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Intelligent micro/nanorobots based on biotemplates

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Intelligent micro/nanorobots based on natural materials as biotemplates are considered to be some of the most promising robots in the future in the microscopic field. Due to the advantages of biotemplates such as unique structure, abundant resources, environmental friendliness, easy removal, low price, easy access, and renewability, intelligent micro/nanorobots based on biotemplates can be endowed with both excellent biomaterial activity and unique structural morphology through biotemplates themselves and specific functions through artificial micro/nanotechnology. Thus, intelligent micro/nanorobots show excellent application potential in various fields from biomedical applications to environmental remediation. In this review, we introduce the advantages of using natural biological materials as biotemplates to build intelligent micro/nanorobots, and then, classify the micro/nanorobots according to different types of biotemplates, systematically detail their preparation strategies and summarize their application prospects. Finally, in order to further advance the development of intelligent micro/nanorobots, we discuss the current challenges and future prospects of biotemplates. Intelligent micro/nanorobots based on biotemplates are a perfect combination of natural biotemplates and micro/nanotechnology, which is an important trend for the future development of micro/nanorobots. We hope this review can provide useful references for developing more intelligent, efficient and safe micro/nanorobots in the future.

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Wider impact

This review aims to be a comprehensive, authoritative, critical, and accessible review of general interest to the scientific community because it covers the recent progress and application of natural biological materials as biotemplates for developing micro/nanorobots, including the common plant tissues, bacteria, cells, and microalgae available in nature. Utilizing natural materials as biotemplates to obtain intelligent micro/nanorobots is a new trend in recent years due to their elegant structures and abundant surface functional groups. To further expand the potential of intelligent micro/nanorobots for applications, several challenges should be urgently considered and addressed. This review will target a broad audience from chemistry, biochemistry to environmental chemistry communities. Main applications covered will be targeted to the chemical/biochemical field, including drug delivery, biological sensing, bacterial inactivation and environmental remediation approaches *via* chemical sorption and degradation. Firstly, the advantages of biotemplates, preparation processes and propulsion modes of micro/nanorobot synthesis using biotemplates with different structures are systematically introduced. Secondly, based on the characteristics of biotemplates, their intelligent applications in environmental chemistry and biomedicine are elaborated. Finally, the current problems and challenges in synthesizing intelligent micro/nanorobots are reviewed, along with future prospects (to stimulate further research in the scientific community).

1. Introduction

With the continuous development of robot technology, robots with different functions play a more critical role in various fields and have become humans right-hand men.[1] However, when the robot operations need to enter from the macro scale to the micro scale, such as intravascular drug transportation and intracellular micro-operation, macro robots should be reduced in size to reach the target location to complete the established tasks.[2] Thus, it is urgent to develop microrobots or nanorobots that can work at the micro/nano scale, namely

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micro/nanorobots. Micro/nanorobots mainly refer to artificial robots that convert energy (such as chemical energy,[3] light,[4] electric energy,[5] magnetic field,[6] and ultrasonic wave[7]) from the external environment into their motion.[8,9] Owing to the controllable motion behavior and the high efficiency of micro/nanorobots, they displayed significant potential for various applications, such as environmental remediation,[10] biodetoxification,[11] detection,[12] active drug delivery,[13] and micro/nanosurgery.[14] Based on the different applications of micro/nanorobots, various preparation methods, shapes, and material sources have emerged.[15] Due to the significant differences in structures and material sources, optimizing the structures and materials of these micro/nanorobots for broader applications is necessary. Despite significant micro/nanorobot fabrication achievements, conventional chemical or artificially synthetic materials emerge with obvious limitations, such as low structural reproducibility, low batch fabrication efficiency and high prices.

The fine structure and easy accessibility of natural organisms have inspired researchers.[16] In order to survive in nature, organisms gradually acquire the ability to adapt to various changes in complex natural environments. They have evolved a large number of dominant structures and biological forms in

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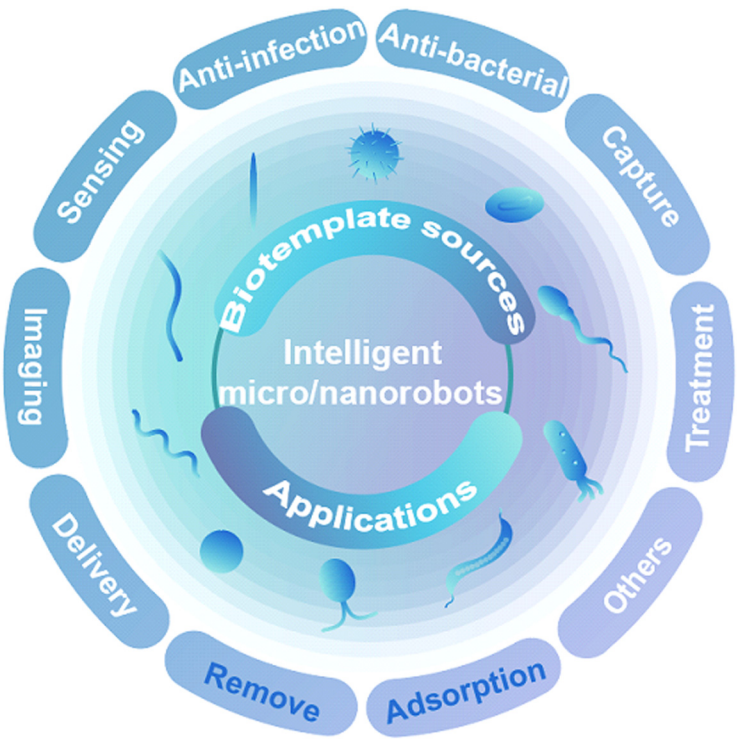
the process of continuous evolution and can accurately control these morphological structures at the micro or nano scale through their regulatory mechanism.[17] From the natural calcified biotube crystals, hollow fibers, helix vessels, and spiny protrusion pollen to magnetostatic bacteria and nature cells, biotemplates can generate various highly ordered hierarchical structures and unique biological activities on different size scales. At the micro and nanometer scales, their structures often have an advanced level of intricacy that rivals the sophistication of current engineered materials and systems.[18] In addition, the surface of biotemplates is rich in active functional groups that can be used directly for synthesis, avoiding the tedious chemical synthesis process.[19] Therefore, in recent years, many researchers have achieved through biotemplates the morphological and functional diversification of synthetic materials that meet the environmental protection requirements for materials. Biotemplates can effectively transform highly structured natural structures into multifunctional materials through artificial modification, such as using plant fibers, microalgae, cell membranes, and bacteria to prepare functional materials with diverse shapes and functions.[15] In addition, using biotemplates as raw materials has many advantages, such as unique configuration, high morphological repeatability, abundant resources, environmental friendliness, easy removal, cheap, easy availability, and renewability.[20,21] It is a new method and way to obtain micro/nanorobots with special structures.[22] Natural biotemplates with inherent good biocompatibility and a delicate structure provide new opportunities for preparing multifunctional micro/nanorobots.[23]

Using the natural structure of biotemplates solves the challenging problems encountered in research to a certain extent. Integrating biotemplates and micro/nanotechnology not only retains the biological activity of biotemplates and excellent structural characteristics but also enables artificially specific functions *via* micro- and nanotechnology. Thus, it promotes the development of micro/nanorobots for application in environmental purification, drug delivery, imaging diagnosis, and cancer treatment.[24,25] Here, we cover the recent progress and application of natural biological materials as biotemplates for developing micro/nanorobots, including the common plant tissues, bacteria, cells, and microalgae available in nature (Scheme 1). Firstly, the advantages of biotemplates, preparation processes and propulsion modes of micro/nanorobot synthesis using biotemplates with different structures are systematically introduced. Secondly, based on the characteristics of biotemplates, their intelligent applications in environmental chemistry and biomedicine are elaborated. Finally, the current problems and challenges in synthesizing intelligent micro/nanorobots are reviewed, and the future development of intelligent micro/nanorobots for intelligent applications is predicted, which provides new prospects for overcoming some urgent challenges in further applications.

2. Fabrication of intelligent micro/nanorobots

Using biotemplates to prepare functional micro/nanorobots has an alluring prospect and more merits than traditional



Scheme 1 Template sources and applications of intelligent micro/nanorobots.

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artificial synthetic materials.[26] First, biotemplates have the advantages of vast sources, strong renewability, low cost, *etc.*[27] Second, natural biotemplates have unique structures, including needle-like biological calcification tubes, sea urchin-like pollen, spherical chlorella, and spiral spirulina. Their unique structure is shown in Fig. 1A. These biotemplates are uniform in shape, widespread and reproducible, and can be directly collected or cultivated from the external environment. For instance, pollen spores, yeast microorganisms, and microalgae with micro/nanosphere characteristics can be obtained through large-scale cultivation.[28] However, traditional artificial synthetic materials require a high cost and will discharge pollutants harmful to the environment.[29] Third, the surface of a biotemplate is rich in active functional groups, which chemical reactions can modify.[30] For example, the cell wall of microalgal cells and yeast is usually composed of cellulose, mannan, dextran, *etc.*, which contain rich glycosidic bonds and hydroxyl functional groups and can conduct a series of polymerization reactions to introduce specific functional groups.[20,31] More importantly, chemical reactions can also convert these groups into new active groups. The naturally formed functional groups avoid the use of tedious chemical synthesis steps.[19] Fourth, the thermal stability of a biotemplate is poor and can be volatilized by high-temperature pyrolysis and carbonization without residue.[27] Finally, biotemplates, as drug carriers, are non-toxic and harmless to the body and have good biocompatibility.[32] It is worth mentioning that living organisms self-propelled micro/nanorobots providing unique advantages for their applications because they can achieve active propulsion without external fuels or energies.[33,34] In short, biotemplates have attracted more and more attention due to their irreplaceable advantages over other template materials. Therefore, the material sources of intelligent micro/nanorobots were classified in this section.

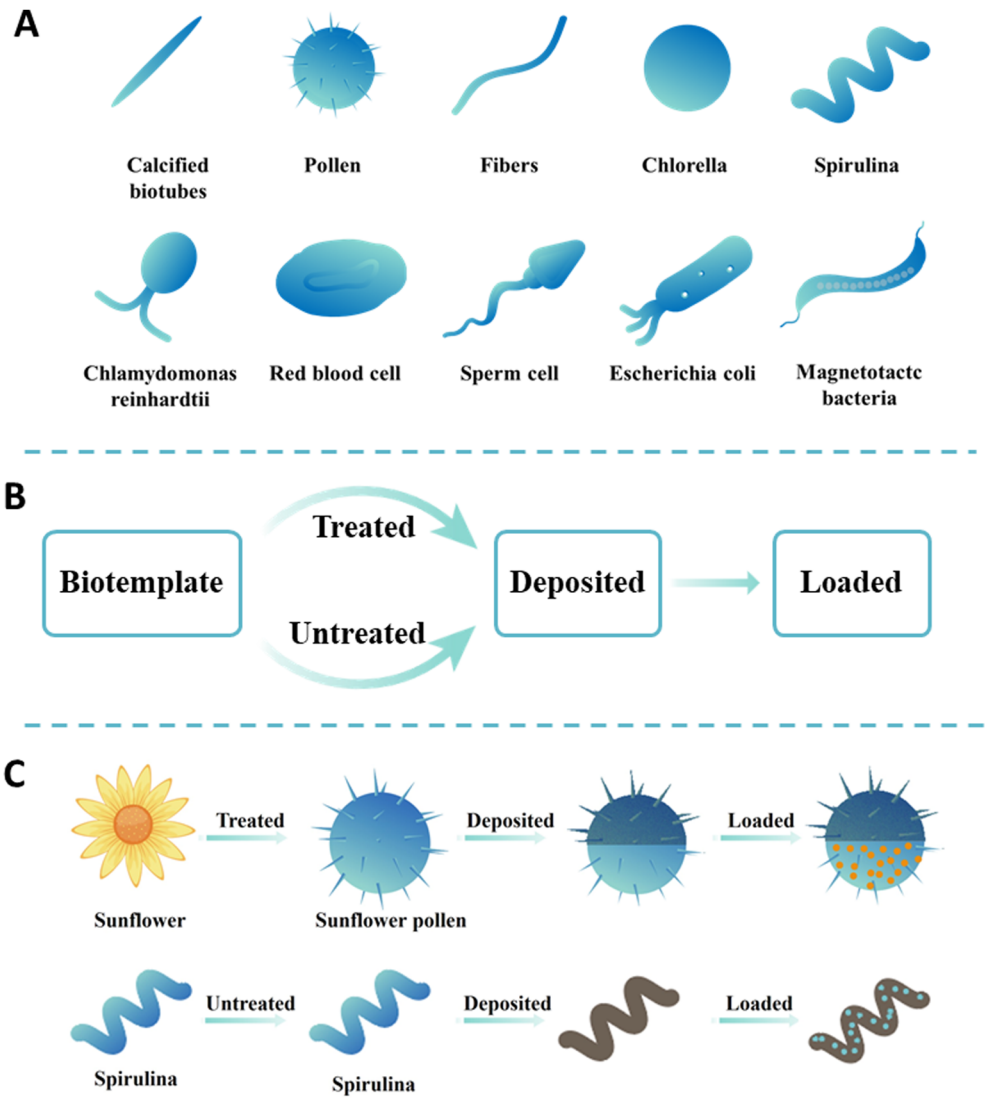

Fig. 1 Typical structure of natural biotemplates and manufacturing strategies of micro/nanorobots. (A) Natural biotemplates with different structures. (B) A brief description of the fabrication process of micro/nanorobots using natural biotemplates. (C) Fabrication schemes of typical biotemplates used for preparing micro/nanorobots.

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The feasibility of the fabrication strategy must be considered when selecting a biotemplate and artificial carriers with specific structures for a specific application. In a comprehensive consideration, the manufacturing strategy is mainly divided into two steps: chemical precipitation and chemical adsorption. The basic process of manufacturing functional micro/nanorobots using a biotemplate is shown in Fig. 1B. First, the target micro/nanomotor is prepared by selecting a specific structure to replicate the template's external shape or internal structure.[35] Subsequently, the functional material is loaded on the surface of the micro/nanomotor by artificial modification to achieve specific applications. To better demonstrate the preparation process, two typical biotemplates (sunflower and spirulina) are shown as biotemplates for preparing multifunctional micro/nanorobots. As shown in Fig. 1C, when the sunflower pollen is used as a biotemplate, it is first necessary to obtain individual pollen particles *via* separation, then a layer of metal or metal oxide is deposited on their surface for propulsion, and finally, drugs can be loaded. When spirulina is used as a biotemplate, it can be directly used for preparing micro/nanorobots without pretreatment. Similarly, magnetic metals or metal oxides can be deposited on its surface by chemical deposition, and then drugs can be loaded onto its surface through surface modification to obtain magnetically propelled micro/nanorobots. In recent years, significant progress has been achieved in transforming biotemplates into functional micro/nanorobots, and various natural materials as new material sources have been introduced in several fields of materials science. According to the different sources of biotemplates, they can be roughly divided into four categories. Therefore, this section highlights several common biotemplates used to fabricate intelligent micro/nanorobots and their main preparation processes.

3. Classification of intelligent micro/nanorobots

3.1. Plant tissue-based micro/nanorobots

Functional micro/nanorobots usually use chemical materials as precursors with complex preparation processes and harsh reaction conditions. In addition, it can greatly increase the production cost of the materials and seriously hinder the application of micro/nanorobots to some extent.[36] Therefore, seeking resource-rich, inexpensive, and readily available new materials to replace traditional chemical materials is significant for large-scale production of low-cost functional micro/nanorobots. Plants are multicellular eukaryotes, one of the primary forms of life, including trees, shrubs, grasses, ferns, vines, mosses, *etc.* The number of species exceeds 300 000, and they cause no pollution, are easy to obtain, and have highly regenerative characteristics.[37] Plant tissues have created uniquely complex patterns and elegant structures over millions of years. They are capable of generating a variety of highly ordered hierarchical structures on different scales, which rival the sophistication of current engineered materials, such as vessels,[17] calcified crystals,[38,39] pollen,[40,41] dandelion fluffs,[21] fibers.[42] These plant tissue materials with exotic microstructures are extracted, can be used as substrate materials after artificial treatment and subsequently transformed into functional micro/nanorobots by synthetic manufacturing techniques.[20] Next, several typical biotemplates will be shown for preparing plant tissue-based micro/nanorobots.

Vascular plants were rich in uniform spiral microstructures, and can be used to prepare micromotors with efficient propulsion. Gao *et al.* proposed the first example of plant vascular-based bioinspired magnetically propelled helical microswimmers.[17] Due to the extremely high density of spiral vessels within the leaves, over a million individual helical swimmers can be generated from a short single segment of the plant stem (Fig. 2A). Geometric variables of the spiral vessels, such as the helix diameter and pitch, can be controlled by mechanical stretching for the precise fabrication and consistent performance of helical microswimmers. Then, sequential deposition of thin Ti and Ni layers directly on the spiral vessels, followed by dicing, leads to extremely simple and low cost plant vascular-based magnetic microswimmers displaying efficient propulsion, with a speed of over 250 μm s^{-1}, as well as powerful locomotion in biological media such as human serum. Such a new method of using the spiral plant vessel as the significant component of the helical micromotor dramatically simplifies the fabrication process by utilizing the intrinsic biological microstructures that nature provides. In addition, the helical microstructures derived from the lotus-root fibers can also be used to prepare microswimmers.[43] A simple and reproducible method is illustrated in Fig. 2B, and the helical fibers are mechanically isolated from the lotus roots. The whole process proceeds sequentially through cutting, breaking, and stretching. The stretching span in Fig. 2B can be controlled thus tailoring the length of the helixes. After that, the obtained helixes are subject to the coating of the Fe_3O_4 magnetic layer, and then they are diced into the desirable lengths to enable magnetic actuation. Moreover, this work also reveals that microswimmers with soft bodies could locomote faster than those with rigid bodies, which shows their prospect for biomedical applications in the future.

In nature, sunflower pollen particles with unique microstructures can be used to prepare micro/nanorobots with specific functions. Liu *et al.* fabricated a bioinspired micromotor based on sporopollenin exine capsules (SECs) extracted from sunflower pollen grains which can encapsulate macromolecular compounds for cargo delivery as well as absorb heavy metals for decontamination of water without further functionalization.[44] As illustrated in Fig. 2C, to demonstrate the encapsulation ability of SECs, bovine serum albumin (BSA) was used as a model biomacromolecule and loaded within the SECs by a vacuum-assisted loading technique. In order to achieve the goal of cargo delivery within the micromotor design framework, a layer of Pt was deposited on one side of the BSA-loaded SECs. The partial Pt layer on the outer surface imparts catalytic properties toward H_2O_2 decomposition to the BSA-loaded SECs, enabling their motion in the presence of a H_2O_2 fuel.

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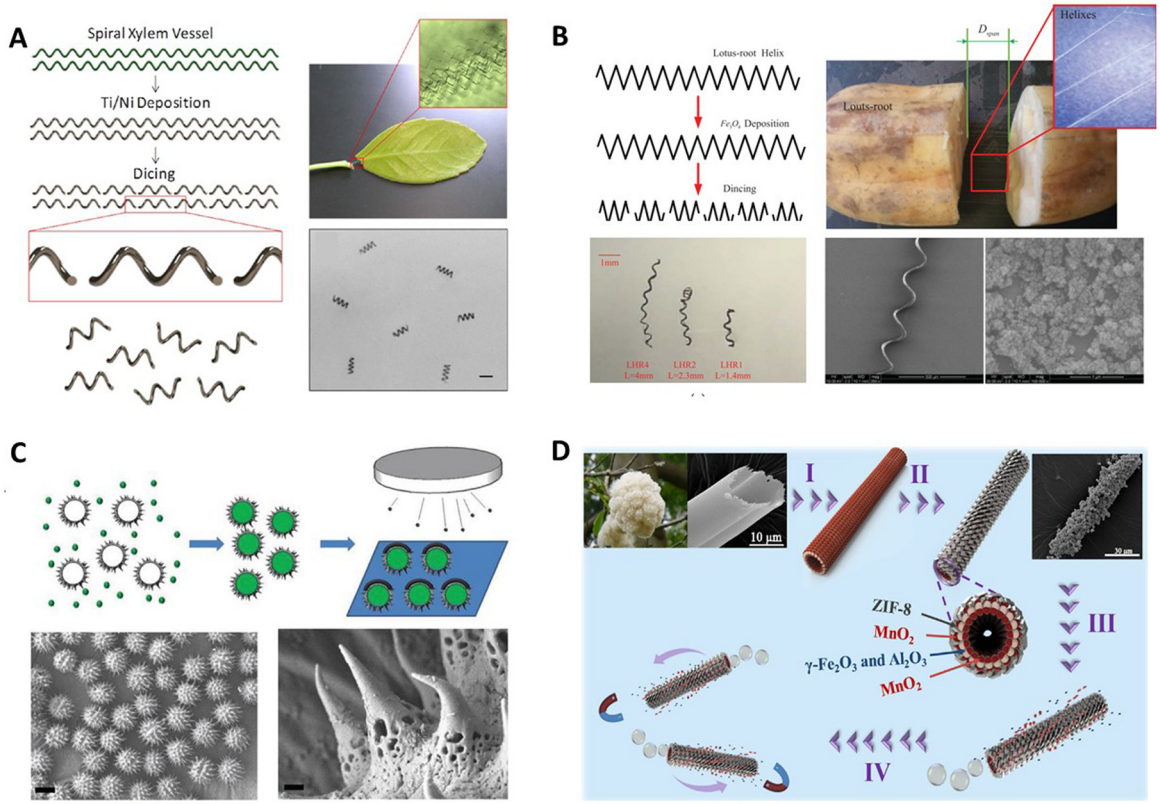

Fig. 2 Plant tissue template-based micro/nanorobots. (A) Bioinspired helical microswimmers based on vascular plants. Reprinted with permission from ref. 17. Copyright 2014 American Chemical Society. (B) Swimming characteristics of bioinspired helical microswimmers based on soft lotus-root fibers from ref. 43. Copyright 2017 Multidisciplinary Digital Publishing Institute. (C) Bioinspired spiky micromotors based on sporopollenin exine capsules from ref. 44. Copyright 2017 Wiley-VCH. (D) Bioinspired zeolitic imidazolate framework (ZIF-8) magnetic micromotors for highly efficient removal of organic pollutants from water from ref. 42. Copyright 2019 Elsevier.

The biocompatibility and large internal cavities of SECs make them suitable for encapsulation and delivery of cargo. The porous polymeric structure and functional groups on the surface offer sporopollenin the ability to absorb heavy metals without any additional modification. By harnessing the advantageous features of SECs, such micromotors open new horizons for using plant pollen-derived materials to address biomedical and environmental issues.

Natural kapok fibers have unique hollow structures, inspiring the design and fabrication of bubble-driving tubular micromotors. Liu *et al.* first demonstrated novel self-propelled Pt-free ZIF-8 magnetic micromotors using a bio-inspired approach as an active adsorbent for highly efficient wastewater treatment.[42] The fabrication process of micromotors is illustrated in Fig. 2D. Briefly, the kapok fiber was used as the template first to fabricate mixed metal oxide (γ-Fe_2O_3/γ-Al_2O_3) magnetic porous microtubes. Then catalytic material MnO_2 particles were synthesized on the microtubes' outer and inner surfaces. Subsequently, ZIF-8 was loaded on the outer side of the above-mentioned magnetic tubes *via in situ* growth. After that, the catalytic layer was only exposed on the inner surface of the microtube, and the final tubular ZIF-micromotors were obtained. In the presence of a fuel (H_2O_2), the micromotors will be driven by the O_2 bubbles and finally cause efficient dynamic adsorption toward pollutants in water. In this, the micromotors prepared by the kapok template method retained the natural asymmetric hollow fiber structure of kapok that provides unbalanced force conditions without further complex procedures.

3.2. Cell-based micro/nanorobots

Most micro/nanorobots obtained from plant tissue templates are rigid. Therefore, creating soft and flexible micro/nanorobots is meaningful because the ability to change shape allows movement through tight spaces or winding channels, enabling specific applications.[45,46] Nature provides myriad sophisticated biological cells (such as red blood cells and sperm cells) that can display and regulate motion in well-established manners over long ages of evolution.[2] They have received substantial interest as model carriers due to their abundance, biocompatibility, biodegradability, non-immunogenicity, inert intracellular environment, and ease of handling.[47] More importantly, in soft micro/nanorobots, cell-based micro/nanorobots constructed by the integration of living cells and flexible materials have reproduced similar organ or tissue construction and functions of organisms. This integration is attributed to the progress of manufacturing technologies and advances in tissue engineering. Compared with traditional rigid micro/nanorobots, cell-based micro/nanorobots

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exhibit superiority in intrinsic softness, environmental safety and compatibility, remarkable energy conversion efficiency, and integrated sensing and control.[48] Furthermore, some cells can direct and transport various synthetic organic/inorganic functional payloads through functionalization with intrinsic chemotactic behavior, thereby generating carrier-cell interactions without mechanical damage, which is critical for biomedical applications.[49] Based on these, cells are promising in designing and fabricating various types of bionic delivery robots due to their natural advantages.[50] Synthetic micro/nanorobots are envisioned to move, sense, and perform specific functions like their biological counterparts.[51] Below, we present several examples of micro-robots using cells as substrate materials for synthesizing microrobots.

Red blood cells (RBCs) are of particular interest owing to their vast availability, unique mechanical attributes, surface immunosuppressive properties, and versatile cargo-carrying capability. Wu *et al.* reported an RBC-derived approach for developing a new generation of cell-based micromotor powered by ultrasound and activated by a magnetic field.[52] Fig. 3A shows the preparation of magnetically guided, ultrasound-propelled RBC micromotors. Initially, citrate-stabilized magnetic Fe_3O_4 nanoparticles were synthesized. Then, the fresh RBCs were collected from mice and anticoagulated with ethylenediamine tetraacetate. Finally, a RBC micromotor was prepared using a hypotonic dilution/encapsulation method to load iron oxide nanoparticles (20 nm) into RBCs. The RBC micromotor was propelled by the pressure gradient generated by the ultrasound waves due to the inherent asymmetric geometry of the RBCs as well as the asymmetric distribution of magnetic particles inside the RBCs. Owing to their inherent biomimetic properties, these new RBC micromotors are not susceptible to macrophage

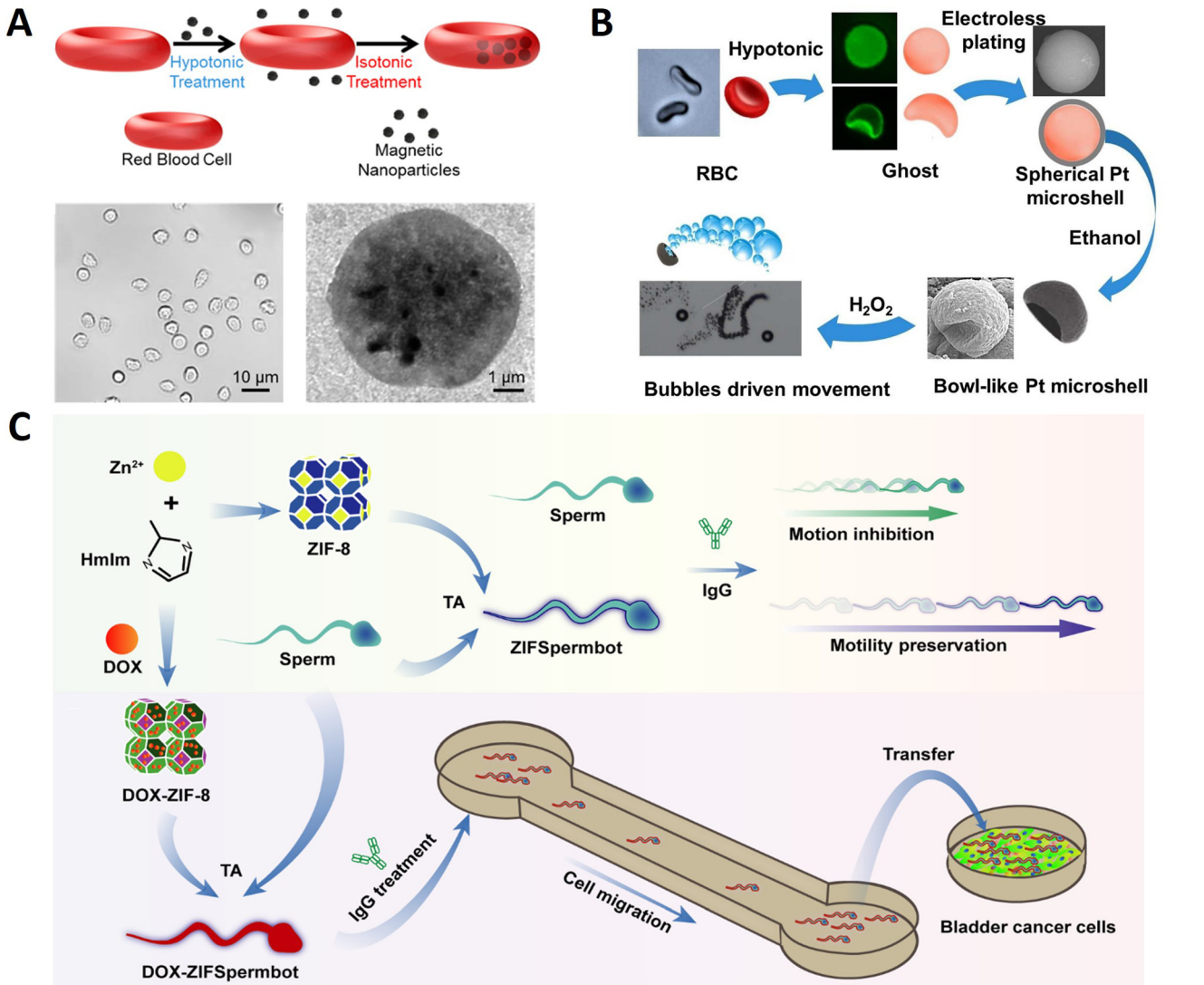

Fig. 3 Cell template-based micro/nanorobots. (A) Turning erythrocytes into functional micromotors. Reprinted with permission from ref. 52. Copyright 2014 American Chemical Society. (B) Bowl-like micromotors using red blood cell membranes a as template. Reprinted with permission from ref. 54. Copyright 2019 Wiley-VCH. (C) Multifunctional metal–organic framework exoskeletons protect biohybrid sperm microrobots for active drug delivery from the surrounding threats. Reprinted with permission from ref. 55. Copyright 2021 American Chemical Society.

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uptake, displaying remarkable biocompatibility essential for practical biomedical uses.

The RBC membrane is the hollow ghost that RBCs obtain through hemolysis. It can form a natural compartment to protect internal materials and couple therapeutic molecules for various delivery applications, making it widely used in the surface modification of nanoparticles.[53] RBC membranes with good deformability and fluidity are excellent natural templates for micromaterial fabrication. Pan *et al.* used RBC membranes as templates to prepare asymmetric Pt bowl-like micromotors responsive to H_2O_2 (Fig. 3B).[54] The red blood cells were collected from a healthy donor, and then hemoglobin was removed by hemolytic swelling to obtain a single-sided concave shape ghost. Subsequently, the ghost was used as a template to prepare bowl-like micromotors by electroless plating of platinum particles onto the membranes. Due to the shrinkage of the internal template and the softness of the platinum shell, the products deformed from the spherical structure to a bowl-like structure with treatment. The recessed portion of the platinum bowl structure has a negative curvature to generate oxygen bubbles, which generates a one-way driving force to push the micromotor forward. These asymmetric bowl-like micromotors are expected as cargoes for drug delivery.

Mammalian sperm cells have strong propulsion, chemotactic behavior, and immune evasion capabilities that are highly advantageous in building sperm-based micro-robots. As shown in Fig. 3C, Pan *et al.* reported sperm-driven biohybrid microrobots.[55] Doxorubicin (DOX) was encapsulated in ZIF-8 NPs through the *in situ* biomineralization method to obtain DOX-ZIF-8 NPs. In order to build DOX-ZIFSpermbot, sperms were mixed with DOX-ZIF-8 NPs and tannic acid (TA) was added to induce the complexation between ZIF-8 and the cell membrane. Combining the effective protection of sperm propulsion with the drug-loading capacity of ZIF-8 NPs provides new applicability to ZIFSpermbots in risky surroundings with AsA, exhibiting rapid migration in a microfluidic device for active drug delivery with enhanced therapeutic efficacy due to their retained effective propulsion. Utilizing spermatozoa as the engine unit of robotic systems at a microscale has revolutionized inspirations and strategies for the biomedical community.

3.3. Microalgae-based micro/nanorobots

Microalgae are photosynthetic unicellular microorganisms and widely exist in nature.[56] They grow rapidly, simple in structures, adaptable to different environments, and have excellent biocompatibility and biodegradability.[57] Microalgae produce a variety of compounds, such as photosynthetic pigments (carotenoids and chlorophylls), sterols, polyunsaturated fatty acids, vitamins, minerals, fibers, polysaccharides, enzymes, peptides, and toxins which have broad applications in many fields.[58,59] They have attracted great interest in recent years due to their potential applications in nutraceutical and pharmaceutical industries, and are a major source of food, energy, health, environment, and biomaterials.[60] Microalgae can rapidly proliferate and be obtained in large quantities through artificial cultivation and can be used as biotemplate without treatment.[61] Micro/nanorobots with special structures and functionalities can be obtained by depositing or loading *via* using microalgae as biotemplates.[62] The strange shapes of microalgae, such as spherical, triangular, elliptical, star-shaped, and other irregular shapes, provide ideas for preparing microalgae-based micro/nanorobots with specific structures for specific applications.[63] Therefore, using microalgae as substrate materials enables the controlled synthesis of functional micro/nanorobots with specific morphology and microstructure.[64] At the same time, using biomaterials rich in elements and chemical components related to life activities to achieve a full range of biotemplates is a major advantage unmatched by other artificially engineered templates.[65,66] Here, several typical examples of preparing microalgae-based micro/nanorobots using microbial algae as templates will be introduced.

Chlorella pyrenoidosa (*C. pyrenoidosa*) has uniform spheroidal structures with diameters around 3–5 μm, even smaller than those of human red blood cells. These fascinating features give them the superiority to act as ideal natural biomaterials for biomedical applications. Liu *et al.* fabricated a bioinspired micromotor to precisely activate muscle.[67] As displayed in Fig. 4A, *C. pyrenoidosa* was used as a biotemplate to prepare magnetic microswimmers *via* a facile dip-coating approach. In this fabrication process, *C. pyrenoidosa* and the Fe_3O_4 nanoparticles were oppositely charged so that discrete Fe_3O_4 nanoparticles could be effectively absorbed on the surface of *C. pyrenoidosa* and grow. Under the wireless actuation of a weak rotational magnetic field, the engineered biohybrid microswimmers could navigate and follow complex trajectories *in vitro*. Meanwhile, the single microswimmer could approach targeted derived myotube accurately by remote manipulation and then efficiently induce myotube contraction under NIR stimulation, with a local temperature increase of approximately 5 °C. The as-developed magnetically actuated microswimmer-based strategy can provide a renovation for tissue engineering and bionics.

Diatoms have a well-defined cell wall known as a frustule, made up of SiO_2, Al_2O_3, and Fe_2O_3, which can act as a catalyst and provide thrust in solution. As shown in Fig. 4B, Panda *et al.* report a novel bio-inspired approach for preparing self-propelled micromotors by catalytic decomposition of H_2O_2 as a fuel.[68] The diatoms are composed of a silicate backbone with biological moieties containing organic molecules and trace amounts of metal ions, such as those of iron. Interestingly, a trace amount of iron oxide (Fe_2O_3) in the diatom was converted into Fe_3O_4, which can act as a catalyst to achieve the facile decomposition of H_2O_2 and unidirectional motion. The unique 3D hierarchical structure of the diatom can provide the bubbling force anisotropically in solutions, resulting in unidirectional motion for diatom-based micromotors. These frustules are mechanically robust, chemically balanced, and eco-friendly; thus, they can easily be used in biological and environmental applications.

Chlamydomonas reinhardtii (*C. reinhardtii)* presents intriguing biological swimmers with high propulsion, autofluorescence,

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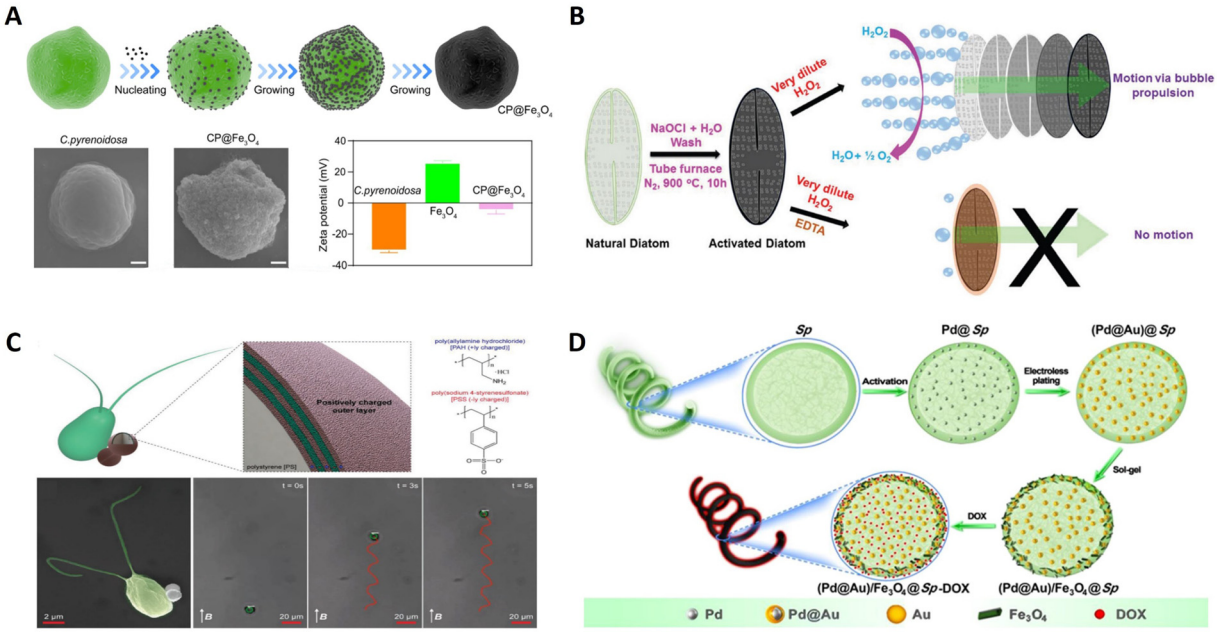

Fig. 4 Microalgal template-based micro/nanorobots. (A) Magnetically actuated biotemplate-based microswimmers for precise photothermal muscle contraction. Reprinted with permission from ref. 67. Copyright 2022 American Chemical Society. (B) Bio-inspired self-propelled diatom micromotors obtained by catalytic decomposition of H_2O_2 at low fuel concentration. Reprinted with permission from ref. 68. Copyright 2018 Royal Society of Chemistry. (C) Microalga-powered biohybrid microswimmers for active cargo delivery. Reprinted with permission from ref. 69. Copyright 2018 Wiley-VCH. (D) Facile fabrication of magnetic microrobots based on spirulina templates for targeted delivery and synergistic chemo-photothermal Therapy. Reprinted with permission from ref. 70. Copyright 2019 American Chemical Society.

and phototactic guidance capabilities. Inspired by this, Yasa *et al.* developed a biocompatible biohybrid microswimmer powered by *C. reinhardtii* as shown in Fig. 4C.[69] This biohybrid algal microswimmer comprises an intact microalga, *C. reinhardtii*, attached to the polyelectrolyte (PE) functionalized 1 μm diameter magnetic polystyrene (PS) particles. Cargos were noninvasively attached to the microalgae without compromising the natural motility, using noncovalent electrostatic interactions between the positively functionalized magnetic PS microparticles and the negatively charged microorganisms. As a result, the biological segment of the biohybrid microswimmers serves as an actuator and sensor, while their artificial segment provides support and other functionalities. Similarly, using natural swimmers as cargo delivery agents presents an alternative strategy to transport therapeutics inside the body to locations otherwise difficult to access by traditional delivery strategies.

Helical magnetic microrobots have attracted particular attention because they can transform the rotation around their helical axis into a translational motion along the helical axis to provide an efficient and precise 3D locomotion behavior. As shown in Fig. 4D, Wang *et al.* proposed a facile method for the mass production of magnetic microrobots with multiple functions using *Sp.* as a biotemplate.[70] Initially, the Pd@Au core–shell NPs were embedded both in the *Sp.* cells and on the cell walls. Subsequently, Fe_3O_4 NPs are deposited on the as-prepared (Pd@Au)@*Sp.*, enabling the obtained (Pd@Au)/Fe_3O_4@*Sp.* microrobots to be actuated in an external magnetic field. Finally, chemotherapeutic doxorubicin (DOX) is loaded to obtain (Pd@Au)/Fe_3O_4@*Sp.*-DOX microrobots. They can elide the process of fabricating spiral configuration by taking advantage of their intrinsic helical morphology compared to other manufacturing methods of microrobots. Furthermore, the helical structure endows the as-prepared microrobots with efficient propulsion performance with the highest speed of 526.2 μm s^{-1} under a rotating magnetic field. Such facile fabrication of magnetic microrobots based on *Sp.* as a template is very promising.

3.4. Bacterial template-based micro/nanorobots

Microorganisms such as bacteria have good micro-organic structures and small sizes, and can be used as templates to synthesize nanostructured materials[71] because bacteria have evolved many dominant structural biological forms in continuous evolution and can precisely control these morphological structures at the nanometer level through their regulatory mechanism. Current scientific and technological means make it difficult to prepare ordered 3D nanospheres, but bacteria such as cocci and helicobacter can easily form such structures. Therefore, using bacteria as templates has the advantages of wide access and potential gene regulation functions, and has a good application prospect.[72] Additionally, bacteria have a high swimming speed and efficiency in the low Reynolds (Re) number flow regime, can sense and respond to external environmental signals, and can be externally detected *via* fluorescence or ultrasound imaging techniques.[25,73] In particular, bacteria offer several advantages as controllable microactuators: they draw chemical energy directly from their environment,

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they can be genetically engineered and employed as sensing elements and they are scalable and configurable in that the bacteria can be selectively patterned.[74] Due to their inherent advantages, various bacteria (*Escherichia coli*,[25] *Magnetotactic bacteria*,[75] *Salmonella typhimurium*,[76] *etc.*) have been used as carriers to prepare as potential microrobots. Next, a few examples are introduced.

Bacteria can be integrated with synthetic substances to produce multiple functionalities through their biological actuation and sensing capabilities. Buss *et al.* present a biohybrid microswimmer composed of a genetically engineered peritrichously flagellated *Escherichia coli* species integrated with red blood cell (RBC) derived nanoliposomes.[25] As displayed in Fig. 5A, firstly, the genetically engineered bacterial species were induced with isopropyl-*b*-D-thiogalactopyranoside (IPTG) to obtain bacterial species with biotin molecules on their cell membranes. Then, RBCs were isolated from whole murine blood, and nanoerythrosomes were fabricated from emptied RBCs using the cell extrusion technique. The nanoerythrosomes were modified with biotin molecules *via* biotin-conjugated anti-TER119 antibodies to realize the non-invasive conjugation of the bacterial actuators with the cargo carriers. Finally, microswimmers were constructed by conjugating streptavidin-modified bacteria with biotin-modified nanoerythrosomes using non-covalent streptavidin interactions. These microswimmers showed enhanced swimming speeds compared to the previously reported biotemplate-based microswimmer designs powered by various *Escherichia coli* strains. Besides, more applications could be achieved by rational design of bacteria's surface. Chen *et al.* designed a biohybrid microrobot able to move by applying a magnetic field and in thermal and hypoxic environments, integrating the properties of both magnetic nanoparticles (MNPs) and *Escherichia coli* Nissle1917.[77] In order to achieve imaging-guided magnetothermal treatment, genetically engineered probiotics were prepared using pBV220 expression vectors encoded with the NDH-2 or mCherry/NDH-2 gene sequences, and the thermally sensitive promoter TcI was integrated. Then, bacterial hybrid microrobots were prepared by conjugating the Zn-doped Fe_3O_4 MNP ($Zn_{0.4}Fe_{2.6}O_4$) on the genetically engineered probiotics (Fig. 5B). Compared with artificial micro/nanorobots, the bacteria endow microrobots with efficient self-propulsion, and integration of the physical, biological and chemical properties, enabling microrobots with triple sensing capabilities of magnetism, heat, and hypoxia to overcome harsh biological environments and achieve satisfactory therapeutic effects.

Magnetococcus marinus strain, magnetospirillum magneticum (AMB-1), can be used to prepare intelligent biotemplate-based microbiorobotics due to its magnetosomes inside the body being susceptible to external magnetic fields. Xing *et al.* developed an AI microrobot system using AMB-1 as the template composed of motile AMB-1 and light-triggered indocyanine green nanoparticles (INPs).[78] The INPs were synthesized with maleimide groups in the phospholipid shell and ICG in

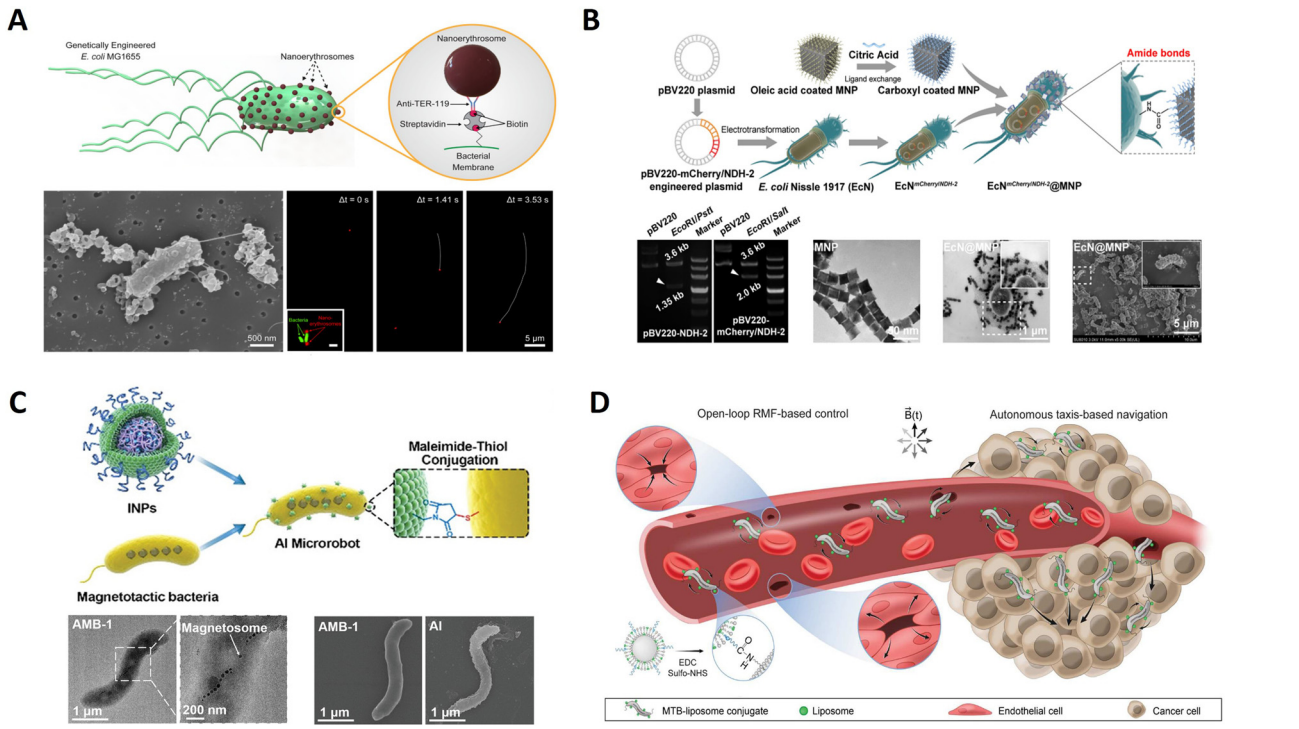

Fig. 5 Bacterial template-based micro/nanorobots. (A) Nanoerythrosome-functionalized biohybrid microswimmers. Reprinted with permission from ref. 25. Copyright 2019 AIP Publishing. (B) An engineered bacteria-hybrid microrobot with a magnetothermal bioswitch for remotely collective perception and imaging guided cancer treatment. Reprinted with permission from ref. 77. Copyright 2022 American Chemical Society. (C) Sequential magneto-actuated and optics-triggered biomicrorobots for targeted cancer therapy from ref. 78. Copyright 2021 Wiley-VCH. (D) Magnetic torque–driven living microrobots for increased tumor infiltration. Reprinted with permission from ref. 75. Copyright 2022 AAAS.

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the poly(lactic-*co*-glycolic acid) (PLGA) core by a single-step sonication method. In parallel, surface protein disulfides of AMB-1 were reduced to activated sulfhydryl by tris(2-carboxyethyl) phosphine (TCEP). Finally, the INPs were chemically conjugated onto the activated sulfhydryl outside the AMB-1 membrane by a Michael addition reaction to form a smart AI microrobot (Fig. 5C). Such AI microrobots with autonomous flagellum propulsion can realize controlled navigation, focal localization, deep penetration, and tumor colonization *in vivo*. Therefore, bacteria-based microrobots were increasingly recognized as promising externally controllable vehicles for targeted cancer therapy. As shown in Fig. 5D, Gwisai *et al.* reported magnetic torque-driven living microrobots for increasing tumor infiltration using *magnetospirillum magneticum* as a magnetically responsive model organism.[75] Bioconjugation was achieved through carbodiimide coupling using an adapted protocol. Briefly, activation of carboxylated liposomes was accomplished by incubating 300 μL of liposome solution with EDC and sulfo-NHS for 20 min in PBS at room temperature with gentle agitation. The activated liposomes were subsequently incubated with *magnetotactic bacteria* (MTB) cells for 2 h at room temperature with gentle agitation. Unbound liposomes were separated from MTB-liposome conjugates (MTB-LP) using a 2D magnetic field. By merging the benefits of bacteria-mediated therapy with a scalable magnetic torque-driven control strategy, their approach enables effective, targeted delivery of living microrobots for improved treatment. A fourfold increase in translocation of magnetically responsive bacteria across a model of the vascular endothelium observed is attributed to torque-driven surface exploration at the cell interface.

4. Applications

Preparing intellect micro/nanorobots using biotemplates has excellent application prospects. On the one hand, creatures in nature have evolved various structures to adapt to external stimuli, and the size and morphology of these structures are very regular. Using these structures as biotemplates introduces the ''smart'' function of biological hybrid materials and avoids the waste of chemical materials.[79] On the other hand, the surface of biotemplates contains wealthy modifiable functional groups, which can be used to prepare functional materials that meet the needs of chemical reactions to connect special functional groups or change their hydrophobicity.[31,80] More importantly, different structures of natural biotemplates give various intelligent applications to micro/nanorobots.[81] For example, large internal cavity pollen grains are ideal for drug or nanoparticle encapsulation,[82] calcified porous microneedles were used for cell-microdrilling,[39] hollow kapok fiber provides unbalanced force conditions in the motion,[83] and helical structures can convert rotational motion to translational motion.[84] Therefore, through appropriate design and assembly, environmentally friendly, cheap, readily available biotemplates and specific functional chemical components can be used in complex and diverse intelligent applications, such as removal of organic pollutants, biosensors, and cancer treatment.[85,86] This part mainly introduces the application of intelligent micro/nanorobots in the environment and biology. Owing to the large variety of biotemplates and the multitude of nanomedicines that have been developed using different materials, structures, coatings, and functional ions, biotemplate-based micro/nanorobots can be combined in a plethora of configurations allowing their tailoring to achieve specific applications defined by the nature of the targeted objects and their microenvironment.[46] Thus, a summary of representative examples of various nature-/structure-inspired micro/nanorobots is presented in Table 1.

4.1. Biomedical applications

4.1.1. Drug delivery. Although remarkable achievements in active cargo delivery have been made over the past decade, delivery systems based on micro/nanorobots are still limited by complex physiological conditions *in vivo*.[142] When exposed to body fluids, the existing microrobot systems may compromise their structures and functions, let alone the encapsulated therapeutic drugs.[143] Besides, large-scale inexpensive production of micro/nanorobots with high biocompatibility and excellent physicochemical robustness is always challenging. A micro/nanomotor made from a biotemplate is expected to overcome this difficulty because of its good biocompatibility and surface-modifiable functional groups.[27] Moreover, performing the on-demand release of the maximum amount of the loaded drug at a specific position is particularly imperative.[64] Here, the self-propelled bio-based micro/nanorobots provide the carriers with continuous driving power to help them transport across biological tissues. In addition, the direction of the micro/nanorobots can also be adjusted to prompt cell targeting and internalization to enhance the controllability and adjustability of the drug delivery system. Compared to passive drug carriers, the self-propulsion abilities of these biotemplate-based micro/nanorobots have unique advantages in drug delivery, which bring distinct improvements for efficient drug delivery.

A significant advantage of using a biotemplate is that contrary to elaborate clean-room fabrication techniques, a large amount of material can be obtained relatively quickly with minimal process control. As displayed in Fig. 6A, Sarvesh *et al.* extracted calcified porous microneedles (40–60 μm long) from the *Dracaena sp.* plants that possess drug carrier capability (much like calcium-based drug carriers) and coated these structures with a magnetic layer to facilitate cellular drilling due to its microneedles structure by external magnetic actuation.[39] Subsequently, loading these calcified biotubes with the anticancer drug camptothecin allows for the site-specific activation of the drug in the acidic environment of HeLa cancer cells. These elongated porous microneedles were used to prepare magnetic biogenic microdaggers that can be used as daggers with microdrilling capability for piercing cells, but also with additional advantages of drug release function, due to which they can be used as a ''cell microsurgery and drug rehabilitation'' package.

Pollen, a renewable biomaterial that exists in nature widely, has a unique architecture, excellent biocompatibility, structural uniformity, good permeability, and a large hollow cavity. These

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Table 1 A summary of biotemplate-based intelligent micro/nanorobots

Natural structure		Main components	Speed ($\mu m\ s^{-1}$)	Propulsion mechanism	Applications	Ref.
Plant tissue	Leave vessels	Vessels/Ti/Ni	250	Magnetic field	—	17
	Banana leaf vessels	Vessels/Ni/Fe^{3+}-TA	51	Magnetic field	Degradation of RhB and capture of cells	87
	Lotus-root fibers	Fibers/Fe_3O_4	—	Magnetic field	—	43
	Tomato callus	Callus/Fe_3O_4	6.23	Magnetic field	Removal of chlorpyrifos	88
	Tomato callus	Callus/Fe_3O_4/Vitamin C	—	Magnetic field	Cell clones	89
	Kapok fibers	Fibers/γ-Fe_2O_3/γ-Al_2O_3/MnO_2/ZIF	∼150	Chemical reaction	Adsorption of organic pollutants	42
	Kapok fibers	Fibers/Eu-MOF/EDTA-NiAl-CLDH–M	56.9	Chemical reaction	Sensing and removal of Fe^{3+}	83
	Lotus pollens	Pollen/MnO_2/$CoFe_2O_4$	∼116	Chemical reaction	Recognition and capture of Pb^{2+}	90
	Chrysanthemum pollen	Pollen/Fe_3O_4/DOX	400	Magnetic field	Tumor assassination and tissue regeneration	82
	Lotus pollen	Pollens/PNIPAM/Mn_3O_4/$CoFe_2O_4$	161	Chemical reaction	Adsorption of erythromycin	91
	Pine pollen	Pollen/Fe_3O_4/DOX	175.19	Magnetic field	Drug delivery	92
	Sunflower pollen	Pollen/Fe_3O_4/Galinstan–Fe alloy	∼90	Magnetic field	Eradicate biofilm	93
	Sunflower pollen	Pollen/polydopamine	1000	Light	Capture and transport of yeast cells	94
	Sunflower pollen	Pollen/polydopamine/vancomycin	—	Light	Capturing and killing targeted bacteria	95
	Sunflower pollen	Pollen/Au/Co/DOX	∼25	Magnetic field	Attract, manipulate and kill cancer cells	96
	Sunflower pollen	Pollen/Ni	110	Magnetic field	Removal of oil and microplastics	97
	Sunflower pollen	Pollen/Ni/Ti/DOX	125	Magnetic field	Intracellular delivery	98
	Sporopollenin exine capsules	Sporopollenin/BSA/Pt	90.83	Chemical reaction	Drug delivery and removal of Pb^{2+}	44
	Calcified biotubes	Biotube/Fe–Ti/camptothecin	—	Magnetic field	Single-cell surgery, drug release	39
Cell	Red blood cell(RBC)	RBC/Fe_3O_4	16	Ultrasound	Anti-biological pollution	52
	Erythrocytes	Erythrocytes/magnetic beads	∼4	Magnetic field	—	99
	Bovine sperm cell	Sperm cell/Fe_2O_3/DOX	12.5	Magnetic field	Drug loading	100
	Bovine sperm cell	Sperm cell/Fe/DOX	—	Magnetic field	Drug loading and ultrasound imaging	101
	Bovine sperm cell	Sperm cell/iron oxide/polystyrene	121.1	Self-propulsion	Assisted reproduction	102
	Human sperm cell	Sperm cell/Fe-Ti/DOX/camptothecin	—	Magnetic field	3D ovarian cancer cell treatment	103
	Human sperm cell	Sperm cell/ZIF-8/DOX/TA	73	Self-propulsion	Active drug delivery	55
	Ciona sperm cell	Sperm cell/Fe_2O_3/DOX Sperm cell/CdSe/ZnS Sperm cell/Pt/FITC	217	Self-propulsion	Drug loading capacity and responsive release	104
	Clarias gariepinus sperm cell	Aqua sperm cells	114	Self-propulsion	Removal of bacterial biofilms	105
	Red blood cell membrane	RBC membrane/Pt	686	Chemical reaction	—	54
Microalgae	Chlorella	Chlorella/Fe_3O_4	∼17	Magnetic field	Precise photothermal muscle contraction	67
	Chlorella	Chlorella/Fe_3O_4/BiOCl	80.45	Magnetic field	Degradation of RhB and bacterial inactivation	106
	Chlorella	Chlorella/Fe_3O_4/BiOX	40	Magnetic field	Degradation of dyes and pollutants	107
	Chlorella	Chlorella/Fe_3O_4/ZIF-8	40.2	Magnetic field	Antibacterial treatment	108
	Chlorella	Chlorella/Fe_3O_4/DOX	107.6	Magnetic field	Targeted drug delivery	109
	Chlorella	Chlorella/Fe_3O_4	35	Magnetic field	Removal of micro/nanoplastics	110
	Spirulina	Spirulina/Fe_3O_4/MnO_2	250	Magnetic field	Removal of Pb(II)	111
	Spirulina	Spirulina/Fe_3O_4/FITC-BSA	—	Magnetic field	Molecular cargo delivery	64
	Spirulina	Spirulina/Fe_3O_4/CuS	583.3	Magnetic field	Anticancer therapy and bacterial killing	112
	Spirulina	Spirulina/Fe_3O_4/PDA	123.84	Magnetic field	Pathogenic bacterial infection treatment	113
	Spirulina	Spirulina/Fe_3O_4	15.2	Magnetic field	Bacterial killing	114
	Spirulina	Spirulina/Fe_2O_3/MIL-125NH_2 Spirulina/Fe_2O_3/UiO-66 Spirulina/Fe_2O_3/ZIF-8 Spirulina/Fe_2O_3/MIL-100(Fe)	∼28	Magnetic field	Drug delivery and degradation of RhB	115
	Spirulina	Spirulina/Fe_3O_4/MoS_2/AuNPs	—	Magnetic field	Cancer ablation	116
	Spirulina	Spirulina/Fe_3O_4/$BaTiO_3$	68.5	Magnetic field	Inducing neural stem cell differentiation	117

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Table 1 (*continued*)

Natural structure		Main components	Speed ($\mu m\ s^{-1}$)	Propulsion mechanism	Applications	Ref.
	Spirulina	Spirulina/Fe_3O_4/Pd/Au/DOX	526.2	Magnetic field	Targeted delivery and chemo-photothermal therapy	70
	Spirulina	Spirulina/Fe_3O_4	78.3	Magnetic field	Cancer therapy	118
	Spirulina	Spirulina/Fe_3O_4	~90	Magnetic field	Imaging-guided cancer therapy	119
	Chlamydomonas pitschmanni	*C. pitschmanni*	105	Self-propulsion	Biomedical operations	120
	Chlamydomonas reinhardtii	*C. reinhardtii*/PLGA/DiI/DiO	104.6	Self-propulsion	Treatment of bacterial pneumonia	121
	Chlamydomonas reinhardtii	*C. reinhardtii*/vancomycin/ciprofloxacin	61.5	Self-propulsion	Against bacterial infections	122
	Chlamydomonas reinhardtii	*C. reinhardtii*/Fe_2O_3/chitosan/DOX	56.3	Self-propulsion	Cargo delivery	123
	Chlamydomonas reinhardtii	*C. reinhardtii*	52	Light	Cargo delivery and therapy	124
	Chlamydomonas reinhardtii	*C. reinhardtii*	100	Self-propulsion	Picking up and transport cargo	125
	Chlamydomonas reinhardtii	*C. reinhardtii*	95	Light	Manipulation and disruption of biological targets	65
	Chlamydomonas reinhardtii	*C. reinhardtii*/PS/polyelectrolyte	162.05	Self-propulsion	Cargo delivery	69
	Chlamydomonas reinhardtii	*C. reinhardtii*/chitosan/heparin	33.3	Self-propulsion	Diabetic wound healing	126
	Chlamydomonas reinhardtii	*C. reinhardtii*/vancomycin derivative 7	—	Self-propulsion	Antibiotic drug delivery	127
	Chlamydomonas reinhardtii	*C. reinhardtii*/NHS-DBCO/ACE2	108	Self-propulsion	Removal of SARS-CoV-2	128
	Euglena gracilis	Euglena gracilis	60	Light	Drug delivery, removal of apoptotic cells, and photodynamic therapy	129
	Thalassiosira weissflogii frustules (TWFs)	TWFs/Fe_3O_4/DOX	28	Magnetic field	Target therapy	130
	Phaeodactylum tricorntum bohlin	Phaeodactylum tricorntum bohlin	209	Light	Trapping and removal of biothreats	66
	Diatoms	Diatom	50	Chemical reaction	—	68
	Volvox	Volvox/Fe_3O_4/PDA/Ce6/chitosan	~90	Magnetic field	Imaging and therapy	131
Bacteria	*Escherichia coli*	*E. coli*/ZIF-8/DOX/TA	30	Self-propulsion	Cytoprotection and drug delivery	132
	Escherichia coli	*E. coli*/dye/streptavidin	6.5	Self-propulsion	Cargo delivery	133
	Escherichia coli	*E. coli*/antibody	11.7	Self-propulsion	Targeted drug delivery	134
	Escherichia coli	*E. coli*//Fe_3O_4/nanoliposomes/DOX/ICG	18.5	Magnetic field	Stimuli-responsive cargo delivery	135
	Escherichia coli	*E. coli*/nanoerythrosomes	14.06	Self-propulsion	—	25
	Escherichia coli	*E. coli*/PEM//Fe_3O_4/DOX	22.5	Magnetic field	Targeted drug delivery	136
	Escherichia coli	*E. coli*/plasmid/MNP	24.62	Magnetic field	Cancer treatment	77
	Bacillus subtilis (*B. subtilis*)	*B. subtilis*/cell membrance	4.7	Self-propulsion	Sensing	137
	Magnetotactic bacteria (MTB)	MTB/liposome	49	Magnetic field	Increase tumor infiltration	75
	Magnetotactic bacteria	MTB/ICG	13.3	Magnetic field	Cancer therapy	78
	Flagellated bacteria	Bacteria	47	Self-propulsion	—	138
Spore	Ganoderma lucidum spore	Spore/Fe_3O_4/QDs	~23	Magnetic field	Remote detection of toxins	139
	Ganoderma lucidum spore	Spore/Fe_3O_4/CDs	3	Magnetic field	Targeted delivery	140
	Ganoderma lucidum spore	Spore/Fe_3O_4	266.3	Magnetic field	Adsorption and removal of heavy metal ions	141

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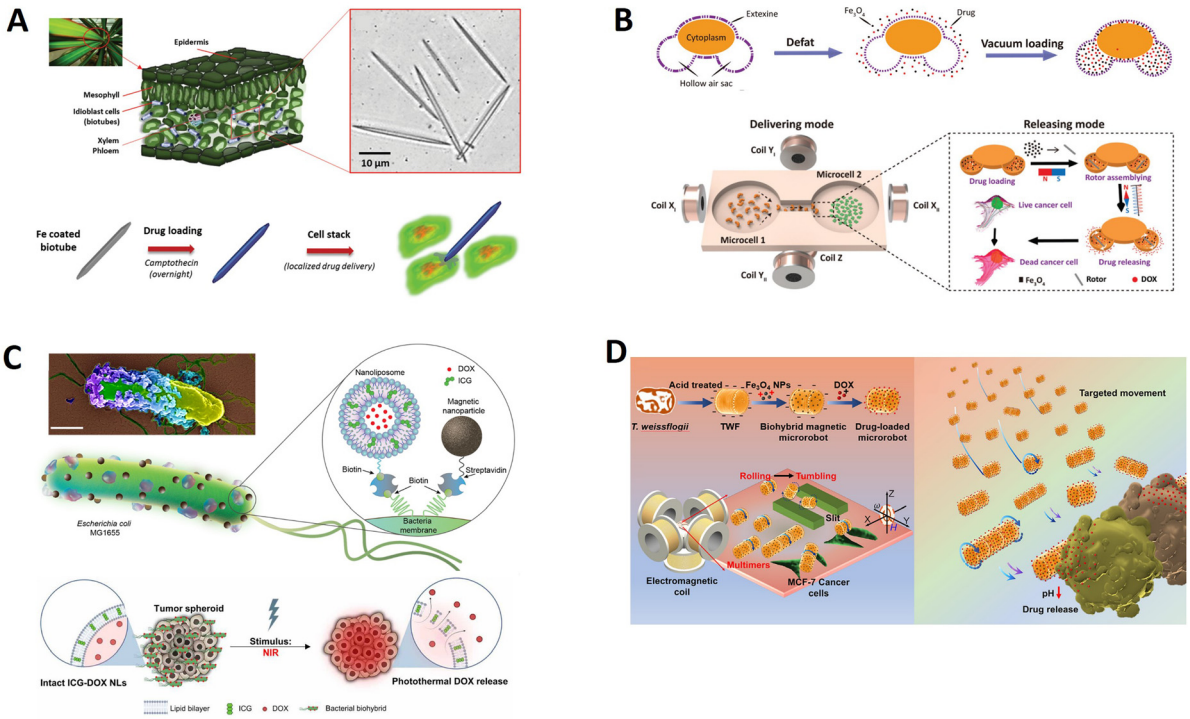

Fig. 6 Biotemplate-based micro/nanorobots for drug delivery. (A) Dual-action biogenic microdaggers for single-cell surgery and drug release. Reprinted with permission from ref. 39. Copyright 2016 Wiley-VCH. (B) Magnetic biohybrid micromotors with high maneuverability for efficient drug loading and targeted drug delivery. Reprinted with permission from ref. 92. Copyright 2019 Royal Society of Chemistry. (C) Magnetically steerable bacterial microrobots moving in 3D biological matrices for stimuli-responsive cargo delivery. Reprinted with permission from ref. 135. Copyright 2022 AAAS. (D) A diatom-based biohybrid microrobot with a high drug-loading capacity and pH-sensitive drug release for target therapy. Reprinted with permission from ref. 130. Copyright 2022 Elsevier.

fascinating properties enable pollen to become promising biotemplates for biomedical applications. Sun *et al.* developed pine pollen-based micromotors for targeted drug release, which provide excellent maneuverability in multiple media, efficient drug encapsulation, and on-demand release (Fig. 6B).[92] These versatile biohybrid micromotors were synthesized for simultaneously encapsulating magnetic particles and drugs into the two hollow air sacs of pine pollen *via* vacuum loading. The micromotors show controllable and continuous locomotion trajectories in complex biological fluids, even on biological tissues (mouse small intestine). Besides displaying controlled propulsion, these micromotors also exhibit a specific mechanism to release therapeutic drugs on demand. Considering the magnetic nanoparticle aggregation phenomenon under a powerful magnetic field, controlled release of a therapeutic cargo is achieved using the fluid field generated by the rotating magnetic agglomeration under a high magnetic field frequency input, which holds great promise for *in vivo* medical applications.

Bacteria-based microrobots, composed of self-propelling bacteria carrying micro/nanoscale materials, can deliver their payload to specific regions under magnetic control, enabling additional effective delivery of minimally invasive medicine. As shown in Fig. 6C, Mukrime *et al.* reported a magnetically controlled bacterial microrobots for targeted localization and multistimuli-responsive drug release in three-dimensional (3D) biological matrices.[135] Magnetic nanoparticles and nanoliposomes loaded with photothermal agents and chemotherapeutic molecules were integrated into *E. coli* with ~90% efficiency. Bacteria-based microrobots, outperforming previously reported *E. coli*–based microrobots, retained their original motility and navigated through biological matrices and colonized tumor spheroids under magnetic fields for on-demand release of the drug molecules by a near-infrared stimulus.

Diatoms, as the naturally porous silica structure, are promising substitutes for artificial mesoporous silica preparation. In Fig. 6D, Li *et al.* proposed a biohybrid magnetic microrobot based on *Thalassiosira weissflogii frustules* (TWFs) as a cargo packet for targeted drug delivery using a simple preparation method.[130] They could be precisely controlled to follow specific trajectories or to move as swarms. The cooperation of the two motion modes of biohybrid microrobots increased microrobots' environmental adaptability. Such microrobots utilize the porous structure of diatoms to load drugs and provide artificially modified magnetic layers to endow them with active and controllable properties, demonstrating great potential in targeted anticancer therapy.

4.1.2. Imaging. Efficient imaging agents can provide precise localization, effective early diagnosis and treatment monitoring for precise treatment, and provide considerable guidance for intelligent therapy, especially cancer treatment.[144] Currently, several biomedical imaging techniques, such as fluorescence

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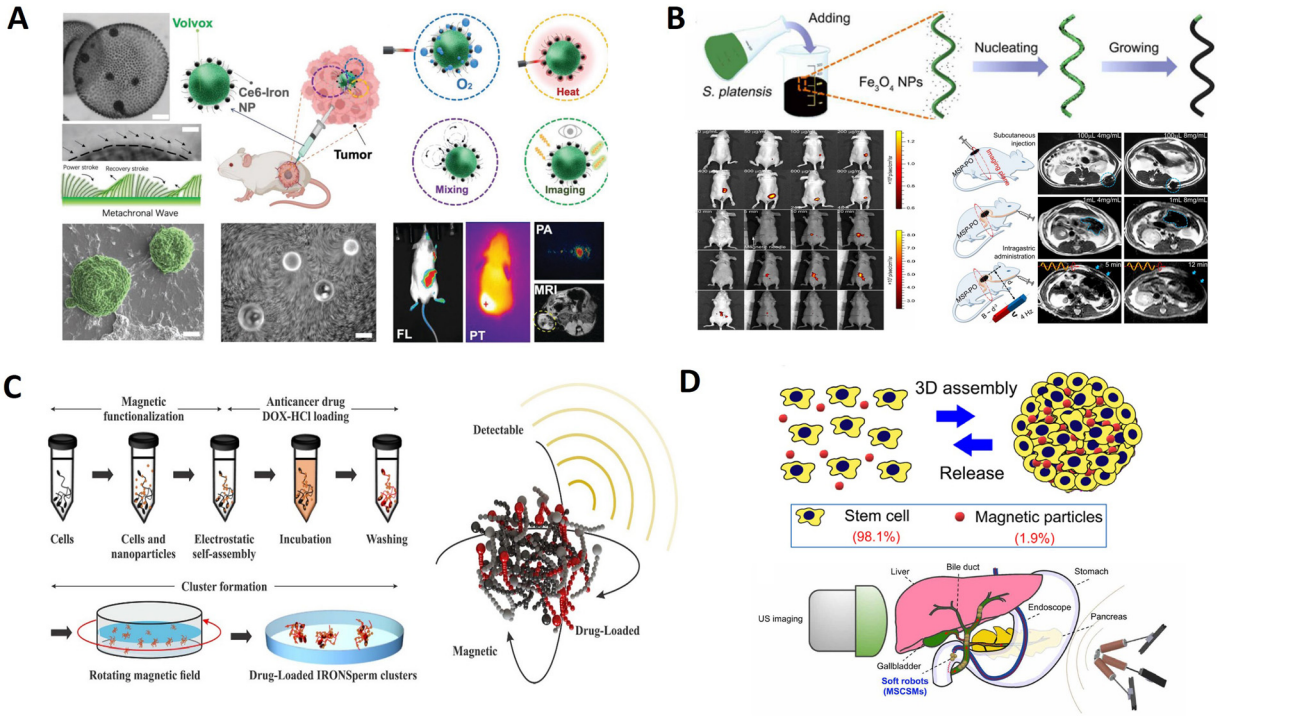

Fig. 7 Biotemplate-based micro/nanorobots for imaging. (A) Volvox microalgae-based robots for multimode precision imaging and therapy. Reprinted with permission from ref. 131. Copyright 2022 Wiley-VCH. (B) Multifunctional biohybrid magnetite microrobots for imaging-guided therapy. Reprinted with permission from ref. 119. Copyright 2017 AAAS. (C) Drug-loaded IRONSperm clusters: modeling, wireless actuation, and ultrasound imaging. Reprinted with permission from ref. 101. Copyright 2022 IOP Publishing. (D) Endoscopy-assisted magnetic navigation of biohybrid soft microrobots with rapid endoluminal delivery and imaging. Reprinted with permission from ref. 153. Copyright 2021 AAAS.

imaging (FLI),[145] photothermal imaging (PTI),[146] photoacoustic imaging (PAI),[147] magnetic resonance imaging (MRI),[148] computer tomography (CT),[149] and positron emission tomography (PET),[150] have been developed, that have improved the spatial resolution of cancer imaging. With the development of nanotechnology, biotemplates with unique properties have recently become an exciting prospect for accurate cancer imaging. Visual positioning of micro/nanorobots based on a biotemplate is crucial for achieving motion, path planning, and autonomous navigation based on visual feedback.[151] To this end, various biotemplate-based micro/nanorobots with imaging functional have been applied to visualization. The following sections will discuss the progress of integrating imaging strategies with the motion-tacking of biotemplate-based micro/nanorobots.

The selection of unique motile microorganisms that combine the advantages of locomotion with imaging materials, such as imaging agents and photothermal agents, could assist in addressing the challenges of cancer regions. As shown in Fig. 7A, Wang *et al.* developed an all-in-one self-propelled volvox-based multifunctional robot, Volbot, with built-in fluid mixing capabilities, multimode imaging, and photosynthesis-mediated *in situ* oxygen generation that can potentially relieve hypoxia.[131] Volbots can follow a pre-specified route and directionality under the control of a magnetic field. Red-light irradiation (λ = 650 nm) can enhance the Volbot's locomotive behavior, enhance the mixing of biofluids, and modulate the oxygen production to improve the efficacy of photodynamic therapy. Moreover, Volbots can absorb near-infrared radiation to produce localized hyperthermia and offer imaging capabilities for treating tumors. The use of volvox as the engine of the robot provides unique advantages over other strategies that employ microorganisms, as volvox *in situ* generates oxygen; self-fluoresces for use in multimodal imaging; has autonomous phototaxis navigation capability; enables built-in fluid pumping/mixing generated by the synchronized beating of its flagella; and facilitates localized photodynamic, as well as photothermal therapy.

The innate properties of microalgae allowed *in vivo* fluorescence imaging and remote diagnostic sensing without any surface modification. As shown in Fig. 7B, Yan *et al.* reported a type of biotemplate-based magnetite microrobot that is imageable, biodegradable, and selectively cytotoxic to cancer cells.[119] This fabricated biotemplate-based magnetite microrobot can perform robust navigation in various biofluids and be noninvasively tracked by auto-FL/MR imaging in either superficial tissues or deep organs. Furthermore, it exhibits desirable biodegradability, remote diagnostic sensing ability, and anticancer potential. With its *in vivo* monitoring *via* bimodal imaging features, tunable degradation *via* dip-coating control, and inclusiveness of functionality extension/drug loading *via* surface modification, this biotemplate-based microagent represents a microbiorobotic vehicle with a high potential for imaging-guided therapy.

Ultrasound imaging is a potential option for noninvasive localization and has been established as a standard clinical

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diagnostic tool. It is radiation-free and provides real-time imaging, allowing microrobot tracking.[152] As shown in Fig. 7C, Middelhoek *et al.* fabricated drug-loaded biotemplate-based clusters and understood their characteristics to enable wireless rolling locomotion and ultrasound imaging simultaneously.[101] Nanoparticle-coated sperm cells can be electrostatically and magnetically entangled in dense clusters of up to 120 cells to obtain biotemplate-based clusters of microrobots. This aggregation of microrobots enables them to roll collectively in a predictable way in response to an external rotating magnetic field. It enhances ultrasound detectability and drug loading capacity compared to individual microrobots. The favorable features of biotemplate-based microrobot clusters emphasize the importance of investigating and developing collective microrobots and their potential for *in vivo* imaging.

Imaging functions can also be achieved through the self-assembly of cells. As displayed in Fig. 7D, Wang *et al.* developed soft and resilient magnetic stem cell spheroid microrobots (MSCSMs) using the three-dimensional (3D) self-assembly of stem cells doped with a low dose of magnetic particles.[153] An integrated robotic platform was developed to deliver the microrobots into the deep and narrow spaces inside the body, termed endoscopy-assisted magnetic actuation with a dual imaging system (EMADIS). In EMADIS, the endoscope offers an "express lane" for the MSCSMs to avoid direct contact with the complex fluidic environments and facilitates rapid passage through multiple biological barriers in organs and tissues. The magnetic field actuation guides the high-precision delivery of the MSCSMs to the targeted position after endoscopic deployment. Moreover, the endoscopic view and ultrasound imaging track the entire process. In this way, EMADIS enables the rapid and high-precision delivery of soft microrobots in real time for the targeted therapeutic intervention of hard-to-reach regions, which are inaccessible and even invisible by means of conventional endoscopes and medical robots.

4.1.3. Biosensing. Biosensors are ubiquitous in various disciplines, such as biochemical, electrochemical, agricultural, and biomedical fields. They can recognize a biological event on a transducing device using a signal proportional to the analyte concentration to quantify a biological or biochemical response.[154] Different from passive materials, active biotemplate-based micro/nanorobots have shown promising prospects in biosensing due to their unique active motion properties and easy functionalization. Especially, the movement of biotemplate-based micro/nanorobots with various receptors can realize "on the fly" capturing analytical targets.[155] Next, some biotemplate-based micro/nanorobots for advanced biosensor research are introduced.

Spores are produced by a wide range of plant or fungi species, and their unique and intricate 3D architecture can protect sensitive genetic materials from extreme environmental conditions. Zhang *et al.* developed highly efficient fluorescent magnetic pore-based microrobots for detecting toxins secreted by *Clostridium difficile* (*C. diff*) bacteria (Fig. 8A).[139] These microrobots were rapidly synthesized inexpensively by stepwise encapsulation and functionalizing the porous natural spores. Incorporating superior magnetic Fe_3O_4 nanoparticles facilitates the magnetic actuation of the droplet-like microstructure and even similar counterparts feasible in different media, showing continuous and efficient propulsion trajectories. Such a continuous and efficient movement greatly increases the diffusion and mass transport of the detected substance, thus facilitating higher detecting ability than static counterparts. Motion-based detection through tracking the emerging micro/nanorobots has shown great potential in chemo- and biosensing due to accelerated "chemistry on the move."

Red blood cells (RBCs) can be trapped and manipulated by optical forces, which benefits their function as living biosensors and micromotors.[156] As shown in Fig. 8B, Li *et al.* constructed a living biosensor and micromotor from *in vivo* RBCs for pH sensing and particle transport applications.[157] The light propagation mode of the RBC waveguide was sensitive to the surroundings. After sensing pH, the formed RBC waveguide could continuously rotate as a micromotor because of the optical torque generated by the asymmetrical distributions of

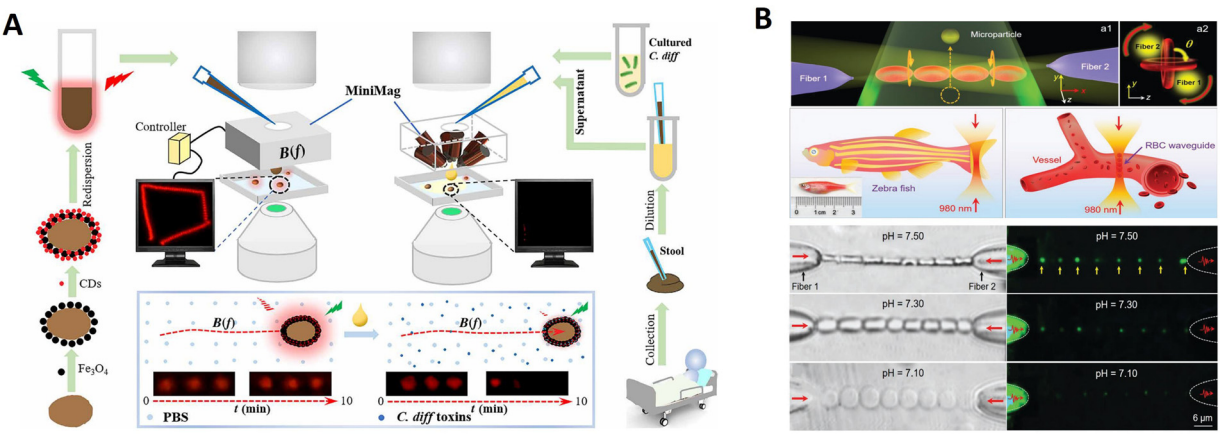

Fig. 8 Biotemplate-based micro/nanorobots for biosensing. (A) Real-time tracking of fluorescent magnetic spore-based microrobots for remote detection of *C. diff toxins*. Reprinted with permission from ref. 139. Copyright 2020 Springer Nature. (B) Red-blood-cell waveguide as a living biosensor and micromotor. Reprinted with permission from ref. 157. Copyright 2019 Wiley-VCH.

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the coherent output light from the fiber probes, enabling controllable microparticle delivery in the blood. In order to extend its potential application, the RBC waveguide was also successfully assembled and operated in zebrafish blood vessels. These phenomena inspired us to directly incorporate *in vivo* cells into a single device with sensing and actuation capabilities.

4.1.4. Anti-biological infection. Clinically, due to the complex interaction between pathogens and hosts, the combination of viruses and bacteria causes a very high mortality rate, posing a severe threat to human health worldwide.[158,159] There are many treatments, but their effects are often not specific because anti-inflammatory drugs are not delivered to specific sites. Thus, developing active dosing of anti-inflammatory drug delivery systems to achieve the effects of local release of anti-inflammatory drugs and auxiliary sterilization has become an important research direction for anti-infection in recent years. Based on the active propulsion characteristics of micro/nanorobots and the excellent biocompatibility of biomaterials, some bio-based micro/nanorobots have been developed for anti-biological inflammation and will be described in the following chapters.

The natural sea urchin-like sunflower pollen (with sharp edges) is converted into capsule micro robots for loading drugs to remove biofilms. Sun *et al.* designed a magnetic urchin-like capsule robot loaded with magnetic liquid metal droplets (MUCR@MLMD) by using natural sunflower pollen as a biotemplate carrier for eradicating complex mixtures of a bacterial biofilm within biliary stents collected from patients (Fig. 9A).[93] Driven by an external magnetic field, the MUCR@MLMD swarms actively target biofilm structures, first physically disrupting the extracellular polymeric substance barrier using the inherited microspikes of MUCRs. The carried MLMDs are then released to penetrate the biofilm and use their sharp edges to kill a variety of embedded bacterial cells, ultimately achieving synergistic biofilm eradication without the development of drug resistance. The robots benefit from the natural spikes of sunflower pollen that can be used to treat biofilms, physically destroying the protective effect and mechanical stability of EPS. Besides, Carmen *et al.* present a new concept using aqua sperm micromotors to destroy bacterial biofilms.[105] They use aqua sperm from North African catfish-as microrobots with head sized $\approx$1.5 μm compared with, for example, bovine sperm of head sizes $\approx$10 μm. Their small size allows them to penetrate and disturb the biofilm matrix. Moreover, research has proved that their ultra-fast speed is efficient at destroying biofilms in a short time (displayed in Fig. 9B).

Furthermore, pathogenic bacteria in deep tissue penetration can also be used as a multifunctional magnetic biomicroswimmer. By mimicking a corkscrew motion of the *Escherichia coli*, such micro/nanoswimmers can perform remotely controlled navigation in a wide range of complex environments filled with biofluidic media. As shown in Fig. 9C, Xie *et al.* developed a multifunctional magnetic microswimmer based on *Spirulina* to treat pathogenic bacterial infection.[113] The microswimmer (PDA-MSP) consists of a magnetized *Spirulina* (MSP) matrix and a polydopamine (PDA) surface, which not only preserve the desirable properties of the original MSP but also endowed it with additional functions aimed at the

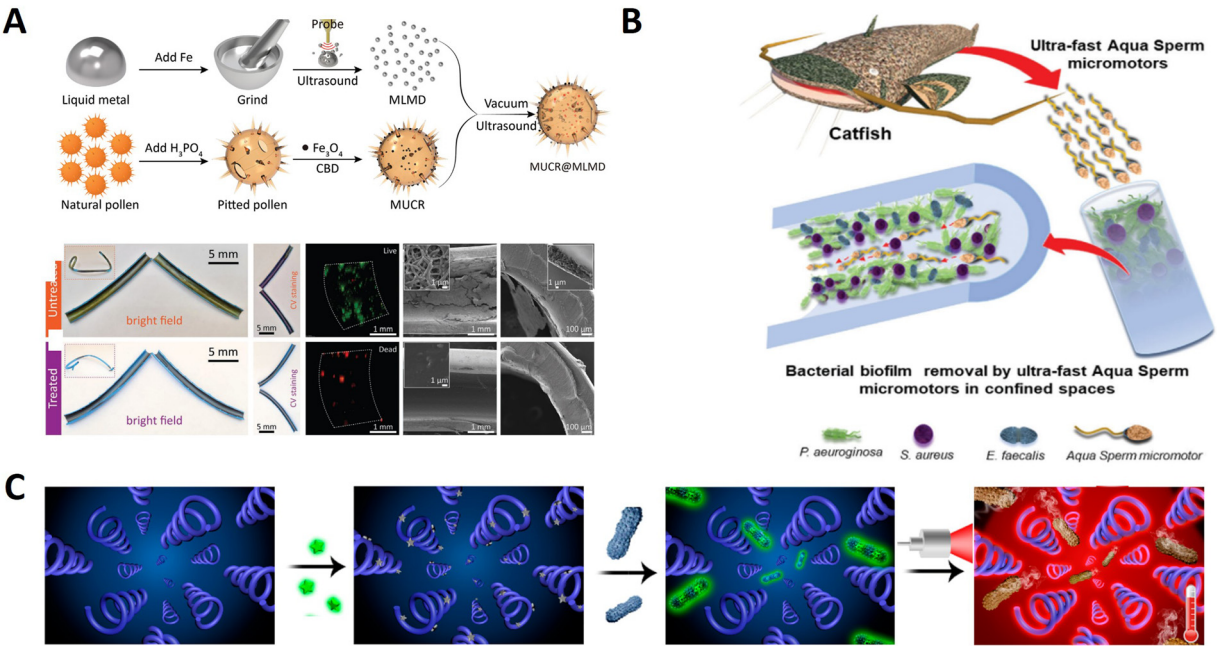

Fig. 9 Biotemplate-based micro/nanorobots for anti-biological infection. (A) Magnetic microswarm and fluoroscopy-guided platform for biofilm eradication in biliary stents. Reprinted with permission from ref. 93. Copyright 2022 Wiley-VCH. (B) Swarming aqua sperm micromotors for active bacterial biofilms removal in confined spaces. Reprinted with permission from ref. 105. Copyright 2021 Wiley-VCH. (C) Photoacoustic imaging-trackable magnetic microswimmers for pathogenic bacterial infection treatment. Reprinted with permission from ref. 113. Copyright 2020 American Chemical Society.

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treatment of pathogenic bacterial infection. In this study, the developed microswimmer based on a spiral shape can undergo motion *in vivo*, and can be used for PDA-enabled PA imaging, off–on fluorescence diagnosis, as well as photothermal therapy for the theranostics of pathogenic MDR KP infection.

4.1.5. Antibacterial. Diseases caused by bacterial infections are once again recognized as a severe global threat to human health due to the emergence and rapid spread of bacterial resistance to available antibiotics and the limited progress in discovering and developing new effective anti-bacterial agents.[158] The preparation of composite micro/nanorobots with special structures and properties by the bio-template method is one of the research hotspots in the field of materials science today. Its advantage lies in the spatial limitation and regulatory role of biological templates that can achieve control over composite materials' surface morphology and structure, not only to obtain composite materials with specific surface morphology but also to achieve an effective composite between nanoscale particles and large-scale biotemplates. In particular, using micro/nanorobots with active propulsion as cargo delivery systems provides an alternative strategy for transporting therapeutic drugs to desired locations that are difficult to reach using traditional strategies. Based on this, a series of biotemplate-based micro/nanorobots for antibacterial application have been developed.

Helical microswimmers can be effectively actuated and can perform controlled locomotion in various fluids; therefore, they can envision precise micromanipulation and efficient environmental purification in low-strength rotating magnetic fields. As displayed in Fig. 10A, Zheng *et al.* reported a core–shell-structured porous hollow helical microswimmer possessing an inner carbon core of porous surfaces and an outer magnetic shell aggregated by mesoporous spindle-like magnetite nanoparticles (NPs).[114] This microswimmer is fabricated using a high-yield template process based on helical *S. platensis*. Attributed to the existing magnetite NPs of the outer shell, the obtained swimmers have superparamagnetic nature and high magnetic saturation; therefore, they can perform magnetically actuated corkscrew motions under low-strength rotating magnetic fields. More importantly, such swimmers inherit good photothermal attributes and high specific surface area from their magnetite–carbon composition and porous hollow structures, respectively, which can be used for photothermal antibacterial treatment, biological detoxification, and targeted delivery.

To avoid harmful NIR light and fully use solar energy, using high efficiency visible light inactivating bacteria *via* the use of natural biotemplates as raw materials is an important target. As shown in Fig. 10B, Xu *et al.* developed a facile and cost-effective biotemplate method to fabricate a visible light stimulated magnetic microrobot with enhanced photocatalytic antibacterial performances.[106] Fe_3O_4 nanoparticles (NPs) and BiOCl nanosheets (NSs) were deposited on bio-templates in sequence to form *Ch.*@Fe_3O_4@BiOCl (CFB) microrobots. The composite

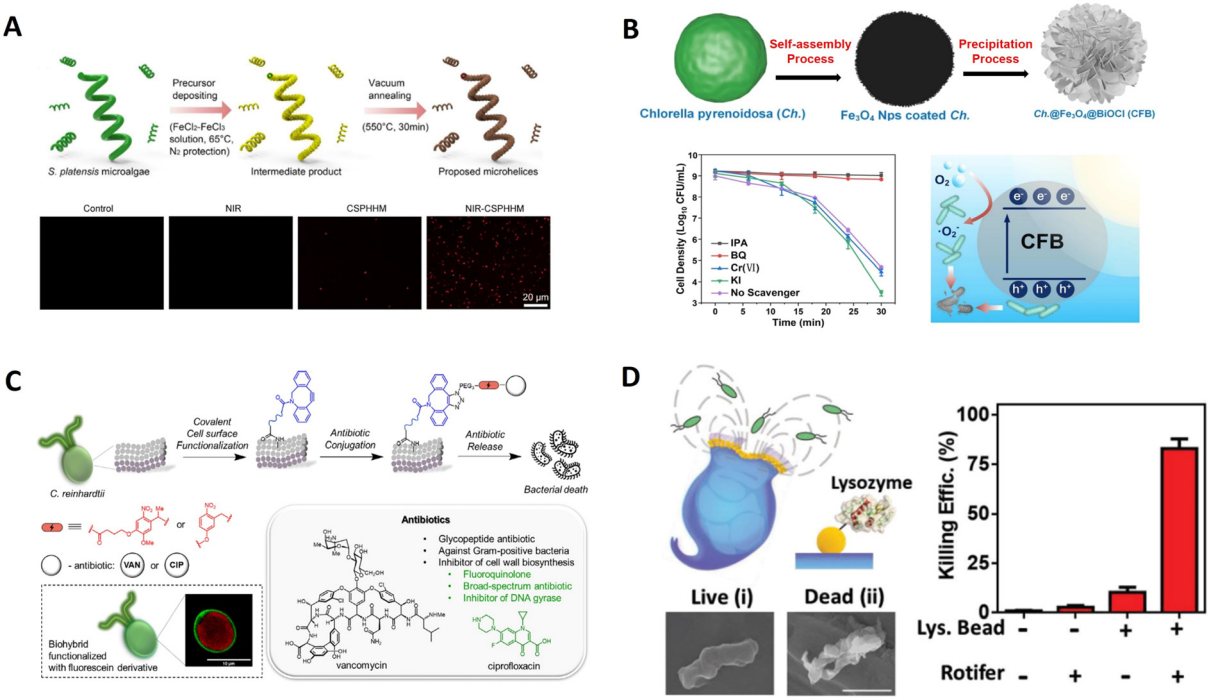

Fig. 10 Biotemplate-based micro/nanorobots for antibacterial. (A) Spirulina-templated porous hollow carbon@magnetite core–shell microswimmers. Reprinted with permission from ref. 114. Copyright 2021 Elsevier. (B) Biohybrid magnetic microrobots for enhanced *E. coli* inactivation under visible light irradiation. Reprinted with permission from ref. 106. Copyright 2022 Elsevier. (C) Biohybrid microswimmers against bacterial infections from ref. 122. Copyright 2021 Elsevier. (D) Rotibot: Use of rotifers as self-propelling biohybrid microcleaners. Reprinted with permission from ref. 160. Copyright 2019 Wiley-VCH.

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structure and abundant natural photosensitizers in the biotemplates endowed them with rapid photocatalytic capability under visible light irradiation, leading to excellent photocatalytic inactivation of *E. coli*. Under collective rolling mode with enhanced fluidic interactions, the bacterial inactivation rate could also be increased over 30%. Such an excellent performance can be ascribed to the composite microstructure, the abundant natural photosensitizers in the biotemplate, and enhanced fluidic interactions under magnetic actuation.

Bacteria-based biotemplate-based systems face multiple issues, including potential pathogenicity or immunogenicity, rapid growth rate, and potential to develop antibiotic resistance.[24] *C. reinhardtii* is known as a phototactic green microalga, and swims steadily towards or away from the light stimulus due to optical receptors. Shchelik *et al.* reported a strategy for biohybrid microswimmers, which features the covalent attachment of antibiotics with a photo-cleavable linker to the algae *C. reinhardtii via* two synthetic steps (Fig. 10C).[122] This surface engineering does not rely on genetic manipulations, proceeds with high efficiency, and retains the viability or phototaxis of microalgae. This study demonstrated the application of biotemplate-based microswimmers for caging and controlled release of different types of antibiotics that can expand their use against various bacterial infections. The microswimmers could be guided to a particular region to precisely release their antibacterial cargo.

Rotifers control fluid flow by beating their cilia bands for efficient locomotion and feeding. In addition, the robots were evaluated initially as potential antibacterial microcleaners. Based on these, Soto *et al.* engineered a new biotemplate-based microswimmer featuring antibacterial properties (Fig. 10D).[160] The microbeads were functionalized with lysozyme enzymes capable of cleaving glycosidic bonds of peptidoglycans present in the cell walls of different bacteria. The high fluid flow toward the mouth, generated by the strokes of rotifer cilia bands, forces an extremely efficient transport of the contaminated sample over the active surfaces of the functionalized microbeads. The reactive particles confined around the rotifer's lip are thus exposed to a high flow rate of the pollutant solution, resulting in dramatically accelerated antibacterial processes without external mixing or harmful fuels. In this, the rotifer can serve as an extremely efficient self-propulsion engine of the biohybrid microrobot and integrate capabilities that respond to environmental signals and maneuver effectively in their environment.

4.1.6. Capture of organisms. A micro/nanorobot with self-propelled properties and navigating in complex fluidic environments allows localization, pick-up, and delivery of microscopic and nanoscopic objects.[161] All these capabilities have made the micro/nanorobot an ideal candidate to serve as a tiny vehicle for capture and targeted drug delivery. In this regard, some special biotemplate-based microswimmers composed of a living microswimmer integrated with artificial structures are designed as practical tools for active capture of organisms and cargo delivery. Next, we will elaborate with some concrete examples.

The natural spiral structure endows micro/nanorobots with excellent motion performance by converting rotational motion to translational motion. In our previous study, we developed a biotemplate-based microswimmer for efficiently capturing and transporting cancer cells as well as killing the cells under light irradiation.[87] The spiral vessels isolated from banana leaves were used as biological templates, where nickel layers with magnetic properties and Fe^{3+}–TA (tannic acid, TA) films with pH-dependent degradation capabilities were modified on their surfaces by simple chemical reactions in solution at room temperature (Fig. 11A). Due to the specific chemical interaction between the microswimmers and the surface of cancer cells, the microswimmers can precisely capture and transport these cancer cells in the presence of a magnetic field. Using biotemplates with spiral structures in this way provides a new approach to preparing multifunctional micro/nanorobots.

Pollen grains have a large inner cavity for encapsulating genetic materials, multiscale channels, and numerous spikes on the outer shell or extine. Based on this, Song *et al.* successfully developed a light-controlled micromotor with efficient motion and loading capacity based on sunflower pollen grains (Fig. 11B).[94] In their experiments, as a live cargo model, yeast cells were captured and located in the gap of the micromotors' spikes. The room between the neighboring spikes was like a grip, which firmly grasped the cells with the increased contact surface. Therefore, micromotors provide a larger surface contact area to increase the binding odds between micromotors and cells, which eventually benefits the capture efficiency. In addition, Song *et al.* developed a light-controlled microrobot for capturing and gathering bacteria based on photothermal effects (Fig. 11C).[95] The sterilization microbots were fabricated from carbonized sunflower pollen grains with a polydopamine coating. A bacterial capture molecule, vancomycin, is grafted onto the outer surface of polydopamine. Under the focused laser, the microbot can show positive phototactic motion and bubble-induced gathering powered by the photothermal-induced Marangoni effect for efficient capture and aggregation of the targeted bacteria. Such microbots could provide a new proof-of-concept perspective on capturing bacteria and sterilization applications.

4.1.7. Cancer treatment. Cancer has been one of the fatal diseases threatening human health in recent decades.[162] Recent studies have shown that preparing multifunctional micro/nanorobots with active control and functionalization at the microscale for *in vivo* cancer therapy is promising. Biotemplates are receiving increasing attention as raw materials for manufacturing micro/nanorobots. Nature provides unique biotemplates with various structures that can be used to manufacture functional micro/nanorobots for different applications.[18] Compared to existing manufacturing methods, biological hybridization methods based on natural materials can eliminate complex processes, showing the advantages of cost-effectiveness and simplicity. At this time, a series of functional biotemplate-based micro/nanorobots for cancer therapy emerged due to their active propulsion characteristics and good biocompatibility.

Among the pollen grains, chrysanthemum pollen grains possess excellent morphological characteristics after sequential treatment, like spiny protrusion, hollow cavities, and porous

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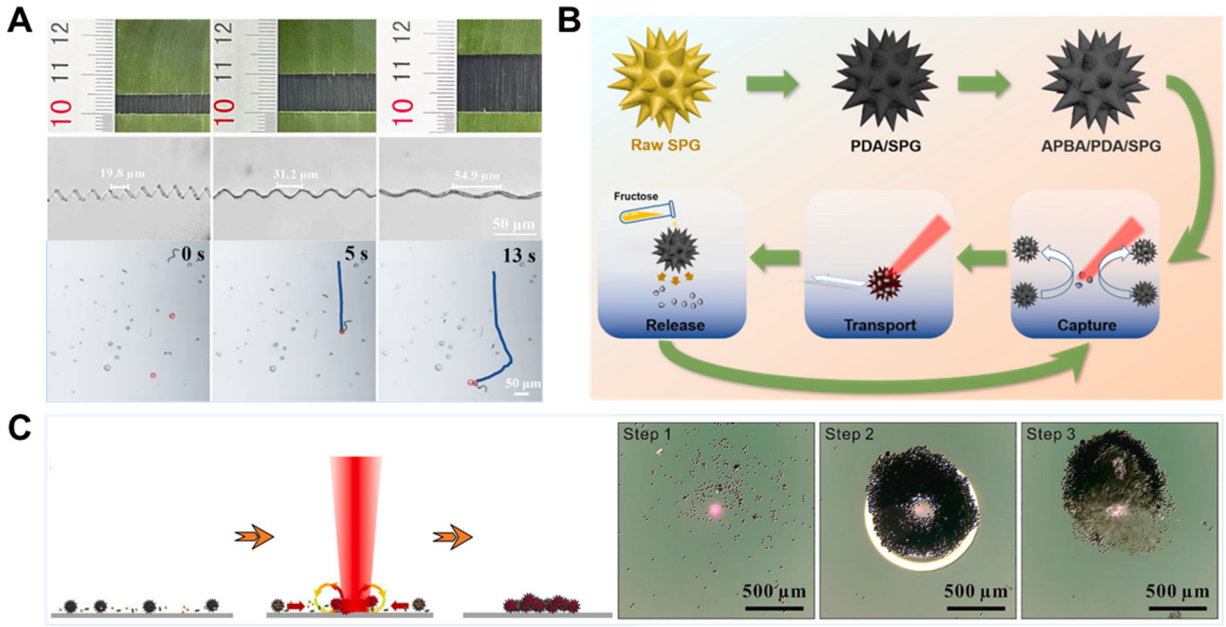

Fig. 11 Biotemplate-based micro/nanorobots for organisms. (A) Bifunctional biohybrid magnetically propelled microswimmer. Reprinted with permission from ref. 87. Copyright 2022 Elsevier. (B) Light-controlled spiky micromotors for efficient capture and transport of targets from ref. 94. Copyright 2022 Elsevier. (C) Light-controlled microbots gathering as a sterilization platform for highly efficient capturing, concentrating and killing targeted bacteria. Reprinted with permission from ref. 95. Copyright 2022 Elsevier.

surface structures. These attractive features could be fully utilized for specific functions, making them an attractive platform to provide comprehensive therapeutic strategies for biomedical applications. Chrysanthemum pollen grains possessing a large internal cavity were used for drug encapsulation and the ordered burr-like microspikes around the surface could be utilized for physical assassination to kill tumor cells. Utilizing natural morphological characteristics, Liu *et al.* developed chrysanthemum pollen-derived biotemplate-based magnetic microrobots for synergistic tumor therapy by combining magnetically controlled physical assassination and active drug delivery.[82] As shown in Fig. 12A, the microrobots could be actively steered for targeted cell delivery and tissue regeneration under a magnetic field. This biotemplate-based microrobot provides a typical example of utilizing natural morphologies to develop multifunctional active matter at the microscale for the next generation of active therapeutics.

Microalgae have a high capacity of light absorption (*e.g.*, UV light) because of their various chromophores and have antioxidant and anti-inflammatory properties. They have been used for other types of phototherapies to treat skin diseases such as cancer and inflammatory diseases. Considering all the factors mentioned above, as shown in Fig. 12B, Wang *et al.* proposed a strategy that uses biomaterial *Sp.* as a scaffold to fabricate magnetic microrobots. They can load anticancer drugs and photothermal agents to achieve synergistic and enhanced therapeutic efficacy.[70] The microrobots can be degraded under NIR irradiation and exhibit pH- and NIR-triggered drug release to realize cancer therapy. This work provides an integrated route for fabricating multifunctional microrobots with high swimming speed, precise directional guidance, ultrahigh drug loading efficiency, and efficient photothermal conversion ability toward targeted delivery applications and synergistic chemo-phototherapy in a single platform.

In addition, bacteria-based microrobots can offer valuable intrinsic characteristics of bacterial microorganisms, such as self-sensing, self-propulsion, fluorescence, and chemotaxis toward tumor sites. Magnetococcus marinus strain, magnetospirillum magneticum (AMB-1), is a candidate for preparing functionalized micro/nanorobots for tumor therapy because magnetosomes inside the body are susceptible to external magnetic fields and can be autonomously manipulated to the tumor site. Xing *et al.* reported a biotemplate-based microrobot (Fig. 12C) composed of motile AMB-1 and light-triggered indocyanine green nanoparticles (INPs).[78] The INPs, as a hitchhiker circulates in the blood, are transported by magnetotaxis bacteria AMB-1 with magneto-anaerobic behavior, and then enriched in tumors for subsequently ablating the tumors by photothermal therapy under NIR laser irradiation. AI microrobots based on autonomous flagellum propulsion of AMB-1 can realize controlled navigation, focal localization, deep penetration, and tumor colonization *in vivo*.

Spermatozoa are highly efficient micromotors perfectly adapted to traveling up the female reproductive system. Indeed, bovine sperm-based micromotors have shown the potential to carry drugs for gynecological cancer treatment.[163] As shown in Fig. 12D, Xu *et al.* presented a fully functional drug delivery system based on human sperm.[103] In order to establish a robust pipeline for anticancer drug loading (DOX, model drug) in human sperm, they investigated the DOX loading mechanism and integrated the system into a versatile enhancement

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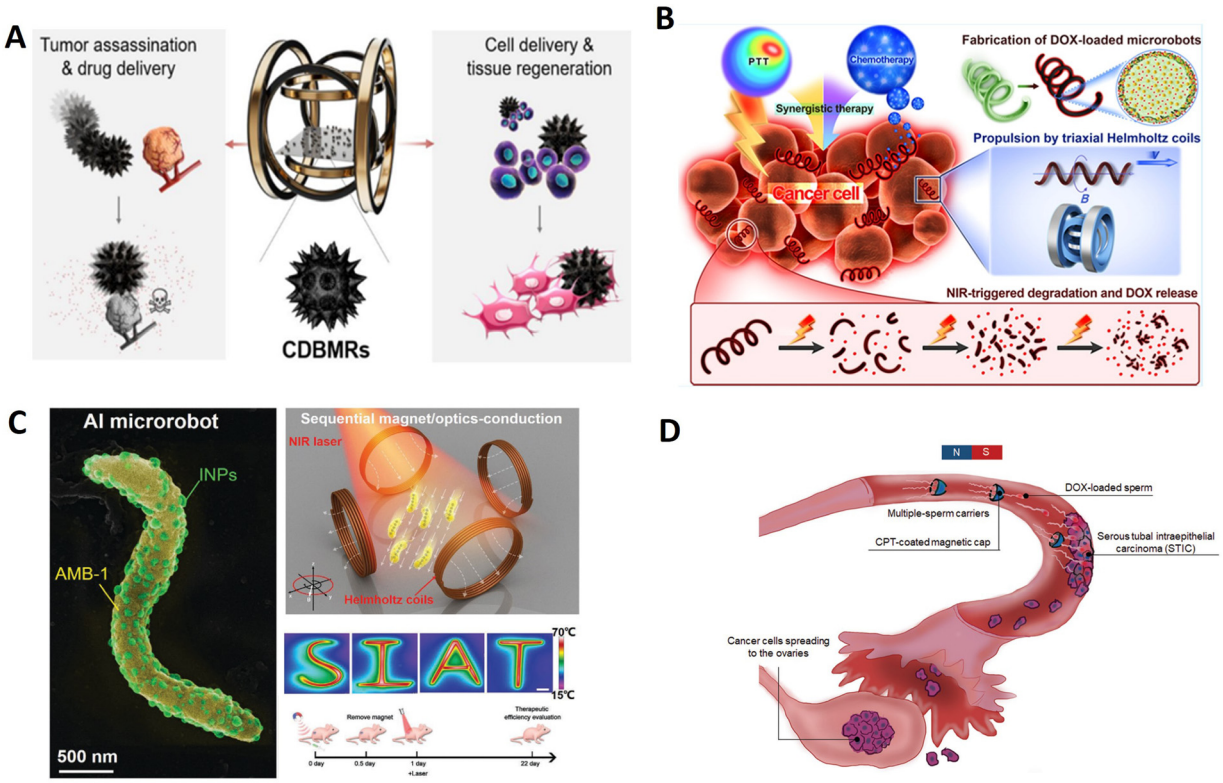

Fig. 12 Biotemplate-based micro/nanorobots for cancer treatment. (A) Biohybrid magnetic microrobots for tumor assassination and active tissue regeneration. Reprinted with permission from ref. 82. Copyright 2022 American Chemical Society. (B) Facile fabrication of magnetic microrobots based on spirulina templates for targeted delivery and synergistic chemo-photothermal therapy. Reprinted with permission from ref. 70. Copyright 2019 American Chemical Society. (C) Sequential magneto-actuated and optics-triggered biomicrorobots for targeted cancer therapy. Reprinted with permission from ref. 78. Copyright 2021 Wiley-VCH. (D) Human spermbots for patient-representative 3D ovarian cancer cell treatment. Reprinted with permission from ref. 103. Copyright 2020 Royal Society of Chemistry.

platform suitable for targeting early ovarian cancer lesions. The study of free-swimming sperm technologies will become more critical in the diagnostic and therapeutic field.

4.1.8. Other biological applications. Functional biotemplate-based micro/nanomotors are a potential development direction of micro/nanorobots. Biotemplate-based micro/nanomotors have good biocompatibility and loading. Combined with outfield driving or self-directional movement, they have played an essential role in drug targeting, imaging, cancer treatment, and other aspects of the human body. Therefore, among many future applications of biotemplate-based micro/nanorobots, applications in the biomedical field will be up-and-coming. Simultaneously, with the continuous deepening and development of research, micro/nanorobots will gradually play a more significant role in biological applications. Next, we will introduce more biological micro/nanorobot applications in biomedicine.

Recently, biotemplate-based micro/nanorobot technology has been applied to improve plant cell growth, aid in the differentiation process, or in their reproduction to produce new plants. Huska *et al.* developed a new methodology to obtain plant cell motors by translocation of ferromagnetic materials (Fe_3O_4) inside tomato-biobots during their callus growth (Fig. 13A).[89] In this study, they have demonstrated that the translocation of Fe_3O_4 did not affect the viability of plant biotemplate-based robots. Developed tomato-biobots can drive by a transversal rotating magnetic field. In addition, the proposed methodology produces tomato-biobots that can load, store, and deliver biomolecules and thus significantly improve health, growth, and dividing plant callus cells. In this way, they have demonstrated that they can generate tomato cell clones from plant biotemplate-based robots. The research is still in the beginning stage; however, it is highly promising and offers unexpected opportunities of great dimensions that could revolutionize the entire biotechnology world.

C. reinhardtii is a biflagellate unicellular freshwater green microalga. Due to their ideal size, abundance, motility, and biocompatibility, *C. reinhardtii* cells are excellent natural candidates as living rotary micro motors to actuate microflows precisely. Pan *et al.* reported optical trapping-driven biomicromotor tweezers by using living *C. reinhardtii* alone for noninvasive delivery of bio-cargos, including microparticles, cells, and drugs further for precise cancer cell therapy (Fig. 13B).[124] By actuating a localized flow field around different targeted bio-cargos, two optically trapped rotating CR cells potentially act as micromotor tweezers for noncontact capture and transport of bio-cargos along arbitrary trajectories in bio-microenvironments in a noninvasive, flexible, and biocompatible manner.

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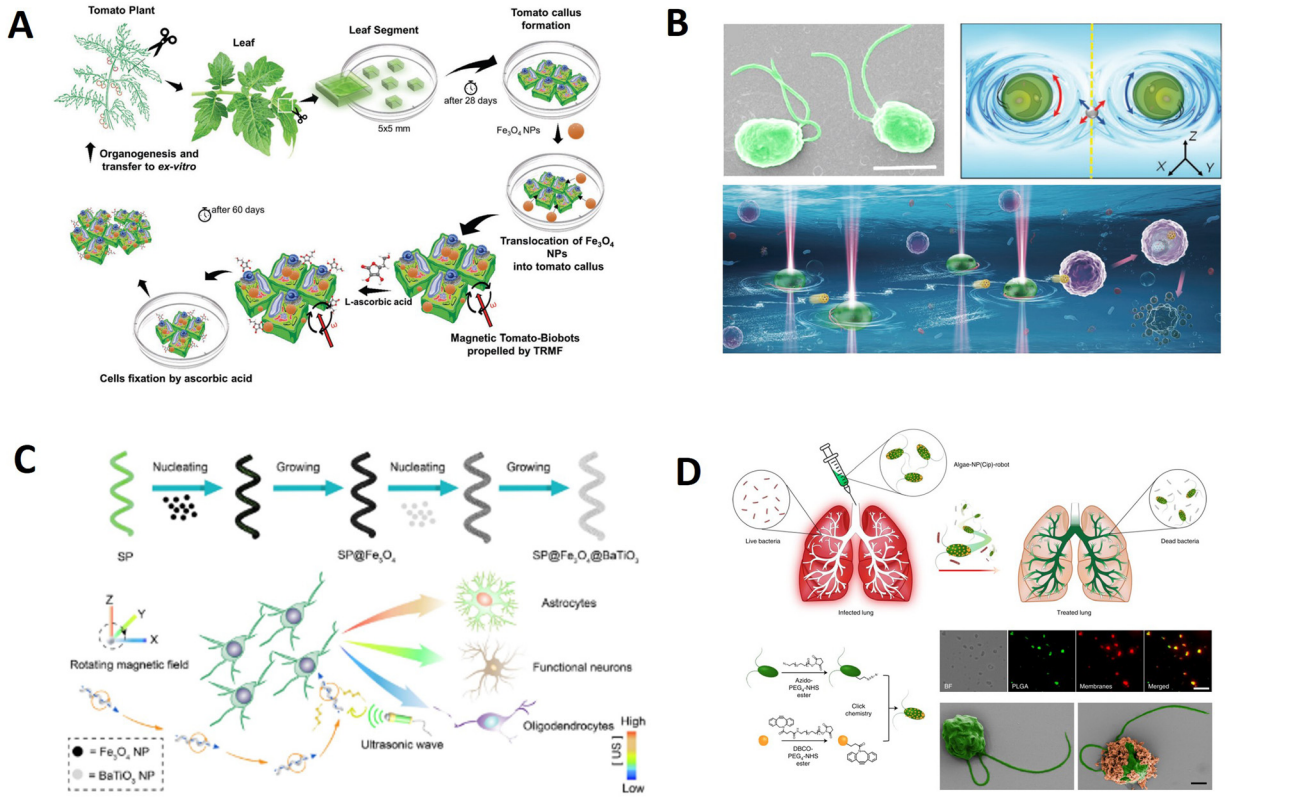

Fig. 13 Biotemplate-based micro/nanorobots for biological applications. (A) Magnetic biohybrid robots as efficient drug carrier to generate plant cell clones. Reprinted with permission from ref. 89. Copyright 2022 Wiley-VCH. (B) Bio-micromotor tweezers for noninvasive bio-cargo delivery and precise therapy. Reprinted with permission from ref. 124. Copyright 2022 Wiley-VCH. (C) Controlling the neural stem cell fate with biohybrid piezoelectrical magnetite micromotors. Reprinted with permission from ref. 117. Copyright 2021 American Chemical Society. (D) Nanoparticle-modified microrobots for *in vivo* antibiotic delivery to treat acute bacterial pneumonia. Reprinted with permission from ref. 121. Copyright 2022 Nature Research.

Such bio-micromotor tweezers depend on the motion of *C. reinhardtii* and provide great potential for different biomedical applications such as targeted drug/cell delivery, drug testing, accurate diagnosis, and precise therapy.

Inducing neural stem cells to differentiate and replace degenerated functional neurons represents the most promising approach for degenerative neural diseases, including Parkinson's disease, Alzheimer's disease, *etc.* While diverse strategies have been proposed in recent years, most of these are hindered due to uncontrollable cell fate and device invasiveness. Thus, Liu *et al.* reported a minimally invasive micromotor platform with biodegradable helical *S. platensis* as the framework and superparamagnetic Fe_3O_4 nanoparticles/piezoelectric $BaTiO_3$ nanoparticles as the built-in function units (Fig. 13C).[117] With a low-strength rotational magnetic field, this integrated micromotor system can precisely navigate in biofluids and achieve single-neural stem cell targeting, which is attributable to helical structures and magnetic layers endowed with directional motion, enabling it to become a system capable of controlling the differentiation fate of the neural stem cells *in situ* in a simple, wireless, and minimally invasive way.

Neutrophil membrane-coated NPs are used because of their unique cell-mimicking properties, including shielding payloads from biological environments, reducing immune clearance and enabling specific binding with target pathogens. Natural algae can be combined with the engineering versatility of biomimetic NPs to yield a hybrid microrobot platform capable of active drug delivery. In Zhang *et al.*'s design, they create a biotemplate-based microrobot consisting of *C. reinhardtii* microalgae modified with neutrophil membrane-coated and drug-loaded polymeric nanoparticles (denoted as 'algae-NP-robot') for the *in vivo* treatment of lung infection (Fig. 13D).[164] In a mouse model of acute *Pseudomonas aeruginosa* pneumonia, the microrobots effectively reduced the bacterial burden and substantially lessened animal mortality with negligible toxicity. Overall, these findings highlight the attractive functions of algae–nanoparticle hybrid microrobots for the active *in vivo* delivery of therapeutics to the lungs in intensive care unit settings.

4.2. Environmental applications

Rapid industrialization generates a large number of chemical wastes, such as dyes, oils, pesticides, heavy metal ions, and others. These harmful organic substances accumulated in our surroundings threaten human health. However, conventional chemical detoxification technology typically needs prolonged operation time and/or mechanical stirring, and is low-efficient for water treatment.[165] Due to their autonomous motion properties, the burgeoning micro/nanorobots can accelerate the

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process by enhancing contact with the treatment solution.[87] Unlike conventional processes, self-propulsion micro/nanorobots are promising in fast and advanced water treatments. The customizable surface of micro/nanorobots can be functionalized with catalysts and adsorbent functions for the catalytic degradation and adsorptive removal processes.[166] By reasonable structure design and surface functionalization, micro/nanorobots have been developed as powerful "on-the-fly" cleaning platforms for removing organic, inorganic, and biological pollutants.[167] Natural biotemplates are renewable plants with special structures and can be easily obtained at a low price, enabling the mass preparation of intelligent micro/nanorobots at an inexpensive cost. Thus, a series of micro/nanorobots with an excellent capacity based on biotemplates as templates were developed.

4.2.1. Adsorbed metal ions. Many heavy metals, such as copper, nickel, cobalt, zinc, arsenic, mercury, cadmium, chromium, lead, and so on, prove cumulatively toxic to living organisms and long biological half-lives.[168] Over the past centuries, the gradually increasing levels of metals in water solutions have reached an alarming value, thus putting forward an urgent need for developing novel materials and technologies to remove them in a green, efficient, and reusable fashion.[168] Benefiting from the excellent adsorption properties of biotemplates, living and dead microorganisms (such as bacteria, fungi, plant fiber, and algae) have remarkable uptake ability for metals, enabling them to sequester metal ions out of the complex solution from the ppm to ppb level effectively and quickly.[169,170] Considering their abundant sources, environmental friendliness, and vast adsorption capacity, integrating them with self-propelled micro/nanorobots is an ideal biosorption way to remove heavy metals in a green and effective manner.

Inspired by the natural kapok fiber with a unique hollow tubular structure containing cellulose and lignin, which could provide unbalanced force conditions in the motion of micro/nanomotors, Yang *et al.* reported a kapok fiber inspired functionalized Eu-MOF-based fluorescent micromotor. It is an active self-propelled micromachine for detecting, capturing, and removing Fe^{3+} from water (Fig. 14A).[83] This micromotor has the merits of high sensitivity, good selectivity, and high dynamic adsorption for Fe^{3+}. Based on this, it can be extended to detecting and removing other target ions, boosting the preparation of fluorescent micromotors for environmental management. Compared with various conventionally static nanomaterials, self-propelled micromotors have greatly enhanced the efficiency of traditional operations due to the phenomena of active motion of matter and have been demonstrated to exhibit an extremely significant effect on the detection of various contaminants.

Lotus pollen grains, the sori of lotus, were selected as the biotemplate to prepare Janus micromotors due to their characteristic porous microporous morphology, acceptable cost, and ready availability.[171] As seen in Fig. 14B, Han *et al.*

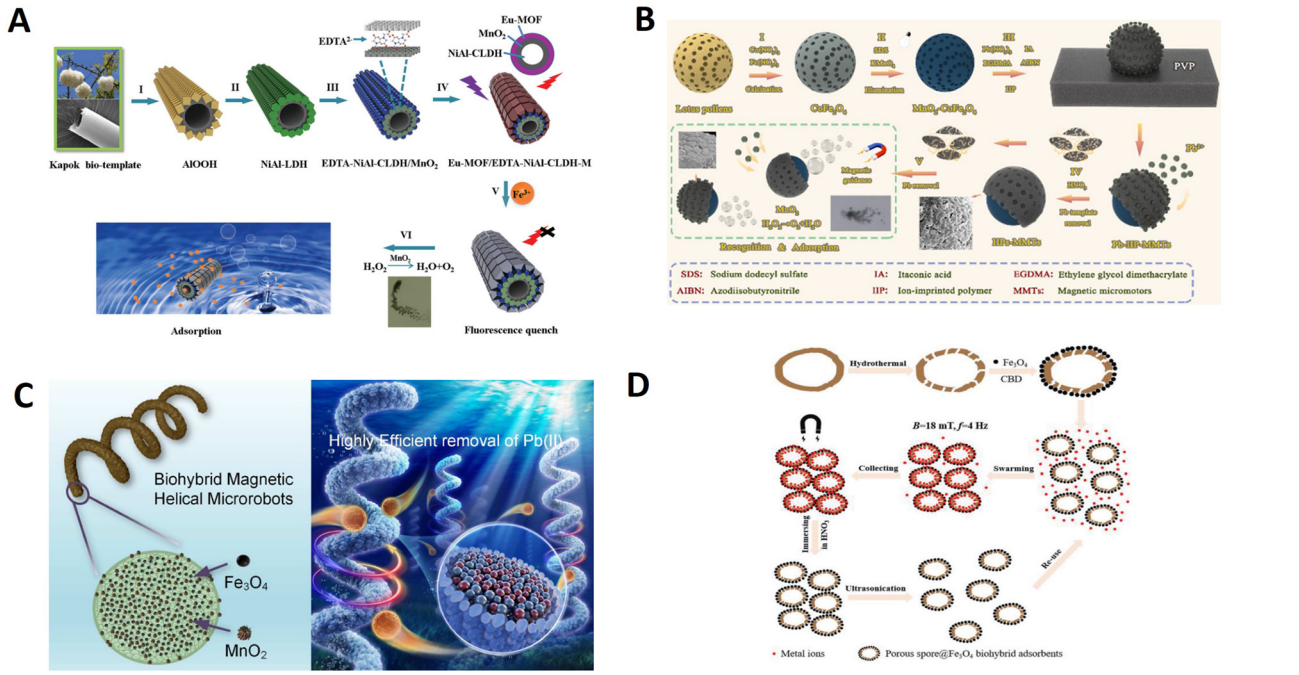

Fig. 14 Biotemplate-based micro/nanorobots for adsorbed metal ions. (A) An Eu-MOF/EDTA-NiAl-CLDH fluorescent micromotor for sensing and removal of Fe^{3+} from water. Reprinted with permission from ref. 83. Copyright 2019 Royal Society of Chemistry. (B) Ion-imprinted $MnO_2/CoFe_2O_4$ Janus magnetic micromotors synthesized by a lotus pollen template for highly selective recognition and capture of Pb(II) ions. Reprinted with permission from ref. 90. Copyright 2022 Royal Society of Chemistry. (C) Efficient removal of Pb(II) from aqueous systems using spirulina-based biohybrid magnetic helical microrobots. Reprinted with permission from ref. 111. Copyright 2021 American Chemical Society. (D) Enhanced removal of toxic heavy metals using swarming biohybrid adsorbents. Reprinted with permission from ref. 141. Copyright 2018 Wiley-VCH.

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developed a novel Janus micromotor based on the combination of ion-imprinted recognition cavities and self-propelling motion for the sensitive recognition and removal of Pb(II) ions from water.[90] Ion-imprinted MnO_2/$CoFe_2O_4$ Janus micromotors inherit the porous structure of lotus pollen grains and reveal sensitive recognition and capture for Pb(II) ions and magnetic recovery capability. This study provides a new strategy for the highly selective removal of metal contaminating ions from water. Besides, microalgae have unique biological structures with plentiful active sites on the surface, such as hydroxyl and carboxyl groups, and both living and dead ones exhibit certain adsorption validity. Gong *et al.* presented Fe_3O_4 and MnO_2-loaded biotemplate-based magnetic helical microrobots (BMHMs) based on *Spirulina* cells for Pb(II) removal (Fig. 14C).[111] The BMHMs could be magnetically actuated forward flexibly and perform continuous cork-screw spinning in swarm for intensive adsorption. Rapid and significant removal of Pb(II) was achieved using the swarming BMHMs. The adsorption capacity could reach 245.1 mg g^{-1}, higher than those of most of the reported MnO_2-based adsorbents. The intriguing properties of the BMHMs enable them to be versatile platforms with significant potential in wastewater remediation.

Porous biotemplates are often used as adsorbents, such as Ganoderma spores. As shown in Fig. 14D, Zhang *et al.* developed a biotemplate-based adsorbent through *in situ* growing magnetic Fe_3O_4 nanoparticles on hydrothermally treated fungi spores.[141] Such organic/inorganic porous spore@Fe_3O_4 biotemplate-based adsorbents (PSFBAs) can effectively adsorb and remove heavy metal ions due to porous structuring and high-adsorbing components. Once combined with a magnetically driven microrobotic technique, magnetic PSFBAs in controllably collective motion show enhanced adsorption capacity and shorter removal time for multiple heavy metal ions compared to nonmotile counterparts. Combining biological entities and swarming microrobotic techniques would provide a promising avenue for decontaminating pollutants in environmental remediation.

4.2.2. Removal of pollutants. Pollutants (such as rhodamine B, chlorpyrifos, oil, and microplastics) can cause severe soil, river, and groundwater pollution.[172–175] Although several porous nano/microscale absorbents have been developed to absorb pollutants, they are less efficient due to their passive motion property.[97,176] Purifying them is also tedious work. In particular, biotemplate-based micro/nanorobots have shown a new dimension in motion-based decontamination processes and led to new "instant" remediation solutions, higher efficiency, shorter decontamination times, and potentially lower costs.

It is meaningful to achieve large-scale reproducible production of biotemplate-based micromotors for removing erythromycin (ERY) using a relatively facile procedure and acceptable cost. Li *et al.* used a facile bio-template route to synthesize a novel Pt-free temperature-responsive micromachine with fascinating recognition, capture and release capacities for erythromycin in water based on the integration of surface imprinted technology, the temperature-response of poly(*N*-isopropylacrylamide) (PNIPAM) hydrogels, and the autonomous motion

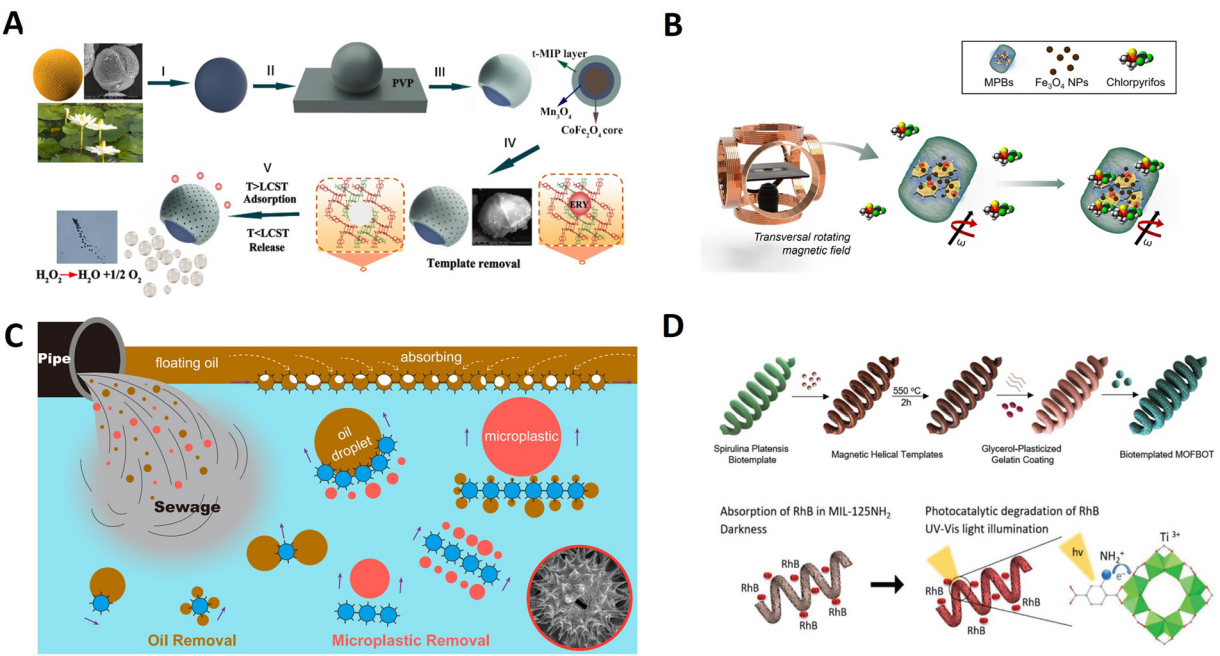

Fig. 15 Biotemplate-based micro/nanorobots for degrading pollutants. (A) Bioinspired Pt-free molecularly imprinted hydrogel-based magnetic Janus micromotors for temperature-responsive recognition and adsorption of erythromycin in water. Reprinted with permission from ref. 91. Copyright 2019 Elsevier. (B) Engineered magnetic plant biobots for nerve agent removal. Reprinted with permission from ref. 88. Copyright 2022 Nature Research. (C) Cooperative recyclable magnetic microsubmarines for oil and microplastics removal from water. Reprinted with permission from ref. 97. Copyright 2020 Elsevier. (D) Biotemplating of metal–organic framework nanocrystals for applications in small-scale robotics. Reprinted with permission from ref. 115. Copyright 2020 Wiley-VCH.

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ability of a micromotor.[91] The resulting Janus micromotor exhibited higher temperature-controlled recognition and adsorption capacities than most reported erythromycin-imprinted materials but also revealed high trajectory control ability and easy recovery by an external magnetic field, showing great potential for biomedical and water purification applications (Fig. 15A). Besides, fabricating plant-derived biobots combined with plant tissue and ferromagnetic materials for decontamination is a new direction for biotemplate-based robots. Song *et al.* used tomato leaf-derived calli to fabricate plant robots, and their efficiency for chlorpyrifos removal was investigated.[88] The Fe_3O_4 NPs were transported through the cell growth media and then taken up into the plant tissue cells, imparting the plant biobot with magnetic function (Fig. 15B). The magnetic plant biobots demonstrated rapid and efficient removal of chlorpyrifos (approximately 80%).

The sunflower pollen grains (SPGs) have several remarkable structural features: large free volumes, multitudinous nanopores, and numerous nano spikes, which could make them attractive for water remediation. Sun *et al.* reported a ''hedgehog'' magnetic microsubmarine based on SPGs, which can simultaneously remove oil and microplastic pollutants.[97] As displayed in Fig. 15C, these hollow microsubmarines were fabricated on a large scale by sequentially treating the natural SPGs with acidolysis and sputtering. The hollow structure allows a double functionality: (i) like a submarine, propel under or above the water, depending on the fillings inside; (ii) oil pollutant storage. The microsubmarine can transport oil droplets 37 times larger than its volume and effectively adsorb floating oil *via* capillary action. And the fluid induced by the cooperative microsubmarines can remove the microplastics controllably in a noncontact method.

Furthermore, biotemplates can be extended to design MOF-based motors for various applications, from biomedicine to environmental remediation. Terzopoulou *et al.* presented a universal biotemplate-based methodology to fabricate 3D helical assemblies of MOF robotics.[115] Specifically, *S. platensis* is used as a biotemplate on which multiple components comprising a magnetic chassis, a gelatin binder film, and a MOF nanocrystal coating are assembled (Fig. 15D). The robot is used to perform microrobotic targeted drug delivery in cancer cells due to high-precision 3D rotation and photocatalytic degradation of an organic pollutant in water. Such helical robots can be used as highly integrated magnetically driven microrobots with multiple functionalities.

4. Conclusion and outlook

Intelligent micro/nanorobots show good potential for applications in drug delivery, imaging, cancer therapy, environmental remediation and cargo handling due to their ability to convert external energy into motion under external magnetic fields. Utilizing natural materials as biotemplates to obtain intelligent micro/nanorobots is a new trend in recent years due to their elegant structures and abundant surface functional groups. Based on the characteristics of biotemplates, our review introduced the advantages of natural materials as biotemplates, then systematically discussed the characteristics and preparation strategies of each type of intelligent micro/nanorobots, and finally summarized the applications of intelligent micro/nanorobots in different fields. Although great progress has been made in intelligent micro/nanorobots, there remain some shortcomings of current biotemplates. To further expand the potential of intelligent micro/nanorobots for applications, several challenges should be urgently considered and addressed. For example:

1. Source

Despite the relative abundance of biotemplates in nature, the sources of biotemplates for the preparation of specific structures are limited and are obtained by large-scale extraction from specific tissues or mass culture of microbial cells, which requires relevant extraction techniques, microbial culture techniques and the support of equipment. Therefore, it is necessary to develop an inexpensive and readily available biotemplate source.

2. Stability

The thermal stability of biotemplates is poor. When biotemplates are removed by heat treatment, high temperature can easily lead to the collapse of their porous structure and the loss of their micro/nanostructure, and they cannot play the role of templates or morphology inducers, which greatly limits their scope of use. Thus, it is important to choose the right biotemplates.

3. Lifetime

Considering that micro/nanorobots need to convert chemical fuels or diverse external energies to propulsion force for specific applications in versatile environments, it requires that micro/nanorobots possess long-term durability. Such micro/nanorobots can be used for recycling, which reduces resource and energy consumption and promotes sustainable development. Especially, live cells such as microalgae can generate strong long-lasting thrust for self-propulsion at a fast speed.

4. Biocompatibility

Biocompatibility is critical for designing microrobots for biomedical applications. In most cases, due to various requirements for drive, control, and functionality, the selected biotemplates cannot be used without without toxicity. Therefore, in the design process, biotemplates should meet the minimum requirements for biocompatibility.

5. Living organisms' self-propulsion

Currently, most intelligent micro/nanorobots are based on inanimate biotemplates. However, biotemplates with life activity usually have unique characteristics or motion properties. Making full use of biotemplates with life activity and integrating the autonomous response, autonomous motion and self-healing properties to develop intelligent micro/nanorobots with dynamic response and autonomous adaptive working is very significant.

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6. Multifunctional materials

Multifunctional materials are the future research trend, not only integrating materials but also combining multiple functions such as imaging, sensing, therapeutic and restorative environments in one system to achieve multifunctional applications.

Biotemplates not only have unique structures but also have specific functions, and are an important development direction in the future development of intelligent micro/nanorobots. We believe that with the development and the expansion of biotemplates and micro- and nanotechnology, the future intelligent micro/nanorobots will be more intelligent, efficient and safe, and become a brand new technological revolution to solve complex problems in the microscopic field in the future.

Note

There are no ethical concerns in this review.

Author contributions

T. Chen conceived the review and wrote the manuscript. Y. Cai, B. J. Sánchez, B. Ren, and R. Dong supervised the review and finalized the manuscript. All authors have given approval to the final version of the article.

Conflicts of interest

There are no conflicts to declare.

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