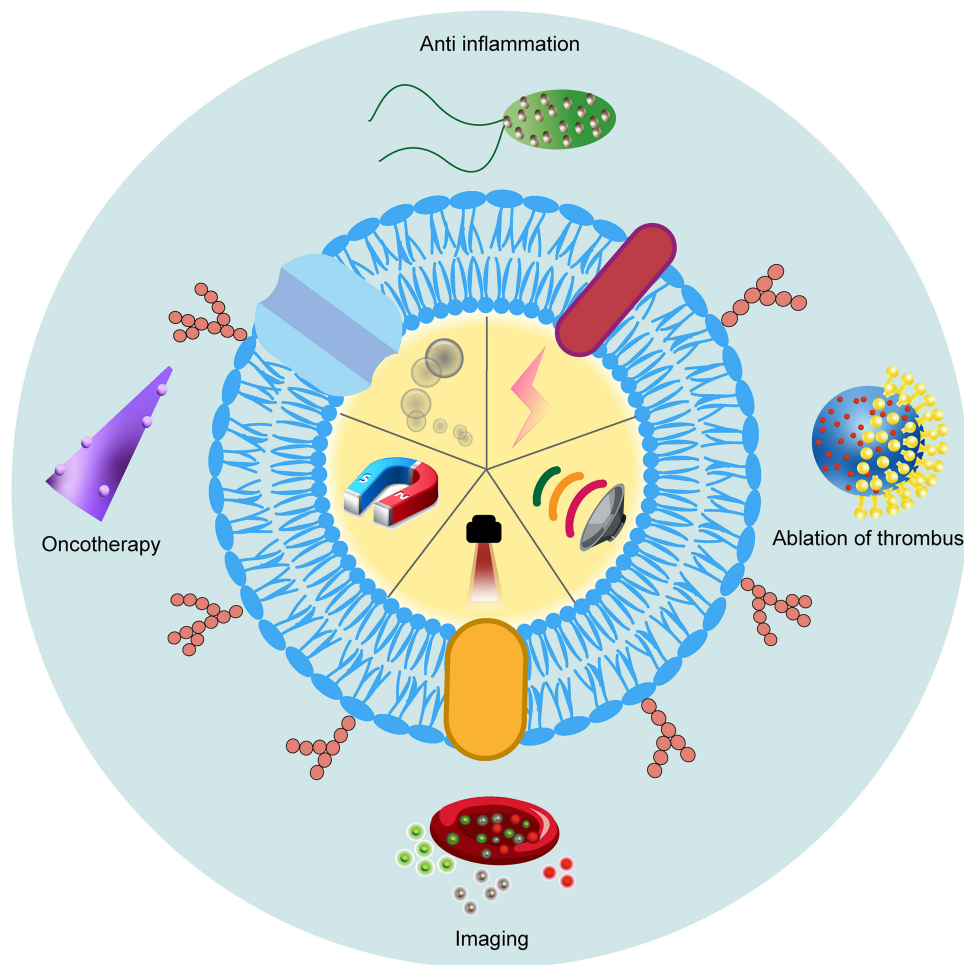
Introduction

MNMs are micro/nanoscale objects capable of using internal (chemical fuel,¹ enzyme-powered^{2,3}) or external energy (electric field,⁴ magnetic field,⁵ light,⁶ ultrasound,⁷ X-ray⁸) energies to create bubbles, local potential differences, diffusion gradients, temperature differences and surface tension gradients. These artificial MNMs have demonstrated exceptional capabilities to navigate through biofluids,^{9,10} while engaging in numerous critical tasks for biomedical applications^{11,12} including targeted drug delivery,^{13–16} immunomodulation,^{17,18} adjunctive therapies¹⁹ such as in vivo imaging,²⁰ barrier penetration,²¹ diagnostics^{13,22,23} and precision surgery.^{16,24–27} However, exposed artificial motors deliver various disadvantages including simple detection and action by the reticuloendothelial system, which also leads to the rapid elimination from the body.²⁸ Synthetic materials are sensitive to immunological responses and biofouling in complex biological systems, which hinder the function and efficiency of MNMs.^{29–32} Therefore, biocompatible and bionic setups are required for MNMs to function in the physiological milieu for an extended period.

Many researchers have explored bionic MNMs that utilize natural cell membranes to camouflage motors³³ to address this critical challenge. The preparation strategies for MNM primarily involve physical assembly (ultrasonication³³ and



Graphical Abstract



extrusion)³⁴, chemical modification (surface anchoring)³⁵ and biological membrane reconstitution,²⁹ focusing on modulating the affinity between the membrane and motor while preserving membrane functionality to meet biological application requirements. In 2011, Zhang et al introduced nanoparticles based on biomimetic materials.³⁶ The research team synthesized RBC-NPs by extruding erythrocyte membranes. In addition, researchers have developed several alternative methods to coat cell membranes derived from stem cells,^{37,38} cancer cells,³⁹ macrophages,^{40,41} neutrophils,⁴² natural killer cells,⁴³ T cells⁴⁴ and platelets.⁴⁵ This approach utilizes the essential biological functions of innate cells including immune cloaking, precise antigen delivery, tissue-specific targeting, long-cycle characteristics and selective binding to bacterial toxins or pathogens. The combination of synthetic motors and the advantages of their dynamic motor has resulted in the development of cell-like micromotors, which exhibit the characteristics of progenitor cells and high efficacy in biocompatibility and autologous appearance.⁴⁶ Due to their rapid advancement, bio-functional MNMs are becoming a key hotspot in biomedical research.¹⁵ The functionalization of cell membranes enables artificial motors to be biocompatible, which further allows micromotor research to move from lab tubes to biological systems. This review focuses on the unique capabilities, recent advancements and representative applications of cell membrane-functionalized micromotors.

Membrane-Functionalized MNMs

RBC Membrane-Functionalized MNMs

Erythrocytes play a vital role in the transportation of oxygen within the bloodstream and represent the majority of blood cells in vertebrates.⁴⁷ Current evidence indicates that erythrocytes possess significant biocompatibility, biodegradability and non-immunogenicity, which can be highly suitable for bioengineering applications (Table 1).^{48–50} Erythrocytes eliminate toxins and circulate for prolonged periods.⁴⁷ Membranes from mature erythrocytes are easier to separate and purify due to the absence of nuclei.⁵¹ Considering these characteristics, erythrocyte membranes are a highly suitable source for the development of MNMs.

In 2014, Wu et al²⁹ proposed and developed a bionic micromotor covered by the erythrocyte membrane (Figure 1A). This motor with cell camouflage was designed by combining ferric oxide nanoparticles (20 nm) into the vesicles of the erythrocyte membrane through a hypotonic dilution/encapsulation technique. Red blood cell motors preserve the discoid form of RBCs with a diameter of $6\pm 8\ \mu\text{m}$. Magnetic fields exhibit stable, high-speed ($13\text{--}14\ \mu\text{m s}^{-1}$), efficient and adaptable ultrasonic transportation in multiple biological media including blood, which can be an effective toxin bait for absorbing membrane-damaging toxins. Wu et al⁵² reported an RBC membrane-functionalized magnesium-based Janus micromotor (Figure 1B) constructed by integrating RBC membranes, gold nanoparticles (AuNPs) and alginate (ALG) onto the exposed surface area of Mg microparticles partially embedded in a paraffin film. Natural motile cells are driven by spontaneous magnesium-water reaction, high-current corrosion of AuNPs and pitting corrosion of coexisting chloride ions. Researchers have revealed that the magnesium core of RBC-Mg Janus motors remains intact after the magnesium core is completely dissolved in the alpha-toxin/albumin solution. The RBC membrane neutralizes alpha toxin and protects the cells. It was found that the detoxifying level was significantly enhanced. An alternative to double concave discs was constructed with a smaller rod-like motor³³ (Figure 1C). Biomimetic motor sponges were designed under ultrasound using gold nanowires modified with a negative charge and erythrocyte membrane vesicles. Motor sponges possessed a “right-side-out membrane orientation”, facilitating the selective uptake of pore-forming toxins and protecting them from non-specific protein adsorption within their biological medium.

Table 1 Summary of RBC Membrane-Functionalized MNMs

Substrate	Propulsion Source	Size	Speed	Environment	Application Field	Ref.
RBCs	Acoustically powered and magnetically navigated	$6\pm 8\ \mu\text{m}$	$13\text{--}14\ \mu\text{m s}^{-1}$	Whole blood	Absorption and neutralization of hemolytic toxins	[29]
RBCs	Acoustically powered and magnetically navigated	$400\ \mu\text{m}$ with 6–8 nm thick fluid-like lipid bilayer	$14\ \mu\text{m s}^{-1}$, $27\ \mu\text{m s}^{-1}$	Whole blood and distilled water	Absorption and neutralization of hemolytic toxins	[33]
RBCs	Bubble propulsion	$20\ \mu\text{m}$	$172\ \mu\text{m s}^{-1}$, $33\ \mu\text{m s}^{-1}$	Distilled water and albumin medium	Absorption and neutralization of hemolytic toxins	[52]
RBCs	Acoustically powered and magnetically navigated	$6\text{--}8\ \mu\text{m}$	$14\pm(1\text{--}2)\ \mu\text{m s}^{-1}/155\ \mu\text{m s}^{-1}$	2.4MHz, a Triton lysis buffer solution: 2V/8V	Cargo transport, drug delivery and thermal imaging	[53]
RBCs	Near-infrared light drive: thermal gradient	$\approx 5\ \mu\text{m}$	Max: $19.8\ \mu\text{m s}^{-1}$ $12.10\ \mu\text{m s}^{-1}$, $3.52\ \mu\text{m s}^{-1}$, $2.33\ \mu\text{m s}^{-1}$	PBS, medium, serum and blood	Ablation of thrombus	[54]
RBCs and Escherichia coli	Self-propulsion and magnetically navigated	$\approx 5\ \mu\text{m}$	$10.2\pm 3.5\ \mu\text{m s}^{-1}$	Magnetic field (20 mT)	Cargo delivery	[55]
RBCs	Acoustically powered and magnetically navigated	$2.1\pm 0.3\ \mu\text{m}$	Max: $56.5\ \mu\text{m s}^{-1}$ $15.39\ \mu\text{m s}^{-1}$, $10.13\ \mu\text{m s}^{-1}$, $7.15\ \mu\text{m s}^{-1}$	2.15Hz, 0.5W: PBS, medium, serum and blood	Cancer therapy	[56]
RBCs	Acoustically powered	$\approx 400\text{nm}$	$8.4\ \mu\text{m s}^{-1}$	Distilled water (49 v)	Oxygen transport	[57]
RBCs	Bubble propulsion	$\approx 25\ \mu\text{m}$	Not mentioned	Vivo: Intestine of mice	Oral antitoxicity vaccine	[58]
RBCs	Magnetically navigated	$9.0\pm 0.3\ \mu\text{m}$	$8.80\pm 0.41\ \mu\text{m s}^{-1}$	20 mT, 10 Hz	Drug Delivery and Image-Guided Therapy	[59]

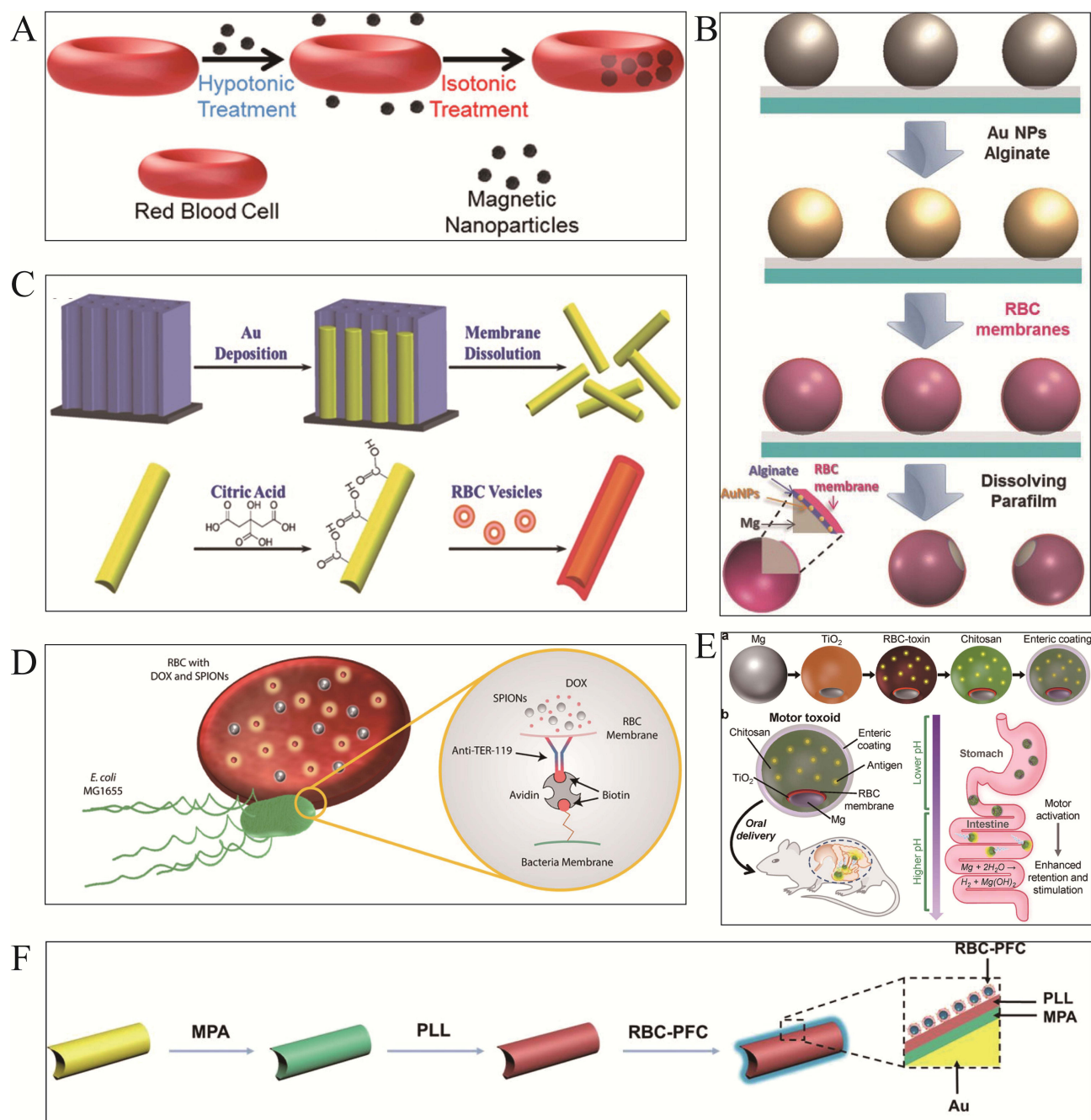


Figure 1 RBC membrane-functionalized micromotors. **(A)** RBC-based magnetic-driven MNMs for toxin neutralization. Reproduced from Wu Z, Li T, Li J, et al. Turning erythrocytes into functional micromotors. *ACS Nano*. 2014;8(12):12041–12048. Copyright © 2014 American Chemical Society.²⁹ **(B)** RBC-Mg Janus MNMs for toxin absorption. Reproduced from Wu Z, Li J, de Avila BE-F, et al. Water-powered cell-mimicking janus micromotor. *Adv Funct Mater*. 2015;25(48):7497–7501. Copyright © 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.⁵² **(C)** RBC was mimicking rod-like MNMs for toxins neutralization. Reproduced from Wu Z, Li T, Gao W, et al. Cell-membrane-coated synthetic nanomotors for effective biodegradation. *Adv Funct Mater*. 2015;25(25):3881–3887. Copyright © 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.³³ **(D)** RBC-based bacterial microswimmer. Reproduced from Alapan Y, Yasa O, Schauer O, et al. Soft erythrocyte-based bacterial microswimmers for cargo delivery. *Sci Rob*. 2018;3(17): eaar4423. Copyright © 2018 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works.⁵⁵ **(E)** RBC-PFC MNMs for oxygen transport. a) The assembly process of RBC-PFC MNMs. b) The detailed structural diagram of RBC-PFC MNMs and their simulated effects in the intestine. Reproduced from Zhang F, Zhuang J, de Avila BEF, et al. A nanomotor-based active delivery system for intracellular oxygen transport. *ACS Nano*. 2019;13(10):11996–12005. Copyright © 2019 American Chemical Society.⁵⁷ **(F)** RBC membrane-coated Mg-TiO₂ MNMs as an oral antitoxicity vaccine. Reproduced from Wei X, Beltrán-Gastélum M, Karshalev E, et al. Biomimetic micromotor enables active delivery of antigens for oral vaccination. *Nano Lett*. 2019;19(3):1914–1921. Copyright © 2019 American Chemical Society.⁵⁸

Erythrocyte membranes can eliminate and neutralize toxins, alter the surface of motors and deliver a variety of biological functions. Yunus et al recently designed a bacterial flagella-driven RBC hybrid microswimmer for drug delivery⁵⁵ (Figure 1D). Bioengineered sports bacterium *Escherichia coli* MG1655 is used to attach RBCs loaded with

doxorubicin (DOX) and superparamagnetic iron oxide nanoparticles (SPION). The results revealed that the release of DOX was significantly enhanced at lower pH values, especially at pH=3. The acidic tumor microenvironment promotes the pharmacological effects of anti-cancer drugs. It has been reported that erythrocyte membrane motors can transport gas molecules. The motor-based gas delivery system by Joseph et al combined sound power Au NWs rapid advance and the RBC membrane with fluorinated carbon nanoemulsion (RBC-PFC) carrying high-capacity oxygen to facilitate active oxygen transport within the cell (Figure 1E).⁵⁷ RBC-PFC nanomotors (Motor-PFC) were designed with a 400 nm diameter and 8.4 μms^{-1} rotating speed. The motor-PFC may penetrate the cell membrane and continuously release intracellular oxygen. Ultrasound irradiation enhances oxygen transport in J774 macrophages and rapidly promotes cell survival by moving the Motor-PFC. Therefore, motor-PFC may be an efficient active transporter for intracellular oxygen and other therapeutic gas molecules. Recently, Wei et al synthesized an RBC membrane-coated Mg-TiO₂ motor (Figure 1F)⁵⁸ with Mg as the core for power supply. Erythrocyte membrane coating neutralizes the toxin and loads onto MNMs for motor antigenicity. In the in vivo experiment, mice were orally administered the vaccine to study its distribution and retention in the gastrointestinal tract and the ability to induce an immune response to generate IgA antibodies.⁶⁰ MNMs are activated and carried in the surrounding fluid upon entering the intestine, which further enhances the retention and penetration of the antigenic payload. The results demonstrated that motor toxoids elicit a greater production of IgA antibodies targeting alpha-toxin, which represents significant progress in the application of nanomotors in immunizations. Erythrocyte membrane acts as a substrate to alter the surface of other motors for photodynamic therapy,⁵⁹ thrombus ablation,⁴⁵ thermal imaging⁵³ and other biomedical applications.

Leukocyte Membrane-Functionalized MNMs

Leukocytes are the primary immune cells in the body and are classified as granulocytes (mainly neutrophils), monocytes-macrophages, lymphocytes, natural killer (NK) cells and dendritic cells (DCs). Leukocytes exhibit active locomotion using pseudopods to move within and outside the blood vessels.⁵⁴ Moreover, leukocytes exhibit chemotaxis and targeted motility in the presence of chemokines.⁵⁶ Consequently, leukocytes have recently been studied as bionic MNMs that can significantly target inflammatory and cancer microenvironments (Table 2).⁶¹⁻⁶³

Macrophage Cell Membrane-Functionalized Micromotors

Macrophages regulate the immune system, which engulfs and eliminates a variety of pathological organisms. In addition, macrophages have distinct receptors for biotoxins including endotoxins. Zhang et al⁶² proposed the idea of hybridizing macrophages with magnesium micromotors (Figure 2A). A layer of titanium dioxide (TiO₂) and polylysine (PLL) was coated on Mg particles, resulting in a diameter of approximately 23–44 μm . Mg core and protons may form a hydrogen bubble tail,

Table 2 Summary of Leukocyte Membrane-Functionalized MNMs

Substrate	Fuel	Size	Speed	Environment	Application Field	Ref.
Leukocyte	Acoustically powered and magnetically navigated	7.03±0.6 μm	52.9 μms^{-1} , 35.6 μms^{-1}	Serum, blood	Cancer therapy	[64]
Macrophage cells	Bubble propulsion: H ₂	23-44 μm	127.3 μms^{-1}	Simulated gastric fluid (pH 1.3)	Endotoxin neutralization	[65]
Macrophage cells	Near-infrared light drive: thermal gradient	≈80 nm	6.44 μms^{-1} , 4.71 μms^{-1} , 1.46 μms^{-1}	2.92Wcm ⁻² :PBS, CM, FBS	Cancer therapy	[66]
Macrophage cells	Bubble propulsion: O ₂	≈50 nm	43.2 μms^{-1}	Vivo: a mouse model with acute pneumonia	Acute pneumonia	[67]
Macrophage cells	Photoacoustic (PA) imaging guided and magnetic guided	182±3 nm	10 μms^{-1}	A gradient Magnetic field (19.2 Tm ⁻¹)	Cancer therapy	[63]
Macrophage cells	Bubble propulsion: NO	102.59 nm	Not mentioned	Blood; vivo: in a Mouse myocardial injury model	Heart repair and regeneration	[34]
Neutrophil	Self-propulsion	Not provided	0.165 μms^{-1}	Agarose Hydrogel containing E. coli	Drug delivery	[68]
Neutrophil	Self-propulsion	≈5-6 μm	104.6±11.2 μms^{-1} , >110 μms^{-1}	22°C Tris-acetate-phosphate medium, simulated lung fluid	Acute bacterial pneumonia	[69]
Neutrophil	Magnetically navigated	≈105 nm	400 μms^{-1}	Rotating Magnetic field (RMF)	Cancer therapy	[70]

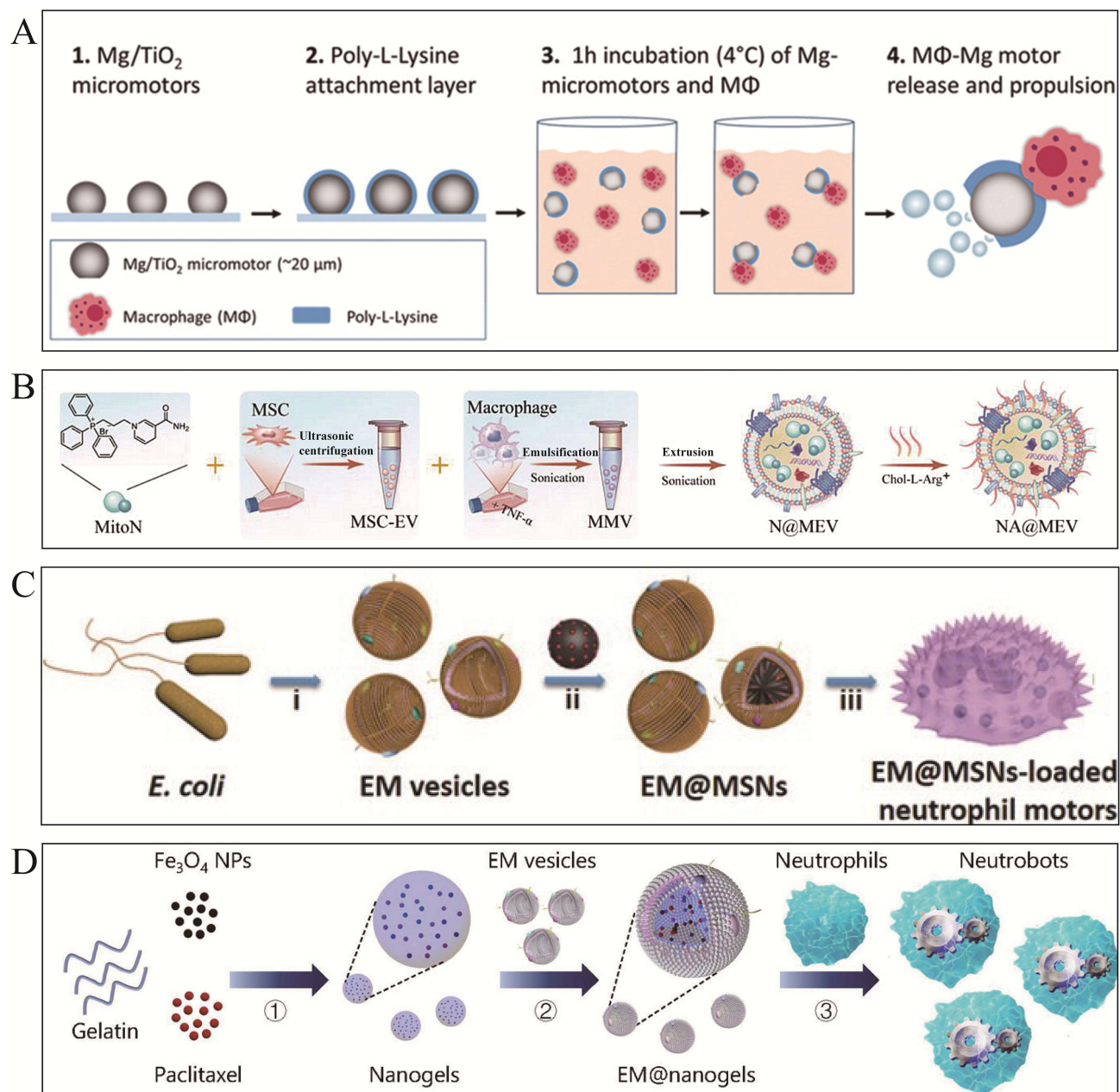


Figure 2 Leukocyte membrane-functionalized MNMs. **(A)** Mφ-Mg hybrid MNMs for toxin absorption. Reproduced from Zhang F, Mundaca-Urbe R, Gong H, et al. A macrophage-magnesium hybrid biomotor: fabrication and characterization. *Adv Mater.* 2019;31(27):e1901828. Copyright © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.⁶² **(B)** NA@MEV MNMs for cardiac repair and regeneration. Reproduced from Zhang N, Fan M, Zhao Y, et al. Biomimetic and NOS-responsive nanomotor deeply delivery a combination of MSC-EV and mitochondrial ROS scavenger and promote heart repair and regeneration. *Adv Sci.* 2023;10(21):e2301440. Copyright © 2023 The Authors. Advanced Science published by Wiley-VCH GmbH. Creative Commons CC BY license.³⁴ **(C)** EM@MNMs-loaded neutrophil MNMs for drug delivery. i) Preparation and synthesis of EM vesicles. ii) Preparation of EM@MSNs via vesicle fusion strategy. iii) Co-incubate EM@MSNs with neutrophils to prepare hybrid neutrophil micromotors. Reproduced from Shao J, Xuan M, Zhang H, Lin X, Wu Z, He Q. Chemotaxis-guided hybrid neutrophil micromotors for targeted drug transport. *Angew Chem Int Ed Engl.* 2017;56(42):12935–12939. Copyright © 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.⁶⁴ **(D)** Neutrophils-membraned EM@nanogels MNMs for blood-brain-barrier crossing. Reproduced from Zhang H, Li Z, Gao C, et al. Dual-responsive biohybrid neutrobots for active target delivery. *Sci Rob.* 2021;6(52). Copyright © 2021 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works.⁷¹

which increases motor functions in acidic environments. The Mφ-Mg hybrid motor effectively neutralizes endotoxins, neutralizing about 50% in the first two minutes, which reveals high detoxification capability.⁴¹ Recently, Zhang et al³⁴ constructed a bionic nitric oxide synthase-responsive nanomotor (NA@MEV) for enhancing cardiac repair and regeneration (Figure 2B), which was coated with a hybrid cell-derived extracellular vesicle (N@MEV) composed of mesenchymal stem cell-derived extracellular vesicles, macrophage cell membrane vesicles and ROS scavenger MitoN. Inflammatory signals

from cardiac damage trigger hybrid extracellular vesicles to target and enhance the injury site.⁶⁶ Therefore, researchers have investigated the application of macrophage membrane-encapsulated MNMs for targeted therapy.

Neutrophil Cell Membrane-Functionalized Micromotors

However, internalized nanodrugs face crucial challenges in penetrating into inflamed tissues and premature outflow, which limits their translational outcomes. To address this critical issue, Yue et al⁶⁴ synthesized hybrid neutrophil micromotors that transported drug-loaded Mesoporous silica nanoparticles (MSNs) by wrapping them in *E. coli* membranes (EMs) and incubating with neutrophils (NEs) (Figure 2C). It was found that encapsulating DOX in EM@MSNs significantly reduced the leakage of DOX. Furthermore, neutrophils migrate to the inflamed areas through chemotaxis, which further produces a superior level of MNMs in drug delivery. A new study has established a micromotor identified as a “neurobot” that is responsive to dual stimuli and utilizes neutrophil⁷¹ (Figure 2D). *E. coli* membrane is wrapped with paclitaxel (PTX)-loaded magnetic nanogels and then engulfed with NEs. *E. coli* membranes also serve as encapsulating mechanisms. Chemotaxis and magnetic propulsion activate the microrobot to cross the blood-brain barrier and release drug-loaded nanogels. Therefore, neurobots can be promising drug transporters for alleviating inflammatory tumors, particularly intracranial tumors.

Platelet Membrane-Functionalized MNMs

Platelets produced from developed erythrocyte cytoplasmic components in the bone marrow regulate hemostasis, thrombosis and inflammatory response.^{68,70} However, early studies have revealed that platelet membrane-coated nanoparticles can significantly enhance the ability to adhere to pathogens,^{65,67,69} reduce cellular uptake by several immune cells,^{68,72} improve targeting and affinity in tumors.⁷³ Platelet membranes have recently been employed to develop autonomous micromotors (Table 3).⁷⁴

In 2018, Chang et al⁴⁵ employed ultrasonic incubation to fuse platelet vesicles with magnetic helical MNMs surfaces, called “Pt-nanomotors” (Figure 3A). Pt-nanomotors displayed strong anti-fouling properties and motility ($12.5 \mu\text{ms}^{-1}$). Experimental data revealed that platelet membrane-functionalized MNMs effectively adsorbed and isolated *Shiga* toxin (STX) and MRSA252 bacteria. This affinity and efficient mobility provide nanorobots with significant detoxifying capability, which offers a novel therapeutic approach for the treatment of infectious disorders. Analogously, Fuel-free RBC-PL hybrid membrane functionalized nanomotors (RBC-PL-motors)⁷⁹ (Figure 3B) were synthesized by mixing AuNW motors with erythrocyte-PL hybrid membrane source vesicles using a template-supported AuNW electrochemical deposition scheme under an ultrasonic field. Ultrasound-guided RBC-PL-motors have been shown to be more effective due to their dual detoxifying properties including binding and eliminating PL-attached pathogens such as MRSA and neutralizing bacterial toxins.

Furthermore, JPL-Motor³⁵ (Figure 3C) is a unique self-driving platelet MSN manufactured as a Janus structure with a 1.4–2.6 μm diameter and is catalyzed by urease. Platelets are suitable carriers for delivering chemotherapeutic drugs including DOX and antibacterial agents, due to their high binding effectiveness to cancerous cells and pathogens. Experimental studies revealed that the JPL-Motor can autonomously function at 50–200 mM urea concentrations driven

Table 3 Summary of Platelet Membrane-Functionalized MNMs

Substrate	Driving Force	Size	Speed	Concentration	Application Field	Ref.
PLTs	Magnetically navigated	$\approx 3\text{--}5 \mu\text{m}$	$\approx 18.5, 17, 14.5, 12.5 \mu\text{ms}^{-1}$	55 Hz, 15 mT: water, plasma, serum and blood	Bacteria isolation	[45]
PLTs	Acoustically powered	400 nm (1.5–2.0 μm)	46 μms^{-1} ; 35 μms^{-1}	Water, the whole blood	Targeting and neutralization of pathogenic bacteria and toxins	[75]
PLTs	Near-infrared light drive: thermal gradient	410 nm	Not mentioned	Vivo: a rat model with abdominal thrombosis	Thrombus ablation	[76]
PLTs	Self-propulsion	1.4–2.6 μm	$\approx 7 \mu\text{ms}^{-1}$	Urea concentrations (200 mM)	Drug delivery	[35]
PLTs	Near-infrared light drive: thermal gradient	$\approx 450 \text{ nm}$	Not mentioned	Vivo: a rabbit model with atherosclerosis	Drug delivery and Atherosclerosis therapy	[77]
PLTs	Near-infrared light drive: thermal gradient	$\approx 2 \mu\text{m}$	12.2 μms^{-1}	NIR light irradiated (808 nm, 2.5 W cm^{-2})	Cancer Therapy	[78]

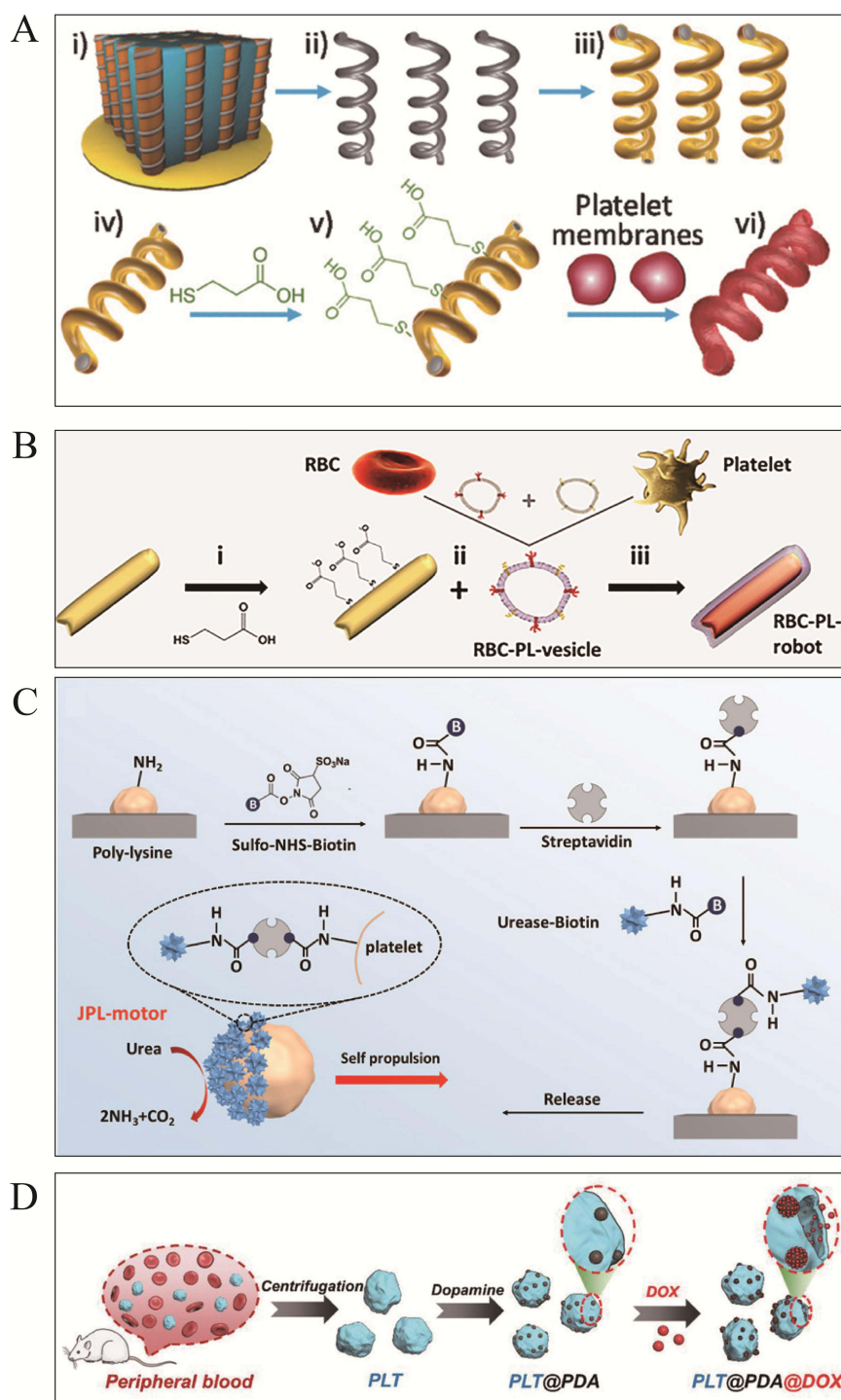


Figure 3 PLT membrane-functionalized micromotors. **(A)** PLT-based magnetic-driven MNMs for toxin neutralization and bacteria separation. i) Pd/Cu co-electrodeposition in polycarbonate membrane pores (pore size: 400 nm). ii) Removal of Cu phase by nitric acid etching and release of helical Pd nanomotors. iii) Ni/Au bilayer deposition on the surface of Pd helical nanostructures. iv) Collection and separation of helical nanomotors. v) Modification of the surface of bare helical nanomotors with 3-mercaptopropionic acid (MPA). vi) Anchoring of PL-vesicles to the surface of MPA-modified helical nanomotors. Reproduced from Li J, Angsantikul P, Liu W, et al. Biomimetic platelet-camouflaged nanorobots for binding and isolation of biological threats. *Adv Mater.* 2018;30(2):1704800. Copyright © 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.⁴⁵ **(B)** RBC-PL hybrid MNMs for detoxification. i) Modification of the gold surface of gold nanowire (AuNW) Robots with MPA. ii) Preparation of hybrid membrane by fusing erythrocyte membrane and platelet membrane at a 1:1 protein mass ratio and its coating of MPA-modified nanorobots. iii) Preparation of red blood cell-platelet membrane robots (RBC-PL-robots) by 5 minutes ultrasonication. Reproduced from Esteban-Fernández de Ávila B, Angsantikul P, Ramírez-Herrera DE, et al. Hybrid biomembrane-functionalized nanorobots for concurrent removal of pathogenic bacteria and toxins. *Sci Rob.* 2018;3(18). Copyright © 2018 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works.⁷⁹ **(C)** Urease-catalyzed JPL-Motor for chemotherapeutic agent carrier. Reproduced from Tang S, Zhang F, Gong H, et al. Enzyme-powered Janus platelet cell robots for active and targeted drug delivery. *Sci Rob.* 2020;5(43). Copyright © 2020, Science Robotics.³⁵ **(D)** PLT@PDA-DOX MNMs for targeted cancer therapy. Reproduced from Li T, Chen T, Chen H, et al. Engineered platelet-based micro/nanomotors for cancer therapy. *Small.* 2021;17(52):e2104912. Copyright © 2021 Wiley-VCH GmbH.⁸⁰

by urease fuel decomposition. A pioneering research conducted by Li et al⁸⁰ constructed engineered PLT micromotors (PLT@PDA-DOX) (Figure 3D) by universal self-polymerizing modification of polydopamine (PDA). P-selectin on PLTs allows the PLT@PDA-DOX motor to target the tumor location by binding to the increased cancer cell CD44 receptor. PLTA and PLT-derived microparticles (PMP@PLTA-DOX) can produce asymmetric thermal effects under NIR light irradiation and drive the motor to penetrate deep into cancer cells (MCF cells). The PLT@PDA-DOX motor has significantly enhanced the efficacy of targeted cancer therapies.

Cancer Cell Membrane-Functionalized Micromotor

Cancer cells exhibit the main characteristic of homotypic binding, leading to the formation of tumors and clumps.⁸¹ Accumulating research suggests that chemotherapeutic agents can be efficiently delivered through nanoparticle drug delivery systems.^{81,82} Several advantages of these systems include high solubility, targeted drug delivery and enzyme protection.⁸³ Intriguingly, a pioneering study revealed that membrane-coated nanoparticles enhance the homotypic binding of cancerous cells, thereby facilitating targeted therapy.⁷⁵ Furthermore, Kroll et al explored that antigen components on the cell membrane can regulate anti-cancer immunity.⁷⁸ Thus, the application of cell membrane coatings exhibits promising potential in drug targeting and imaging techniques for the treatment and management of cancers.⁷⁶

Zhang et al⁷⁷ functionalized CaCO_3 motors with gold nanoshells (Figure 4A). Nanoparticles were attached to membrane vesicles prepared from G422 mouse cancer cells. Micromotors can be detected by antigen-presenting cells using the cell membrane coating. Micromotors can target cancerous cells by binding homologously with their membranes. Subcutaneous injection of CaCO_3 motors resulted in anti-tumor immunity in mice within 24 hours. Zhou et al⁸⁴ designed a semi-yolk, spiky-shell carbon-based@silicon (C@SiO_2) nanomotor ($\text{MC@SiO}_2\text{@DOX}$) coated with MCF-7 breast cancer cell membranes (Figure 4B). Thermal gradients in $\text{MC@SiO}_2\text{@DOX}$ cause efficient self-heating propulsion in near-infrared light. Tumor cell membrane coating enhances cell adhesion and absorption efficiency, resulting in faster migration ($2.42 \mu\text{m s}^{-1}$) and homologous target binding. Moreover, tumor cell membrane coating significantly improved photodynamic therapy and synergistic chemotherapy (intracellular light/pH responsive DOX release) and decreased MCF-7 cell proliferation. The outer shell may be utilized entirely for loading DOX, resulting in a higher drug efficiency with a capacity of $596 \mu\text{gmg}^{-1}$. Intriguingly, Wang et al⁸⁵

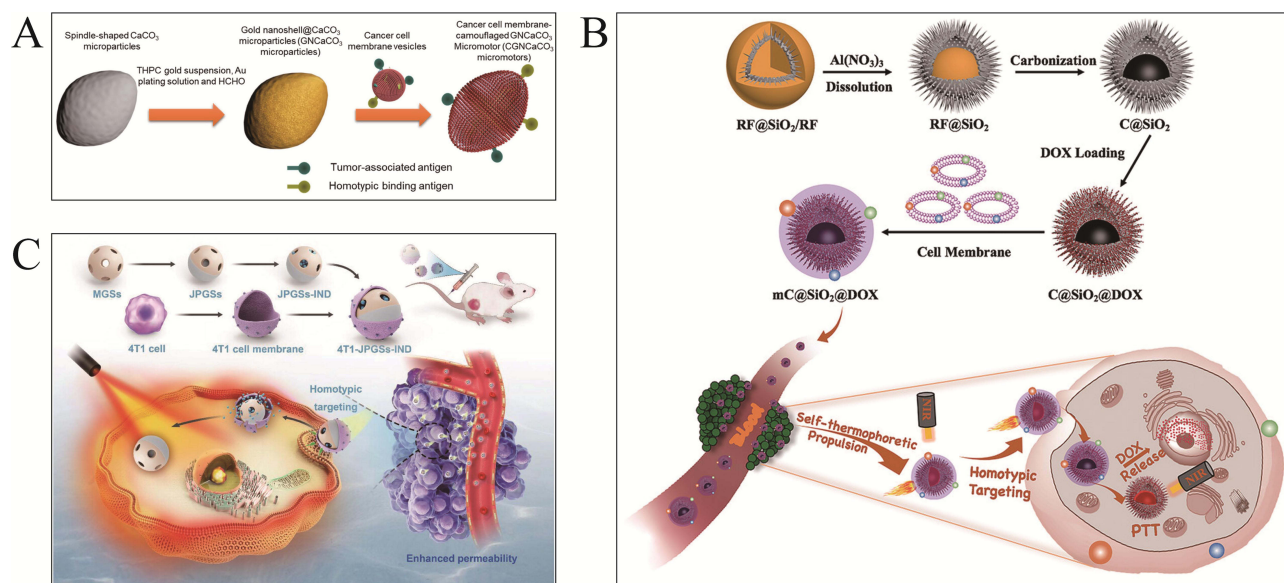


Figure 4 (A) Gold nanoshells modified CaCO_3 MNMs for anti-tumor immunity. Reproduced from Zhang H, Li Z, Wu Z, He Q. Cancer Cell Membrane Camouflaged Micromotor. *Adv Ther.* 2019;2(12):1900096. Copyright © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.⁷⁷ (B) $\text{MC@SiO}_2\text{@DOX}$ MNMs for drug loading. Reproduced from Zhou M, Xing Y, Li X, Du X, Xu T, Zhang X. Cancer cell membrane camouflaged semi-yolk@spiky-shell nanomotor for enhanced cell adhesion and synergistic therapy. *Small.* 2020;16(39):e2003834. Copyright © 2020 Wiley-VCH GmbH.⁸⁴ (C) 4T1 cell-coated mesoporous gold nanospheres for tumor photothermal therapy. Reproduced from Wang H, Gao J, Xu C, et al. Light-driven biomimetic nanomotors for enhanced photothermal therapy. *Small.* 2023;e2306208. Copyright © 2023 Wiley-VCH GmbH.⁸⁵

developed a Janus nanomotor (Figure 4C) performed by near-infrared light in 4T1 cell membranes loaded with indomethacin (IND) via 217.1 ± 1.79 nm mesoporous gold nanospheres. The external tumor cell membrane promotes homologous tumor enrichment. Near-infrared light driving motors may enhance photothermal therapy in tumors and IND release may inhibit the inflammatory response. Therefore, this strategy can potentially eradicate tumors while reducing therapeutic adverse effects.

Biological Applications of Cell-Membrane-Functionalized Micromotors

This section classifies applications based on different disease types to provide a comprehensive and organized overview.

Thrombosis

Thrombosis can be classified as arterial or venous thrombosis depending on the site of formation.⁸⁶ The mechanisms of vascular and arterial thrombosis differ due to their physiological environment.^{87,88} Most of the arterial thrombosis is formed based on the rupture of atherosclerotic plaques.^{89,90}

Currently, drug-eluting stents (DES)⁹¹ and drug-coated balloons (DCB)⁸⁹ are the primary therapeutic options for the treatment of atherosclerosis. DES is initially effective, but it is a foreign body that can cause vascular restenosis over time.⁹² DCB, placed via catheter for local plaque treatment, avoids long-term foreign-body-related restenosis, offering clinical advantages.⁹³ Thus, Mao et al⁹⁴ studied DCB coatings combined with nanomotor therapy for the treatment of atherosclerosis. The researchers developed an autonomously moving, porous nanomotor coated with an anti-vessel cell adhesion molecule-1 antibody (JAMS/PTX/AV MNMs) (Figure 5A). Past studies have indicated that JAMS enhances nanoparticles deep into plaque, increases drug retention and attenuates the activation of inflammatory macrophages in atherosclerosis under near-infrared light.⁹⁵ The inhibitory effect of paclitaxel-carrying MNMs appropriately supplied by the balloon on atherosclerotic blood vessel proliferation may provide additional evidence for the application of drug balloon coatings.

Short-term thrombolytic recanalization and long-term anti-coagulant prophylaxis are the current treatment options for ameliorating venous thrombosis.^{99,100} Short half-lives of thrombolytic drugs, low drug utilization, poor drug penetration at thrombus sites and recurrence risk are current therapeutic challenges.^{101,102} Thus, the development of self-actuated nanomotors can overcome these challenging issues.

Shao and his colleagues⁹⁶ developed layer-by-layer Janus polymer motors (EM-JPMs) using self-assembly. The EM-JPMs were capable of auto-motility and photothermal ablation of thrombi under NIR illumination. The EM-JPMs experienced rupture upon NIR irradiation, resulting in the release of Hep. The release of heparin contributed to the enhancement of the photothermal-mediated thrombolytic effect (Figure 5B). However, only specific qualitative trials did not exhibit substantial thrombolytic effects and in vivo thrombolysis was not assessed.

Wan and his colleagues developed a platelet membrane-modified mesoporous or macroporous silica/Pt nanomotor⁹⁷ containing urokinase and heparin in the macropores and mesopores (Figure 5C). The resonance of the macroporous structure generates asymmetric Pt NPs under near-infrared irradiation to form thermophoresis-driven nanoparticles, which can rupture the thrombus and release urokinase and heparin. The movement of MNMs under near-infrared irradiation can penetrate thrombi and increase the thrombolytic effects.

Pan et al⁹⁸ developed a glucose oxidase (GOX)-driven Janus nanomotor (GPNP-PA) loaded with urokinase plasminogen activator (uPA) (Figure 5D). GOX catalyzed the production of H_2O_2 from glucose and enhanced the targeting of the outer platelet membrane. It was shown that the GPNP-PAs treatment group had excellent thrombolytic action. In addition, GPNP-PAs are glucose-powered nanomachines that exhibit characteristics such as safety, cleanliness and accessibility. This type of nanomotor has a high degree of adaptability for delivering several therapeutic agents.

Surface-engineered cell membrane-cloaked MNMs demonstrate enhanced thrombus-targeting precision through rational ligand modification on their biointerfaces. This active targeting strategy promotes site-specific drug enrichment at vascular occlusion sites while reducing off-target distribution, improving thrombolytic performance and mitigating hemorrhagic complications. The endogenous membrane architecture endows MNMs with prolonged circulatory persistence via inherent immune-evasion properties, enabling sustained therapeutic action. Motor-enabled thrombolysis systems have shown superior clinical potential in preventing secondary thromboembolic events through regulating dynamic biodistribution over passive drug diffusion methods.

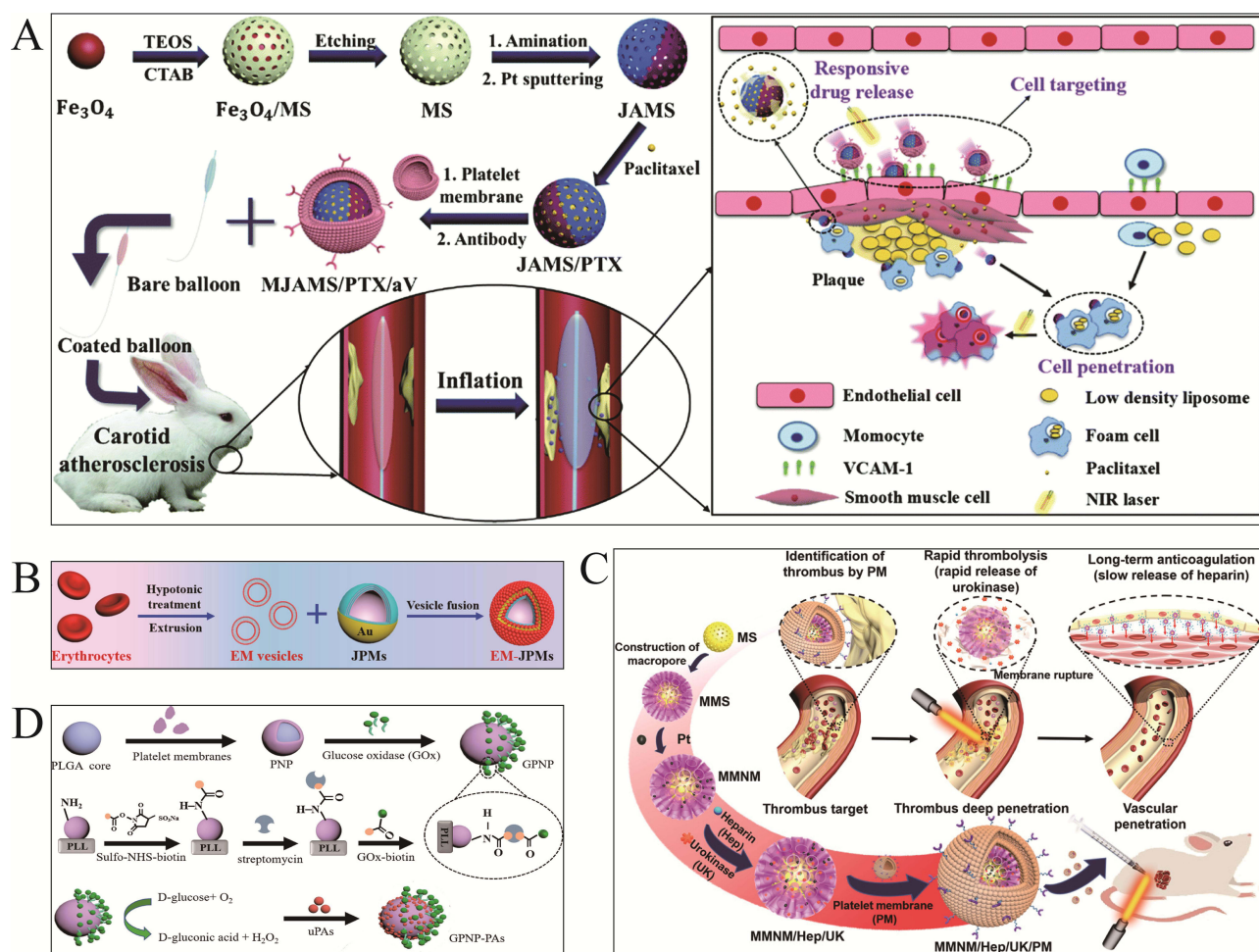


Figure 5 MNMs for Thrombosis treatment. **(A)** JAMS/PTX/AV combined with DBC for atherosclerosis treatment. Reproduced from Huang Y, Li T, Gao W, et al. Platelet-derived nanomotor coated balloon for atherosclerosis combination therapy. *J Mater Chem B*. 2020;8(26):5765–5775. Copyright © 2020, Journal of Materials Chemistry.⁹⁴ **(B)** RBC-membraned MNMs with gold shells for atherosclerosis treatment. Reproduced from Shao J, Abdelghani M, Shen G, Cao S, Williams DS, van Hest JCM. Erythrocyte membrane modified janus polymeric motors for thrombus therapy. *ACS Nano*. 2018;12(5):4877–4885. Copyright © 2018 American Chemical Society.⁹⁶ **(C)** INR-driven MMNM/Hep/UK/PM for venous thrombosis treatment. Reproduced from Wan M, Wang Q, Wang R, et al. Platelet-derived porous nanomotor for thrombus therapy. *Sci Adv*. 2020;6(22):eaz9014. Copyright © 2020 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC).⁹⁷ Copyright 2020, Science Advances. **(D)** GOX-driven and uPA-loaded MNMs for venous thrombolysis. Reproduced from Fang X, Ye H, Shi K, et al. GOX-powered janus platelet nanomotors for targeted delivery of thrombolytic drugs in treating thrombotic diseases. *ACS Biomater Sci Eng*. 2023;9(7):4302–4310. Copyright © 2023 American Chemical Society.⁹⁸

Tumor-Related Diseases

Photothermal Therapy

This novel tumor therapy utilizes photothermal agents (PTA) to generate enough heat to eliminate tumor cells under near-infrared light irradiation.¹⁰³ Low photothermal conversion efficiency, poor PTA stability, inadequate tumor accumulation and cell uptake, tumor thermostability, tumor recurrence and metastasis are still challenging to overcome utilizing PTT.¹⁰³ Due to its photothermal conversion and near-infrared radiation absorption, nanostructure technology has contributed to cancer therapies in recent years.¹⁰⁴

A Janus mesoporous silica nanoparticle motor (JMSNM) with 10 nm thick Au half-shells was developed to function in NIR light (Figure 6A).¹⁰⁵ The macrophage cell membrane (MPCM) on the surface may disguise, inhibit biological adhesion and detect cancerous cells. NIR light induces localized heating that eliminates cancer cells. MPCM coating and self-propulsion provide a novel nanomotor-driven photothermal therapeutic strategy. Wang⁶³ and his co-workers recently developed a needle-like white cell membrane-coated gallium nanoswimmer (LMGNS) (Figure 6B). LMGNS motors were found to sustain longer and move rapidly in biological conditions compared to bare-gallium nanomotors. In

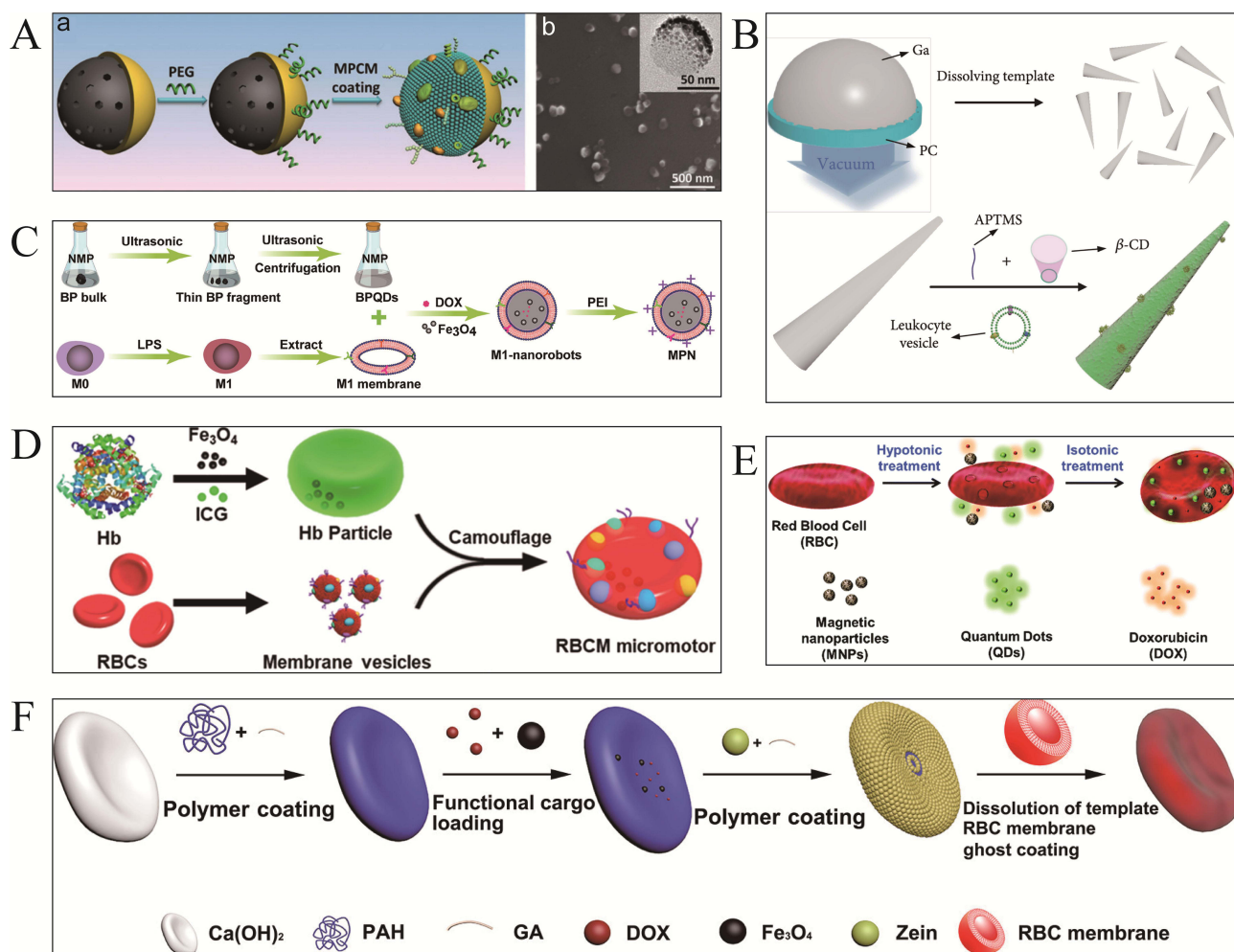


Figure 6 MNMs for Tumor Imaging and precise on-demand drug delivery. **(A)** Macrophage-cell-membrane-coated MNMs for the thermomechanical portion of cancer cell membranes. **a)** Schematic diagram of the preparation process of MPCM@JMSNMs. **b)** SEM image of JMSNMs. Inset: TEM image of a Single JMSNM. Reproduced from Xuan M, Shao J, Gao C, Wang W, Dai L, He Q. Self-propelled nanomotors for thermomechanically percolating cell membranes. *Angew Chem Int Ed Engl.* 2018;57(38):12463–12467. Copyright © 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.¹⁰⁵ **(B)** Needle-like white cell membrane-coated gallium MNMs for photothermal therapy. Reproduced from Wang D, Gao C, Zhou C, Lin Z, He Q. Leukocyte membrane-coated liquid metal nanoswimmers for actively targeted delivery and synergistic chemophotothermal therapy. *Research.* 2020;2020:3676954. Copyright © 2020 Daolin Wang et al.⁶³ **(C)** Magnetic anticancer DOX@MPN for chemophototherapy. Reproduced from Song X, Qian R, Li T, et al. Imaging-Guided biomimetic M1 macrophage membrane-camouflaged magnetic nanorobots for photothermal immunotargeting cancer therapy. *ACS Appl Mater Interfaces.* 2022;14(51):56548–56559. Copyright © 2022 American Chemical Society.⁶¹ **(D)** RBC-based and Fe₃O₄-encapsulated hemoglobin MNMs for oxygen and PSs activity delivery. Reproduced from Gao C, Lin Z, Wang D, Wu Z, Xie H, He Q. Red blood cell-mimicking micromotor for active photodynamic cancer therapy. *ACS Appl Mater Interfaces.* 2019;11(26):23392–23400. Copyright © 2019 American Chemical Society.¹⁰⁶ **(E)** Multi-cargo-loaded RBC micromotors for imaging. Reproduced from Wu Z, de Avila BE-F, Martin A, et al. RBC micromotors carrying multiple cargos towards potential theranostic applications. *Nanoscale.* 2015;7(32):13680–13686. Copyright © The Royal Society of Chemistry 2015.⁵³ **(F)** Bio-RBC-based MNMs as a potential mobile thermal therapy and imaging tool. Reproduced from Hou K, Zhang Y, Bao M, et al. A multifunctional magnetic red blood cell-mimetic micromotor for drug delivery and image-guided therapy. *ACS Appl Mater Interfaces.* 2022;14(3):3825–3837. Copyright © 2022 American Chemical Society.⁵⁹

addition, LMGNS strongly target and penetrate cancerous cells under acoustic conditions. Pharmacokinetic studies indicated that LMGNS can be used as pH-sensitive cargo. LMGNS-Dox changes from needle-like to spherical, fuses and releases DOX in an acidic environment (pH 5.0). It was confirmed that leukocyte membrane camouflage induced cancer cells to absorb a significant amount of LMGNS-Dox. The short-term administration of LMGNS induces notable morphological alterations and necrosis in cancer cells. Membrane-functionalized MNMs exhibit tumor-homing specificity through biomolecular recognition, promoting spatially-precise accumulation at malignant lesions. This targeting mechanism optimizes PTA depth penetration while containing therapeutic activity within pathological regions to minimize systemic toxicity. Furthermore, these hybrid systems enable combinatorial chemo-photothermal regimens where laser-triggered hyperthermia facilitates drug liberation from the nanoplateforms, establishing synergistic therapeutic

effects. The engineered membrane architecture additionally provides stimuli-responsive gatekeeping functions for on-demand cargo delivery through endogenous microenvironmental triggers.

Chemo-phototherapy is a synergistic technique that combines PT and chemotherapy, which delivers significant anti-cancer effects.^{107–109} The MPN (182±3nm) magnetic anti-cancer nanocomposite was synthesized by Song et al⁶¹ utilizing macrophage characteristics^{110,111} (Figure 6C). Exposure to oxygen degrades black phosphorus quantum dots (BPQDs) in MPNs with photothermal and photoacoustic imaging properties.^{112,113} To overcome this critical challenge, BPQDs were encapsulated in macrophage membranes. MPN may form macrophage proteins and evade the immune system. DOX@MPN possessed more significant chemotherapeutic effects on DOX release and ROS production in the tumor microenvironment under a magnetic field and NIR. The membrane-wrapped MNMs significantly improve the drug utilization rate by stabilizing the contents. Furthermore, photoacoustic (PA) and magnetic resonance imaging can enhance the visualization of the tumor microenvironment.

Photodynamic Therapy

Photodynamic therapy (PDT) has demonstrated promising efficacy in the treatment of malignancies by the conversion of biologically inert oxygen into reactive oxygen species (ROS), facilitating the eradication of cancerous cells.^{114,115} Hypoxia and poor targeting and aggregation of PSs still limit the efficacy of PDTs.¹¹⁶ Nanomedicine-based delivery systems improve the selectivity of PSs in tumors.¹¹⁷ PDT for cancer was developed using a red blood cell mimicking (RBCM) micromotor (Figure 6D). Hypotonic treatment causes red blood cells to leak hemoglobin, which leaves motors oxygen-dependent. The high levels of Fe₃O₄-encapsulated hemoglobin microparticles in RBCM compensate for this deficiency. Under acoustic fields, they can move at speeds up to 56.5 μm s⁻¹ in biological media using an external magnetic field to navigate the direction of motion. The RBCM micromotor significantly promotes the anticancer effect of PDT due to excellent loading, oxygen release, PS loading and directional movement. Therefore, this fuel-free RBCM micromotor provides an efficient, fast and novel approach to more precise and effective PT in the future.

Tumor Imaging and Precise On-Demand Drug Delivery

Synthetic MNMs have been employed for tumor imaging and therapy due to their active mobility.^{118–121} In 2015, Wu et al⁵³ embedded quantum dots (QDs), iron oxide magnetic nanoparticles (MNPs) and DOX into red blood cell micromotors (Figure 6E) through hypotonic dilution encapsulation. Since MNPs are asymmetrically distributed, ultrasound pressure gradients may convert acoustic energy into kinetic energy and magnetic guiding under acoustic propulsion moves multi-loaded micromotors. Two wavelengths of QDS and DOX fluorescence allow the direct observation of their loading in the erythrocyte motor. Recently, Hou and his colleagues⁵⁹ developed an LBL assembly method-based red blood cell-mimetic micromotor (RBCM) (Figure 6F). DOX and Fe₃O₄ nanoparticles on the RBCM surface promoted drug delivery and enhanced magnetic manipulation. MNMs can also be imaged with fluorescence contrast agents and MIR contrast agents, both of which can be stabilized through the stabilization of their signal expression. This method utilizes encapsulation of fluorescent dyes and MIR contrast agents within cell membranes and allows both to be verified for more complete and accurate localization.

Neurological Disorders

Precise targeted delivery of drugs to the brain lesions is critical for effective treatment of neurological disorders, yet remains challenging due to the blood-brain barrier (BBB) and the intricate anatomy of the brain.

To overcome these critical challenges, Ye et al engineered a macrophage membrane-cloaked nanomotor (MM@MnO₂-Au-mSiO₂@Cur) for neuroinflammation therapy (Figure 7A).¹²² The asymmetric MM coating utilizes membrane transporters/adhesion molecules to bypass the BBB and target inflammation via chemotaxis. MnO₂ catalyzes H₂O₂-to-O₂ conversion for self-propulsion and oxidative stress reduction, while encapsulated curcumin shifts macrophages from M₁ to M₂ phenotypes. The preclinical validation confirmed precise BBB penetration, neuroinflammation mitigation, functional recovery promotion and biosafety. Expanding this design, the team developed a dual-driven nanomotor (HM@MnO₂-AuNR-SiO₂) for glioblastoma (Figure 7B). A hybrid MM/GM coating synergizes homologous tumor targeting (GM) with BBB penetration (MM), outperforming single-ligand approaches. Dual propulsion via H₂O₂-

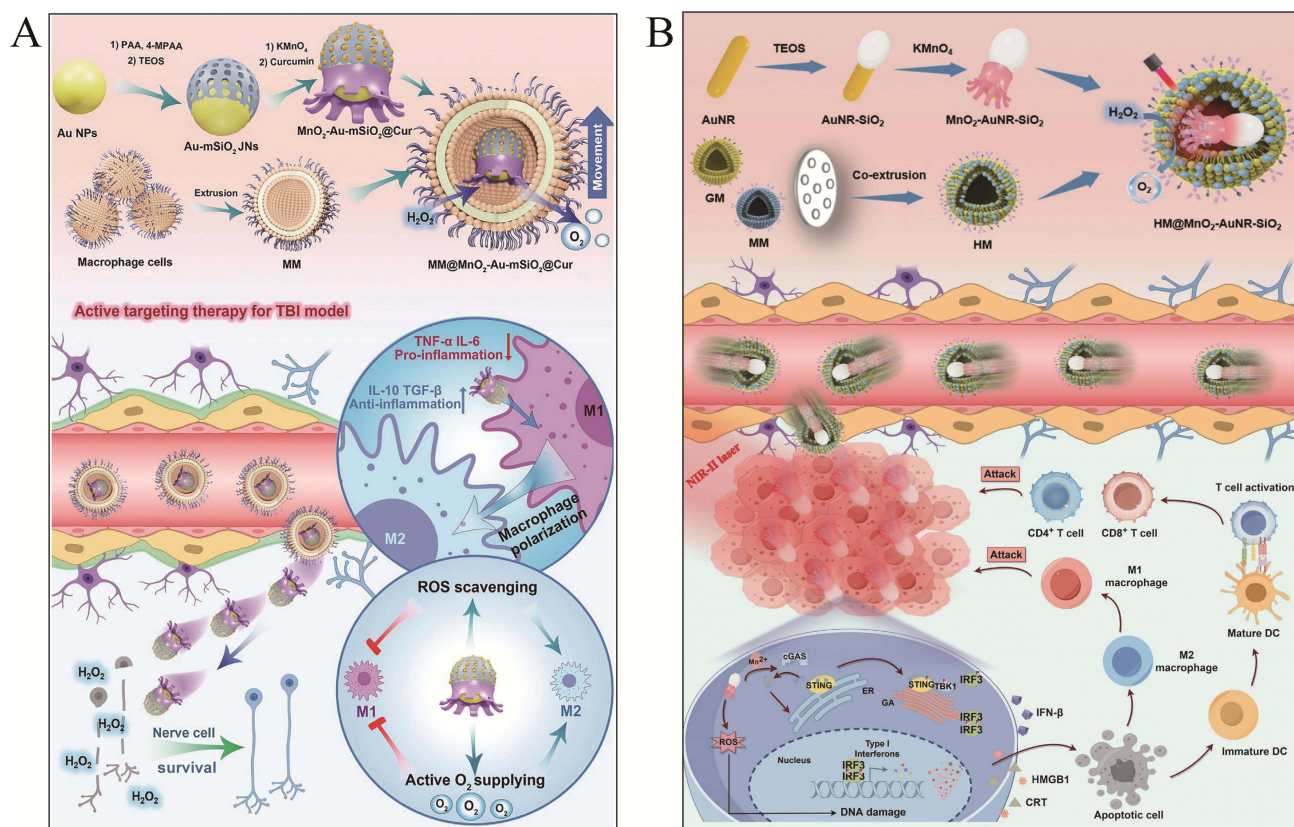


Figure 7 MNMs for neurological disorders. **(A)** macrophage membrane-cloaked nanomotor for neuroinflammation therapy. Reproduced from Ye J, Fan Y, She Y, et al. Biomimetic self-propelled asymmetric nanomotors for cascade-targeted treatment of neurological inflammation. *Adv Sci.* 2024;11(22):2310211. Copyright © 2024 The Authors. Advanced Science published by Wiley-VCH GmbH. Creative Commons CC BY license.¹²² **(B)** dual-driven nanomotor for glioblastoma. Reproduced from Ye J, Fan Y, Kang Y, et al. Biomimetic dual-driven heterojunction nanomotors for targeted catalytic immunotherapy of glioblastoma. *Adv Funct Mater.* 2025;35(9):2416265. Copyright © 2024 Wiley-VCH GmbH.¹²³

derived O₂ bubbles and photothermal actuation enhances deep tumor penetration. The nanomotor induces immunogenic cell death (ICD) through ROS production and activates cGAS-STING signaling pathway via Mn²⁺ release, linking catalytic therapy to antitumor immunity. This multimodal approach enhances immune surveillance and suppresses recurrence, showing efficacy in GBM models. Membrane coatings enhance the targeting of MMNs, which improves their therapeutic effect.

Acute Bacterial Pneumonia

Acute pneumonia is an inflammatory response to alveolar and interstitial lung tissue infection. A high mortality rate is associated with severe pulmonary dysfunction characterized by respiratory failure and hyperinflammation. Anti-inflammatory drugs are limited by their short systemic circulation time and poor pulmonary specificity. MNM drug delivery systems have been studied to efficiently deliver anti-inflammatory drugs to the lungs.

Zhang et al¹²⁴ developed an algae-nanoparticle-motor (Figure 8A) to administer antibiotics in vivo to treat lung infections. Past studies have revealed that encapsulated neutrophil membranes can escape alveolar macrophages.⁷⁶ Encapsulation of ciprofloxacin (Cip) within motors produces prolonged retention and sustained release in the lung. Microorganisms and nanomotors have significant potential for improving antibiotic delivery to treat lung infections. The MNMs exhibit autonomous actions, increased lifespans in the particular environment, microbial autofluorescence and potential for targeted actions.

A self-propelled macrophage motor with chemotaxis characteristics has recently been developed (Figure 8B). Activated M2 macrophages can be used as vectors for targeted drug delivery, deep tissue penetration in inflamed lungs and local drug release for synergistic anti-inflammatory effects by polarizing M2 cells, anti-inflammatory curcumin and reducing the

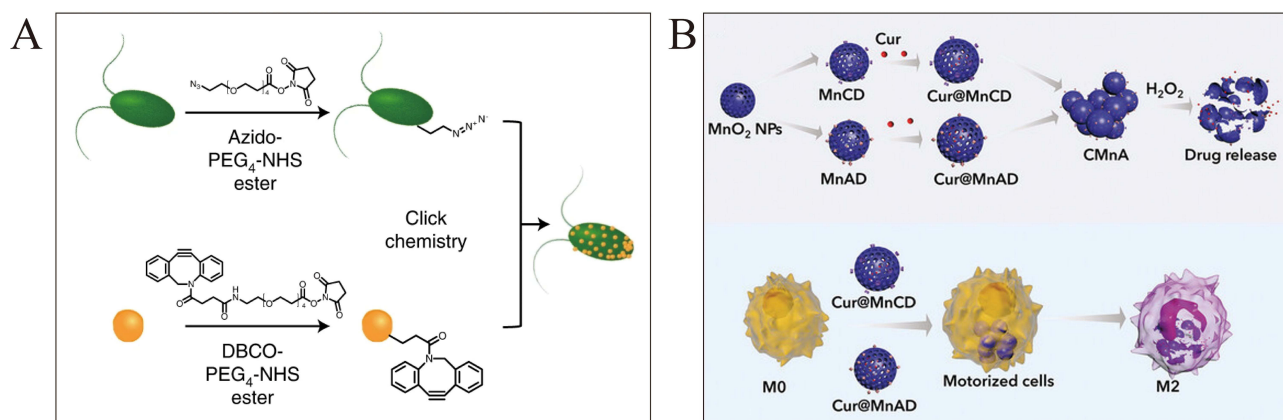


Figure 8 MNMs for acute Bacterial Pneumonia treatment. **(A)** Algae-neutrophil hybrid MNMs are used for antibiotic transport. Reproduced from Zhang F, Zhuang J, Li Z, et al. Nanoparticle-modified microrobots for in vivo antibiotic delivery to treat acute bacterial pneumonia. *Nat Mater.* 2022;21(11):1324–1332. Copyright © 2022 Nature Materials.¹²⁴ **(B)** Macrophage-based MNMs for anti-inflammation. Reproduced from Yue L, Gao C, Li J, et al. Chemotaxis-guided self-propelled macrophage motor for targeted treatment of acute pneumonia. *Adv Mater.* 2023;35(20):e2211626. Copyright © 2023 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.¹²⁵

production of H_2O_2 . Studies revealed that the motor reduced the risk of acute pneumonia complicated with heart disease in mice.^{126,127} New drugs can ameliorate the progression of multiple diseases and mitigate several complications.

Current Challenges and Future Prospects

The unique advantages of membrane-coated MNMs stem from their biomimetic camouflage and biocompatibility and their inherent smart and stimuli-responsive capabilities. MNMs achieve precise control by dynamically adjusting their locomotion modes or functionalities in response to environmental signals such as light, temperature, ultrasound and magnetic fields. Despite these advancements, several barriers must be addressed before MNMs can achieve widespread clinical application. First, membrane coatings can degrade and biofoul in complex environments due to biological instability. This issue can be addressed by enhancing membrane stability through crosslinking techniques, multilayer membrane structures and advanced engineering modifications to improve resistance to degradation. Second, while MNMs show improved immune evasion, challenges persist in optimizing their targeting specificity and avoiding clearance by the reticuloendothelial system. These can be mitigated by selecting membranes with specialized properties such as immune or cancer cell membranes, preserving functional membrane proteins and incorporating stimuli-responsive materials to enhance precision and efficacy. Third, the scalable and standardized production of MNMs remains a critical challenge, which can be overcome by employing automated microfluidic technologies and establishing reproducible protocols to ensure consistency in large-scale manufacturing. Moreover, the lack of comprehensive data on long-term safety, biodistribution and pharmacokinetics hinders regulatory approval and clinical adoption. The therapeutic effects of MNMs are currently confined to the pre-clinical and clinical research stages. More studies are highly required to evaluate and confirm their effectiveness and biological applications. There are currently no registered or publicly reported clinical trials involving MNMs. Clinical translation developments should be monitored and forwarded to academic research collaborations in order to contribute to the advancement of this field. Finally, integrating artificial intelligence (AI) offers transformative opportunities to overcome these barriers by optimizing MNM design, improving targeting through patient-specific data, and enabling adaptive monitoring during treatment. The advancement of MNMs towards clinical application can lead to breakthroughs in precision medicine by addressing these limitations.

The future of MNMs is highly promising with potential applications extending beyond their current use in targeted drug delivery and biomedical imaging. The ability of MNMs to navigate complex biological environments opens up possibilities for advanced therapeutic strategies including personalized medicine. Second, their inherent biocompatibility and functional versatility make them suitable for tissue engineering and regenerative medicine, aiding in precisely delivering growth factors or stem cells to damaged tissues. Third, MNMs could revolutionize environmental monitoring within the human body, acting as active sensors to detect biomarkers, pathogens and toxins in real-time. Fourth, they hold

potential in non-medical fields such as environmental remediation, where their biomimetic properties and efficient propulsion mechanisms could be adapted for removing contaminants or delivering agents in challenging settings. Lastly, integrating MNMs with artificial intelligence and advanced robotics could lead to the development of autonomous nano-systems capable of intelligent decision-making, adaptive targeting and coordinated actions.

The path from in vitro studies to in vivo application has made some encouraging progress, but there is still a long way to go. In conclusion, this review will promote the further development of membrane-encapsulated micro- and nanorobotics approaches in the field of nanomedicine and further benefit clinical research.

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Disclosure

The authors declare no conflict of interest for publication in this journal.

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