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Smart MXene-based microrobots for targeted drug delivery and synergistic therapies

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MXenes and their composites exhibit remarkable electrical conductivity, mechanical flexibility, and biocompatibility, making them ideal candidates for microrobot fabrication. Their tunable surface chemistry allows for easy functionalization, which enhances their interaction with biological environments, thereby facilitating targeted therapies. Such smart microrobots can be engineered to navigate through complex biological systems with precision *via* the integration of responsive elements, such as stimuli-sensitive polymers or magnetic components. MXene-based microrobots are able to actively seek out specific tissues or cells. This capability is crucial for applications in cancer treatment, where localized drug delivery minimizes side effects and enhances therapeutic efficacy. The primary advantage of MXene-based microrobots lies in their ability to deliver therapeutic agents directly to diseased cells. Utilizing ligand–receptor interactions, these microrobots can bind to target cells and release their payload in a controlled manner. This targeted delivery system not only improves the effectiveness of the drug but also reduces the required dosage, thus mitigating potential side effects. Moreover, smart MXene-based microrobots can facilitate synergistic therapies by co-delivering multiple therapeutic agents. For instance, combining chemotherapy drugs with immunotherapeutic agents could enhance treatment outcomes in cancer therapy. The ability to simultaneously deliver different types of drugs allows for more comprehensive treatment strategies that can tackle tumor heterogeneity. Significant advancements are anticipated in synergistic therapies, particularly in chemo-photothermal, chemodynamic, and photothermal/photodynamic therapies. These strategies leverage multiple therapeutic modalities to enhance cancer treatment outcomes. Despite their outstanding potential, several challenges remain in the development of MXene-based microrobots namely matters pertaining to scalability, stability in biological environments, and associated regulatory hurdles which ought to be addressed. Future research should focus on optimizing the design and functionality of these microrobots, including enhancing their navigation capabilities and ensuring their safety and effectiveness *in vivo*. By presenting the innovative capabilities of MXene-based microrobots, this perspective aims to inspire additional explorations in the field of advanced targeted drug delivery systems and synergistic therapies, ultimately contributing to the future of personalized medicine and oncology.

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1. Introduction

With their noninvasive nature, precise control, and autonomous mobility, microrobots are transforming the landscape of minimally invasive medicine.[1,2] They can navigate deep tissues, which is crucial for targeted therapies. One of the most compelling aspects of microrobots is their ability to navigate biological systems. These microrobots can be engineered to respond to specific stimuli, such as temperature or pH changes. With this exceptional capability, they can effectively target diseased cells or tissues, ensuring that therapeutic agents are delivered precisely where they are needed.[1,2] Recent advancements have led to the development of microrobots powered by various external energy sources, such as magnetic

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fields, light, and acoustic waves. Among these, magnetically driven microrobots are particularly noteworthy for their ability to reach challenging areas within the body, like blood vessels and the brain, under the guidance of an external magnetic field. However, before they can be applied clinically, concerns such as cytotoxicity and biodegradation need to be addressed. Modifying microrobots with tailored (nano)materials allows for the creation of function-specific devices suited for various therapeutic applications.[3]

Two-dimensional (2D) layered nanomaterials are among different types of nanomaterials that could be used for the fabrication of microbots due to their interesting therapeutic features such as mechanical flexibility, photo-stability, high photo-thermal conversion efficiency. Therefore, various types of microbots have been fabricated in which different types of 2D materials are deployed including two-dimensional transition metal dichalcogenides (TMDCs), phosphorene (black phosphorus (BP)), graphene (and its derivatives), hexagonal boron nitride (h-BN), and MXenes.[4–6] In this context, graphene exhibits remarkable properties such as high carrier mobility, superior mechanical strength, exceptional electrical and thermal conductivity, flexibility, and optical transparency; however, it showed limitation in chemical reactivity and large-scale production. On the other hand, graphene oxide (GO) is rich in oxygen-containing functional groups, making it non-conductive yet highly hydrophilic. Due to its strong interactions with water and the ultrafast transport of water molecules through stacked GO sheets, GO disperses well in aqueous solutions and forms strong associations with various guest molecules. GO nanosheets can also be reduced to reduced graphene oxide (rGO), which regains electrical conductivity. However, this reduction process inevitably removes hydrophilic functional groups, diminishing the performance of rGO-based films in humidity gradient fields. Unlike graphene, which lacks a bandgap, TMDs feature adjustable bandgaps that allows them to efficiently absorb light at specific wavelengths, making them highly suitable for photothermal-driven applications and biomedical uses, including photothermal therapy. Moreover, the tunable bandgap of TMDs is not only an intrinsic feature of their structure but can also be modulated by external factors such as light exposure, gas adsorption, or mechanical stress, leading to notable changes in their electronic properties and conductivity. As a result, TMDs are excellent candidates for various sensing applications, including photodetectors, gas sensors, and pressure sensors. Unlike graphene, which has a planar structure, phosphorene possesses stable single-element layers arranged in a buckled hexagonal honeycomb pattern, leading to a wide range of unique properties and functionalities. The remarkable influence of this compound has accelerated its rapid advancement in numerous emerging applications, including optoelectronics, energy harvesting and storage, biosensors, bioimaging, therapeutic delivery, and theranostics.[5,7] MXene-based microrobots are a cutting-edge area of research that combines the unique properties of MXenes—two-dimensional (2D) transition metal carbides, nitrides, or carbonitrides—with microrobotic technology.[8–10] These materials are known for their superior electrical conductivity (compare with GO and TMDs), high mechanical stability and flexibility (in comparison to TMD and borophene), photothermal and electrochemical features (compare with TMDs), and hydrophilicity, making them suitable for various applications in fields such as medicine, environmental monitoring, and materials science.[11–13] The integration of MXenes into microrobots enhances their functionality, allowing for improved control, responsiveness, and adaptability in complex environments. For instance, MXene-based microrobots can be designed for targeted drug delivery, where they navigate through biological systems to release therapeutic agents precisely where needed. Additionally, their unique properties enable them to respond to external stimuli, such as magnetic fields or light, facilitating controlled movement and operation.[13–15]

So far, various methods have been introduced for the fabrication of MXene microbots in which composite of MXene with other compounds were used to fabricate the microbot structure. Indeed, the composite could be fabricated in the form of layer-by-layer sandwiched structure,[16,17] hydrogel,[18] and fibers.[19] 3D printing, as a novel fabricating technique, was used for the fabrications of microbots as well;[20,21] however, no article is available for producing MXene microbot *via* this method. Despite the advantages of each of these techniques, they have some limitations that could affect their usage and need to further research to overcome these limitations. For example, 3D printing has challenges such as limited material compatibility, slow fabrication speeds, and difficulties in integrating multiple functional components at the nanoscale. Microfluidic system, which use controlled fluid dynamics to assemble microrobots with high reproducibility, has limitations in scalability issues, batch-to-batch variations, and the need for specialized equipment, that limit widespread application in clinical settings. Self-assembly method has drawback in precise control over final structures, leading to heterogeneous sizes and morphologies that may affect microrobot performance. Therefore, it is important to have profound research on different fabrication methods to overcome these limitations.

The advent of smart microrobots, particularly those based on MXene materials, presents a novel approach to targeted drug delivery and synergistic therapies (Fig. 1). The integration of MXene-based systems into targeted drug delivery systems represents a significant leap forward in medical technology[22,23] wherein the versatility of MXenes allows for the customization of these microrobots; their surfaces can be modified to enhance drug loading or improve the targeting capabilities.[19] For instance, attaching antibodies or ligands specific to certain receptors be able to optimize the delivery process. This targeted approach significantly reduces the side effects often experienced with traditional drug delivery methods. Another application of MXene-based microrobots is in cancer treatment. By integrating multiple therapeutic modalities, such as chemotherapy and photothermal therapy, these microrobots can launch a multi-pronged attack on tumors.

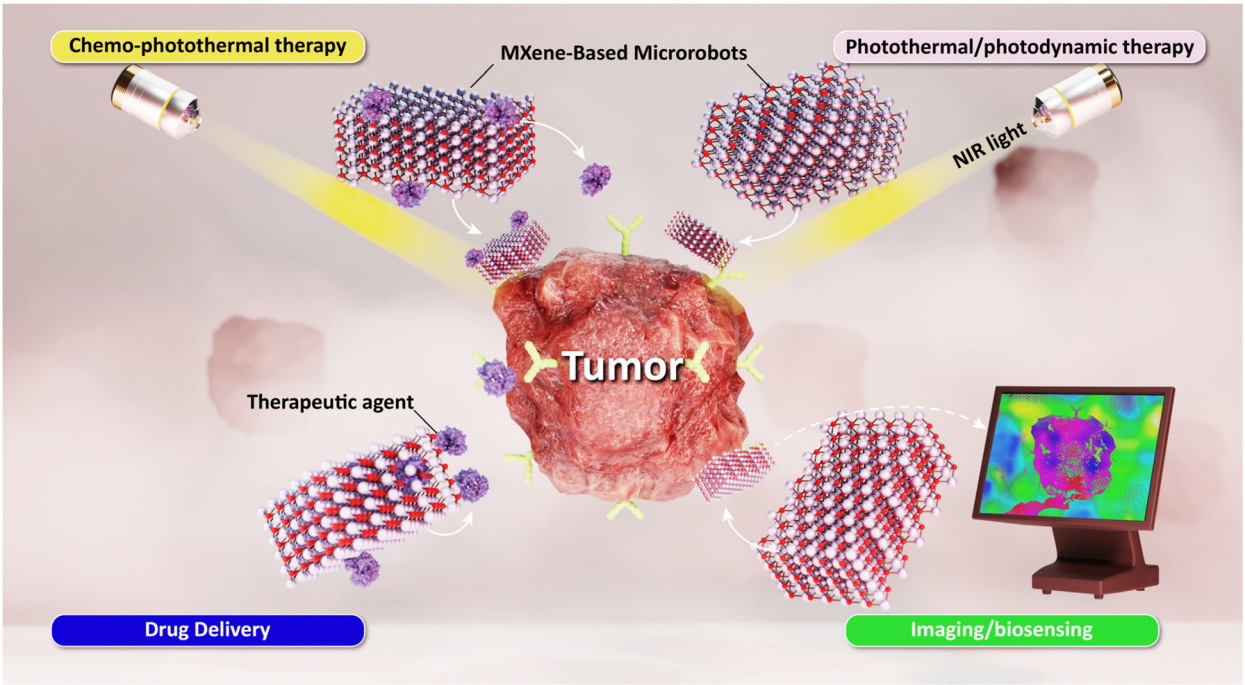

Fig. 1 Smart MXene-based microrobots represent a promising advancement in targeted drug delivery and synergistic therapies.

This synergistic effect increases the overall efficacy of treatments while minimizing harm to healthy tissues.[24]

MXene-based microrobots have been explored for synergistic chemo-photothermal therapy, offering innovative strategies for enhancing cancer treatment efficacy.[19] Such microrobots leverage the unique properties of MXenes, including excellent electrical conductivity and thermal conductivity, to create a multi-faceted approach to combating tumors.[25] One significant application is their ability to deliver chemotherapeutic agents directly to cancer cells. By utilizing external stimuli such as magnetic fields or light, MXene-based microrobots can navigate to targeted tumor sites with precision. This targeted delivery minimizes systemic side effects and maximizes drug concentration at the site of interest, enhancing therapeutic outcomes. In addition to drug delivery, these microrobots can simultaneously harness photothermal therapy.[26] Upon exposure to near-infrared (NIR) light, MXenes exhibit significant heat generation. Such localized heating can effectively destroy cancer cells while simultaneously enhancing the cytotoxic effects of the delivered chemotherapy. The combination of heat and drug action can lead to a synergistic effect, allowing for lower drug dosages and reduced resistance development. Furthermore, the design of MXene-based microrobots enables the incorporation of imaging agents which allows for real-time monitoring of therapy progress and treatment efficacy through techniques such as fluorescence or photoacoustic imaging.[19]

The purpose of this perspective is to illuminate the groundbreaking potential of MXene-based microrobots for targeted drug delivery and synergistic therapies. The underlying objective is to discuss the intricate mechanisms of their targeted drug delivery and synergistic therapies, as well as the important challenges that researchers face such as targeting precision, cytotoxicity, biodegradability, scalability, and long-term toxicity. Herein, the novelty lies in its focus on the integration of smart MXene-based microrobots for targeted drug delivery and synergistic therapies, an area that remains largely unexplored. Unlike conventional drug delivery systems, these microrobots exploit the unique properties of MXenes, enabling them to navigate complex biological environments with precision and enhanced therapeutic efficacy. This strategy offers a groundbreaking approach by detailing how these microrobots can be designed to co-deliver multiple therapeutic agents, providing a synergistic effect that traditional methods cannot achieve. Furthermore, it emphasizes the potential for real-time monitoring and control, thus allowing for personalized treatment strategies that adapt to the dynamic nature of diseases, particularly in cancer therapy.

2. MXenes in soft robotics and their biomedical potentials

Soft robotics is a subfield of robotics that focuses on creating robots from highly flexible materials, allowing them to mimic the adaptability and dexterity of biological organisms.[27] Unlike traditional rigid robots, soft robots can deform, stretch, and compress, enabling them to navigate complex environments and interact safely with humans and delicate objects. This technology leverages materials such as silicone, hydrogels, and

other soft composites, which can be actuated through various means, including pneumatic, hydraulic, or electrical systems.[27,28] The applications of soft robotics are diverse, ranging from medical devices and prosthetics to search-and-rescue operations and agricultural automation, highlighting their potential to develop how robots operate in dynamic and unpredictable settings.[29]

Soft robotics has emerged as a transformative approach in the field of targeted drug delivery, leveraging the unique properties of soft materials to navigate complex biological environments.[30] These robotic systems can be designed to deform and adapt to various anatomical structures, allowing for precise targeting of drug delivery to specific tissues or cells. This adaptability is particularly beneficial in minimizing off-target effects and enhancing the therapeutic efficacy of drugs. By integrating soft robotics with advanced imaging techniques, clinicians can achieve real-time monitoring of drug delivery processes, ensuring that therapeutic agents are released at the optimal time and location within the body.[31] In addition to targeted drug delivery, soft robotics can synergistically enhance therapies such as photothermal, photodynamic, chemo-dynamic, and chemo-photothermal treatments. These therapies often rely on the precise application of energy or drugs to induce therapeutic effects, such as localized heating or reactive oxygen species (ROS) generation. Soft robotic systems can be engineered to deliver these modalities in a controlled manner, improving the overall effectiveness of the treatment. For instance, soft robots can be equipped with light-emitting diodes (LEDs) for photothermal therapy, allowing for targeted heating of tumor cells while simultaneously delivering chemotherapeutic agents. This combination not only increases the sensitivity of cancer cells to treatment but also reduces systemic toxicity, showcasing the potential of soft robotics in advancing synergistic therapeutic strategies.[32] Recent advancements in soft robotics have brought to light the remarkable integration of photothermal materials and techniques within soft actuators. This innovative approach allows robots to respond dynamically to light stimuli, broadening their functional capabilities. The ability to harness light enables soft robots to perform intricate tasks, such as gripping and transporting objects. Additionally, these photothermal materials facilitate therapeutic actions through controlled heating. This capability is particularly valuable in medical applications, where targeted treatments can significantly enhance outcomes. The modulation of temperature using photothermal effects is a game-changer in drug delivery systems. By applying heat specifically to tumor sites, the efficacy of treatments can be improved. This targeted approach minimizes side effects and maximizes therapeutic benefits. Soft robots equipped with photothermal materials can ensure that heat is delivered precisely where it is needed most, creating a more effective treatment regimen. These advancements open up exciting possibilities for developing intelligent robotic systems that adapt not only to their environment but also to the specific needs of patients.[32–34]

2.1 MXene-based microrobots in modern (bio)medicine

The evolution of next-generation micro/nanorobotics hinges significantly on the development of advanced materials that enhance functionality, efficiency, and adaptability. These materials not only provide unique properties but also contribute to the versatility required for a myriad of applications, particularly in biomedical and environmental fields. Emerging 2D materials such as MXenes, TMDs, and carbon nitrides (C_3N_4) have become integral in micro/nanorobotics.[35–37] These materials exhibit unique properties distinct from their three-dimensional counterparts, making them ideal for novel functionalities. For instance, they can be employed in the development of light-driven micro-engines or bio-affinity interfaces that enhance catalytic and photothermal interactions. The potential for these materials in nanotechnology is vast, with applications ranging from targeted drug delivery systems to advanced sensors. Additionally, MOFs present another exciting avenue in the realm of micro/nanorobotics. Known for their high porosity and large surface area, MOFs are versatile materials that can be tailored for specific applications. Their capabilities for molecular adsorption and dynamic mass transport make them particularly suitable for targeted drug delivery and enhanced catalytic performance. The stability and biocompatibility of MOFs further enhance their attractiveness for biomedical applications.[38,39]

The interaction between active materials and light as an energy source is a highly appealing research area. Semiconductors play a crucial role in the creation of light-driven, photocatalytic micro/nanorobots. These systems can be actuated by ultraviolet (UV), visible (Vis), or near-infrared (NIR) light, allowing them to generate motion efficiently.[40] The ability to create fuel-free micro/nanorobotic platforms opens significant potential for environmental remediation and biomedical interventions. By harnessing light, researchers can develop systems that operate autonomously, paving the way for innovative solutions to pressing challenges.[41] Polymers also play a pivotal role in the advancement of smart micro/nanorobotic systems. Their versatility and responsiveness to various stimuli enable controlled motion and manipulation at micro- and nanoscale levels.[42,43] Programmable and adaptable, polymers can respond to factors such as temperature, pH, light, magnetic fields, and ultrasound. This responsiveness enhances soft functionalities, making polymers ideal candidates for applications in drug delivery, tissue engineering, and environmental monitoring.[44] Notably, the hybridization of biological cells with synthetic functional materials gives rise to small-scale living robots, which hold promise in advanced therapeutic technologies.[45] These cell-hybrid robots exhibit autonomous actuation and low toxicity, navigating efficiently through various guidance mechanisms. Their unique capabilities position them as biological templates for fabricating biocompatible microrobots, making them attractive candidates for next-generation medical applications.[44,45]

With their exceptional properties such as high conductivity, chemical stability, ease of surface functionalization, and out-

standing photothermal conversion efficiency, MXene-based microrobots have emerged as promising tools for targeted drug delivery and synergistic therapeutic applications.[46–48] Besides, the photothermal properties of MXenes, activated by near-infrared (NIR) light, generate localized heating to ablate tumors while concurrently enhancing the permeability of cell membranes. This effect amplifies the intracellular uptake of chemotherapeutic agents, allowing for reduced dosages and mitigating systemic side effects.[49] For example, the combination of $Ti_3C_2T_x$ MXene, Au nanoparticles, and doxorubicin (as a chemotherapeutic drug) showed significant reduction in viability of 4T1 cells (less than 10%) after exposing with NIR irradiation that was comparable with free DOX (60%), NIR (about 80%), and Au@$Ti_3C_2T_x$ (about 45%), alone.[50] It was shown that the inclusion of photodynamic capabilities *via* the generation of ROS offers a secondary pathway to induce tumor cell apoptosis.[51] Besides photothermal effect, MXene could exhibit enzyme like activity. For instance, $Ti_3C_2T_x$ showed catalase (CAT)-like activity that convert H_2O_2 into the O_2 molecules. A nanoformulation was fabricated using phloretin (Phl) loaded degradable mesoporous silica nanoparticles (DS-MSN) functionalized with glucose oxidase (GOx) which were loaded on the surface of $Ti_3C_2T_x$ MXene nanosheets. This system displayed PTT and chemotherapy effects (less than 20% cell viability in the presence of 64 μg ml^{-1} of MXene). Indeed, in the presence of MXene, O_2 molecules were produced inside the cells that were used by the Gox to produce H_2O_2 molecules. Moreover, Phl molecules were released in the presence of reduced microenvironment of cancer cells and therefore the combination of chemo-PTT led to synergistic anticancer activity specifically in the microenvironment of cancer. The other interesting point was the anti-inflammation feature of MXene and Phl that adsorbed reactive oxygen species (ROS) and reduced inflammatory condition prepared by PT effect.[52] The combination of PTT, chemotherapy, and Glucose oxidase-mediated starvation therapy (GST) was produced in another study through covalently immobilization of glucose oxidase and horseradish peroxidase on the surface of Ti_3C_2 MXene followed by the adsorption of DOX and coating the complex with hyaluronic acid. In here, photothermal effect was activated under NIR irradiation led to increase the temperature inside the cells that produce situation for GOX to demonstrate its optimal catalytic activity. On the other hand, GST can lower ATP levels by depleting glucose in tumors, suppress the overexpression of heat shock proteins at the tumor site, and enhance the effectiveness of PTT in tumor cells. Moreover, presence of DOX induced chemotherapeutic effect on cells and therefore synergistic anticancer feature was achieved that exhibited IC50 for the concentrations less than 50 μg ml^{-1} and reduced tumor size within 14 days.[53] The combination of PTT, chemotherapy (CDT), and chemodynamic therapy was deployed in another research *via* fabricating doxorubicin loaded hollow mesoporous manganese dioxide nanoparticle (DOX@HMDN) that were functionalized with polyethyleneimine (PEI) modified $Ti_3C_2T_x$ MXene quantum dots (TQDs). Presence of HMDN in the structure of this formulation induced CDT effect resulted from Fenton/Fenton-like reactions of Mn^{2+} ions. On the other hand, the chemotherapeutic effect of DOX and PT property of MXene led to improve treatment performance (less than 10% cell viability in the presence of 10 μg ml^{-1} drug) due to the combination use of three different treatment methods, simultaneously.[54] The composite of MXene and metal–organic frameworks (MOFs) were used in a study to fabricate a formulation for combination of chemotherapy and gene therapy *via* co-delivery of doxorubicin (DOX)/clustered regularly interspaced short palindromic repeats (CRISPR).[55] The integration of these modalities within microrobots not only improves the therapeutic outcomes but also addresses drug resistance, a formidable challenge in cancer treatment.

On the other hand, MXene-based microrobots equipped with targeted drug delivery mechanisms provide a significant advantage in terms of precision and specificity. By functionalizing MXene surfaces with targeting ligands such as antibodies or aptamers, these microrobots are able to selectively bind to overexpressed receptors on tumor cells, ensuring localized drug release.[55–57] This capability is further enhanced by stimuli-responsive systems, where external triggers such as pH, temperature, or light activate the release of therapeutic payloads. In this context, Yang *et al.*[19] introduced multifunctional Ti_3C_2 MXene-based magnetically actuated microrobots, referred to as MXBOTs. These innovative devices have been meticulously crafted through a process that involves the sequential electrostatic coating of Ti_3C_2 nanosheets alongside Fe_3O_4 nanoparticles (Fig. 2) wherein this coating performed outstandingly on the surface of biodegradable gelatin methacryloyl-based helical microstructures. Remarkably, these MXBOTs exhibited the ability to navigate along predefined paths when subjected to a rotating magnetic field with significant advantage being the integration of Ti_3C_2 nanosheets. Not only they provided a photothermal effect, but they also enhanced the microrobots' capacity for photoacoustic imaging. This dual functionality was crucial for both therapeutic and diagnostic applications. Additionally, these MXBOTs could be loaded with fluorescent molecules, thus enabling fluorescence imaging. Notably, the potential of these microrobots was investigated for targeted drug delivery. After incorporating the chemotherapeutic agent doxorubicin (DOX), the MXBOTs@DOX exhibited an accelerated release of the drug when exposed to temperature changes and acidic pH thus unveiling a promising strategy for the development of biodegradable and multifunctional microrobots. These devices hold immense potential for targeted delivery and synergistic chemo-photothermal therapy (with cell viability less than 25%), paving the way for future innovations in the field.[19]

The integration of imaging and biosensing functionalities within MXene-based microrobots represents a significant advancement in real-time monitoring and diagnostic capabilities. Photothermal imaging, fluorescence imaging, and photoacoustic imaging could be successfully incorporated into MXene microrobots, enabling clinicians to track their movements and therapeutic effects with high spatial resolution.[58–61] This multifunctionality not only enhances treatment accuracy

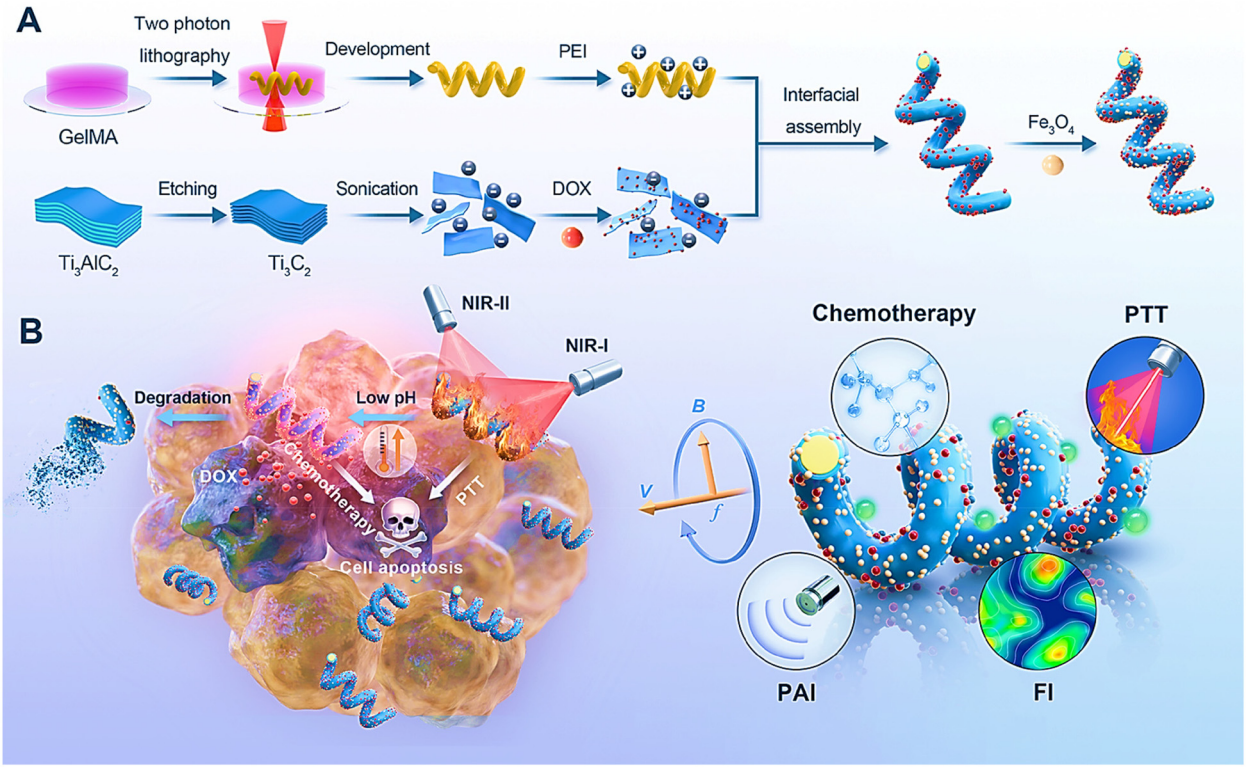

Fig. 2 (A) Process for creating MXBOTs@DOX. (B) Schematic representation of motion control, combined chemo-photothermal therapy (Chemo-PTT), imaging, and biodegradation mechanisms of MXBOTs@DOX. Reproduced with permission from ref. 19 2024 American Chemical Society.

but also allows for adaptive therapy adjustments based on real-time feedback.[62] Furthermore, MXenes' exceptional conductivity and high surface area make them ideal candidates for biosensing applications.[63] Researchers can integrate miniature sensors into the microrobot's MXene components to continually measure local physiological parameters – for instance, pH, temperature, or specific biomarker concentrations. In cancer tissue, such a microrobot might detect the acidic microenvironment and use that as a trigger to release a drug; in an infected area, it might sense a bacterial toxin and respond by releasing antibiotics. The integration of these biosensors enables real-time health monitoring at the microscale. Data gathered by the microrobot's sensors can be sent to an external receiver (or processed by onboard AI algorithms) to adjust the robot's actions, creating a feedback loop for truly intelligent therapeutics.[64–66] By coupling MXenes with biorecognition elements, microrobots can detect biomarkers or environmental cues within the tumor microenvironment.[67] This capability opens avenues for smart therapeutic responses, where the microrobots adapt their behavior based on detected stimuli, such as ROS levels or specific enzymatic activities.[68–70]

All of the above-mentioned features could be used for the development of "all-in-one" systems capable of delivering chemotherapy, performing tumor ablation *via* photothermal/photodynamic therapies, and providing continuous biosensing feedback to optimize treatment strategies dynamically. These microrobots could revolutionize cancer care by offering integrated solutions that adapt to the unique needs of each patient and so appropriate them accordingly for the aim of personalized medicine applications.

3. Challenges of MXene-based microrobots in (bio)medicine

While MXene-based microrobots present promising advancements in targeted drug delivery and synergistic chemo-photothermal therapy, several challenges hinder their broader application in clinical settings:

3.1 Cytotoxicity and long-term toxicity

Although different types of MXenes, like Ti_3C_2 and Ti_3AlC_2, exhibit biocompatibility, their long-term effects on human tissues and cells remain uncertain.[71,72] Ensuring that these materials do not elicit adverse reactions *in vivo* is crucial for their safe deployment in medical applications. Rigorous testing must be conducted to assess potential toxic effects, particularly when these microrobots are loaded with therapeutic agents. The composition and structure of the MXenes themselves play a significant role in determining their cytotoxic effects. The toxicity mechanism of MXenes primarily involves the non-specific "nanoknife" effect, as their nanosheets possess sharp edges. When these nanosheets adhere to the cell surface, direct physical interactions can compromise the

cell envelope, leading to cytoplasmic leakage and eventual collapse. Additionally, smaller MXene particles enter the cytoplasm *via* endocytosis, causing internal cellular damage. It was revealed that inducing apoptosis (resulted from increasing level of ROSs) is the main result of toxicity effect of MXenes. Indeed, MXenes interact with O_2 and H_2O to generate superoxide anion radicals ($O_2^{\bullet -}$) and hydroxyl radicals ($HO^{\bullet}$), respectively. Exposure to infrared light or ultrasonic further enhances ROS production due to their tunable bandgap and surface plasmon resonance (SPR) effects. Moreover, the presence of metals with variable valence in their structure enables them to participate in Fenton-like reactions, leading to additional $HO^{\bullet}$ generation.[73–77] Various MXene materials exhibit varying degrees of toxicity depending on their chemical composition, surface properties, and dimensionality. Thus, a comprehensive evaluation of these properties is necessary to identify the safest formulations. Additionally, the functionalization of MXenes be able to influence cytotoxicity as well.[78,79] While adding therapeutic agents or targeting ligands can enhance their functionality, it may also alter their interactions with cells. Some modifications may lead to increased cell adhesion or internalization, which could either promote therapeutic effects or result in unintended cytotoxicity. Rigorous *in vitro* studies are therefore essential to assess these interactions before proceeding to *in vivo* applications. While initial assessments may demonstrate acceptable safety profiles, the chronic effects of MXene exposure remain largely unexplored. Degradation products of MXenes, when released into the body, warrant careful investigation too. Researchers be obliged to determine whether these products are biocompatible or if they could accumulate and pose risks over time. Longitudinal studies are vital to evaluate the potential for adverse effects during prolonged exposure to MXene-based microrobots. Furthermore, the immune response to these microrobots need be thoroughly examined. The body's immune system may recognize MXenes as foreign substances, leading to inflammatory responses. An understanding of how these microrobots interact with immune cells will be essential for predicting their long-term behavior *in vivo*. The assessment of long-term *in vivo* toxicity is crucial for MXenes and their composites.[47] To safely integrate MXenes into clinical applications, comprehensive studies on their long-term biocompatibility, potential immune responses, and biodegradability are essential. Besides, detailed investigations are needed to determine effects of these formulations on different parts of body and confirm their safety. Indeed, MXenes are relatively new materials, and their long-term safety and biocompatibility remain incompletely understood. Additionally, the clinical application of MXene-based composites requires regulatory approval, a process that can be both time-intensive and expensive. This needs the collaboration among researchers, medical professionals, and regulatory bodies to translate MXene research into practical medical applications, ultimately contributing to the advancement of safer, more effective, and personalized healthcare solutions.[80–82]

3.2 Stability and biodegradability

MXenes are typically introduced into the body through oral or intravenous administration. Once in the bloodstream, they are distributed to different organs and enter cells *via* endocytosis. Biodistribution studies indicate that both MXenes and early transition metals accumulate in various organs, with the highest concentration found in the liver, followed by lower levels in the spleen, kidneys, lungs, and heart. Over time, the accumulated metal content in organs declines, while its presence in feces and, to a lesser extent, urine increases. The plasma half-life of modified MXenes varies significantly.[79] While MXenes can be designed to degrade in biological environments, achieving a controlled degradation rate that aligns with therapeutic needs is complex.[83,84] If microrobots degrade too quickly, they may release their payload prematurely, thereby reducing treatment efficacy. Conversely, if they persist too long, they could accumulate and cause complications. Developing biodegradable MXene formulations that provide reliable drug release profiles is essential. However, aligning the degradation rate of MXenes with therapeutic requirements presents a significant challenge, largely due to their intricate surface chemistry and structural properties.[85] The rate at which MXenes degrade can fluctuate considerably, influenced by various factors including the specific composition of the MXenes, environmental conditions such as pH and temperature, and the presence of other compounds. Ongoing research aims to deepen the understanding of how these variables can be adjusted to achieve the desired degradation profiles that meet therapeutic objectives effectively. Additionally, MXenes, while exhibiting remarkable properties for applications in targeted drug delivery and therapies, face a significant challenge of susceptibility to oxidation.[86] This vulnerability is especially pronounced under ambient conditions or when these materials are suspended in aqueous environments. Oxidation can lead to alterations in their chemical structure, adversely impacting their stability, conductivity, and overall performance. Consequently, it becomes imperative to develop oxidation-resistant variants to ensure their efficacy in practical applications. Upon synthesis, several diverse factors markedly influence the susceptibility of MXenes to oxidation. The selective chemical etching process, typically executed under strongly acidic conditions, invariably leads to the formation of numerous defects or vacancies. These imperfections often manifest on both the surface and edges of MXene flakes. Such defect-rich sites in MXenes exhibit a heightened vulnerability to oxidative degradation.[87] This degradation can occur upon exposure to ambient conditions or while immersed in aqueous suspension, ultimately compromising the essential properties that make MXenes so valuable. Moreover, beyond the vulnerabilities introduced by acidic etching, external environmental factors play an equally significant role. For instance, the stability and reactivity of MXenes are distinctly affected by crucial parameters such as the pH of the MXene dispersion, storage temperature, concentration of MXenes, and even flake size.[86,88,89] Thus, to combat this oxidative

degradation, several strategies have been proposed. One prominent approach involves the surface modifications. By altering the surface chemistry of MXenes, researchers can create a protective layer that mitigates the effects of oxidation. This may include the functionalization of MXenes with various organic molecules or polymers that can shield the underlying material from environmental factors. Another effective strategy is the application of protective coatings. Coating of MXenes with materials that exhibit superior oxidative resistance be able to provide a barrier against environmental exposure. These coatings are designed to prevent direct contact with oxygen and moisture, thus preserving the integrity of the MXenes during use. Additionally, the deployment of antioxidants has gained attention. By incorporating these substances, the oxidative stress on MXenes can be significantly reduced. Furthermore, the exploration of organic solvents and ionic liquids presents new avenues for safeguarding these materials. Notably, the development of hybrid structures that integrate MXenes with other materials can enhance their resistance to oxidation as well. For instance, combining MXenes with more stable nanomaterials could create composite structures that maintain the desired properties of MXenes while significantly improving their durability in challenging environments.[84,86,90]

3.3 Scalability and reproducibility

The syntheses of MXene-based microrobots consistently and at a scale suitable for clinical use remains a barrier. Variability aspects in production can lead to differences in performance and effectiveness, which could hinder regulatory approval processes. Furthermore, the integration of multifunctionalities into MXene-based microrobots can complicate their design as the incorporation of assorted nanomaterials for enhanced therapeutic effects requires precise engineering. However, advances in nanofabrication techniques, such as 3D printing or automated assembly lines, could pave the way for more efficient production processes. Balancing the mechanical stability, drug loading capacity, and responsive behavior of these microrobots is a complex task that demands advanced fabrication techniques and thorough optimization.

3.4 Targeting precision

There are two different mechanisms for preciously deliver the microbots toward their targets; engineering the structure of microbots *via* addition of magnetic particles or surface functional groups and mimicking from nature by the addition of artificial systems that provides autonomous movement. In this context, remote controllability and responsiveness have limitations in movements that make it important to use external controlled mechanisms—such as optical and magnetic actuation—to achieve to the dynamic navigation and rapid response. This magnetic field serves as an excellent external power source due to its ability to penetrate deep into human tissues while ensuring safety for biomedical applications.[91] Presence of magnetic compounds in the structure of these microbots not only provides them the capability of targeting toward a specific part in the presences of an external magnet, but also enable us for real-time monitoring of microbot using magnetic resonance imaging.[92,93] While magnetic fields can guide microrobots to specific locations, achieving high targeting accuracy in complex biological systems is not always straightforward. Tumor heterogeneity and the dynamic nature of biological environments can affect the microrobots' ability to reach their intended targets effectively. Achieving high accuracy in directing these microrobots to specific tissues or cells is vital for maximizing therapeutic benefits while minimizing side effects. However, several factors influence this precision, and addressing these challenges is crucial for advancing this technology. Notably, surface functionalization plays a critical role. By attaching specific ligands, antibodies, or other targeting moieties to the surface of MXene microrobots, researchers can enhance their ability to recognize and bind to target cells. Utilizing cell membrane, as coating, is another strategy for targeted delivery of microbots. This targeting mechanism allows for selective delivery of drugs, which could lead to more effective treatments. However, the choice of targeting agents must be carefully considered; improper selection may result in reduced specificity or unintended interactions with non-target cells.[94] Utilizing active targeting approaches could offer the capability of overcoming the limitations of non-active targeting methods particularly in target distribution and delivery efficiency, especially in atypical lesion sites with complex fluid dynamics *in vivo*. Meanwhile, to enhance targeted distribution, a perceptual sensing module and a control module could be integrated to the microrobots that provides the capability of controlled movement, allowing them to counteract natural body flows and achieve selective propulsion while enhance the retention time at the targeted site.[95] In this context, different types of targeting compounds have been introduced among them are ligands related to the cellular receptors (such as folic acid, transferrin, hyaluronic acid, *etc.*), peptides and proteins (like Arg-Gly-Asp (RGD) peptide), antibody, and aptamer.[96–100] Among these, targeting with aptamer is the most specific type that could target a specific marker of cancer cell and other compounds showed less specificity.

Environmental factors within the body can impact targeting precision. The heterogeneous nature of tumors, for instance, can lead to varying expression levels of target markers. This variability complicates the ability of microrobots to locate and attach to their intended sites. The strategies ought to be developed to account for these differences, possibly by incorporating multiple targeting mechanisms to increase the recognition rates. Furthermore, real-time tracking and monitoring of microrobots are necessary for ensuring targeting accuracy. Techniques such as imaging modalities or biosensors be able to provide valuable feedback on the location and behavior of microrobots in real time. This information can facilitate adaptive responses, allowing for adjustments in navigation or drug release based on the microrobots' positioning. Notably, the size and shape of microrobots are essential factors in targeting precision. Smaller microrobots may navigate more easily through biological fluids, while specific shapes can enhance their ability to penetrate tissues. Optimizing these physical

characteristics can improve the targeting capabilities of MXene-based microrobots.

3.5 Clinical translation studies

The clinical application of medical microrobots necessitates effective tracking, precise localization, and the ability to execute designated medical tasks at targeted sites. Achieving this requires the seamless integration of suitable design, actuation strategies, and advanced medical imaging systems within a single microrobot.[92] The clinical translation of MXene-based microrobots for targeted drug delivery and synergistic therapies faces a myriad of challenges that ought to be addressed to ensure successful implementation in healthcare settings. One of the primary hurdles is the translational gap between laboratory research and clinical applications.[101] While *in vitro* and animal studies may demonstrate promising results, replicating these outcomes in human subjects poses significant difficulties due to biological complexity and variability. Another critical challenge lies in the regulatory approval process. Navigating the intricate landscape of regulatory requirements can be daunting. The introduction of novel materials like MXenes in medical devices necessitates extensive safety and efficacy evaluations. Regulatory agencies often require comprehensive data on biocompatibility, manufacturing processes, and long-term effects, which can prolong the timeline for clinical trials. Moreover, the manufacturing scalability of MXene-based microrobots presents logistical concerns. Producing these microrobots in large quantities while maintaining consistency in quality and performance is essential for clinical use. The development of cost-effective methods for mass production, without compromising the unique properties of MXenes, remains a significant challenge. Notably, patient-specific factors also complicate clinical translation. Individual variations in anatomy, disease states, and responses to treatment be capable of influencing the effectiveness of targeted drug delivery. Personalizing therapies to accommodate these differences adds complexity to the design and implementation of clinical studies. To enhance the application potential of MXenes, it is essential to tailor their design based on the clinical requirements of specific applications which could be achieved through several approaches. Selecting different parent phases of MAX ($M_{n+1}AX_n$) allows for the adjustment of the M (metal) and N elements in the MXene structure, influencing its conductivity, magnetism, and photothermal properties. By carefully choosing the appropriate MAX phase and optimizing the synthesis process, MXenes with improved performance or unique functionalities can be developed. Once MXene-based biomaterials are designed with clinical applications in mind, extensive *in vitro* evaluations and *in vivo* animal studies are necessary to refine the system and pave the way for clinical trials. Additionally, to establish personalized treatment strategies, further research is required to elucidate the interactions between MXene-based materials, tissues, and cells.[47] Additionally, there are ethical considerations that arise when introducing new technologies into clinical practice. Ensuring informed consent, addressing potential risks, and managing patient expectations are crucial aspects that require careful planning and communication.

4. Future perspectives of MXene-based microrobots in (bio)medicine

The future of MXene-based microrobots in targeted drug delivery and synergistic chemo-photothermal therapy appears promising, driven by ongoing research and technological advancements:

4.1 Advancements in biocompatible materials

The improvement in biocompatibility as well as long-term toxicity studies are essential.[102] Future research needs to focus on understanding the long-term effects of MXenes and their derivatives on biological systems. By conducting comprehensive *in vitro* and *in vivo* studies, researchers be able to optimize these materials to minimize cytotoxicity while maximizing therapeutic efficacy. Researchers are conducting extensive tests to assess cytotoxicity, immune responses, and long-term effects on biological systems. These studies are essential for establishing safety profiles that will facilitate clinical translation.[24,71] Recent investigations into the biocompatibility and genotoxic effects of MXenes have revealed crucial insights, particularly regarding their impact on DNA integrity in cultured cells.[103] Despite their established low cytotoxicity, the potential genotoxicity of MXenes remains a significant concern. In a study aimed at addressing this issue, researchers loaded murine melanoma and human fibroblast cells with MXenes, specifically $Ti_3C_2T_x$ and $Nb_4C_3T_x$, and conducted a DNA comet assay to assess chromosomal DNA fragmentation.[103] As a result, both types of MXenes generated DNA comets, indicating a strong genotoxic effect. This finding suggests that while MXenes may be well-tolerated by cells in terms of cytotoxicity, they can still interfere with DNA integrity. Interestingly, the lateral size of the MXene flakes played a pivotal role in this process. Submicrometer-sized flakes were responsible for inducing DNA comets, whereas larger flakes did not exhibit the same effect. This highlights the importance of particle size in determining the biological interactions of MXenes. Furthermore, the study demonstrated that MXenes did not induce DNA comets in dead cells, reinforcing the notion that the living cellular environment is essential for observing these effects. Additional experiments revealed that extracting chromosomal DNA from MXene-loaded cells or mixing purified DNA with MXenes did not show any signs of DNA fragmentation. This observation suggests that MXenes do not directly damage DNA but may instead interact with live cells in a manner that leads to DNA cleavage. The mechanism behind the formation of DNA comets appears to be linked to the movement of submicrometer MXene flakes within cells under an electric field. The razor-sharp edges of these flakes likely contribute to DNA shredding, resulting in the observed fragmentation. Notably, under all other experimental conditions, titanium- and niobium-carbide-based MXenes exhibi-

ted excellent biocompatibility and did not display cytotoxicity or genotoxicity. Consequently, these findings may inform the development of innovative strategies for cancer therapy, utilizing the unique properties of MXenes. By understanding the mechanisms at play, researchers can explore ways to harness the beneficial aspects of MXenes while mitigating any potential genotoxic risks.[103]

Future research will likely focus on modifying MXene surfaces to improve their interaction with biological tissues. By developing coatings or functional groups, scientists can minimize potential toxicity and enhance cellular uptake. This step is crucial for ensuring the safe application of these microrobots in clinical settings. One notable advancement involves surface modification techniques to improve the biocompatibility of MXenes. By functionalizing MXene surfaces with biocompatible polymers, such as polyethylene glycol (PEG) or chitosan, researchers can create a protective layer that reduces cytotoxicity and enhances cellular interactions. This modification not only minimizes immune responses but also promotes cellular adhesion, facilitating better integration of microrobots within the human body.[104–106] Additionally, the exploration of natural materials is gaining traction. Future explorations ought to be focused on the incorporation of naturally derived biopolymers, such as alginate or hyaluronic acid, into MXene microrobots. These materials offer excellent biocompatibility and biodegradability, making them ideal candidates for medical applications. As an example, alginate can form hydrogels that encapsulate MXene microrobots, providing a protective environment while allowing for controlled drug release. Furthermore, advancements in the synthesis of MXenes themselves are contributing to their biocompatibility. Researchers are developing environmentally friendly synthesis methods that reduce toxic byproducts, making the production process safer. This focus on sustainability not only enhances the safety profile of MXenes but also aligns with the growing demand for eco-friendly materials in healthcare.[107] Moreover, the integration of smart materials into MXene-based microrobots is enhancing their functionality while maintaining biocompatibility.[108] Notably, incorporating stimuli-responsive hydrogels allows microrobots to release therapeutic agents in response to specific biological signals, such as changes in pH or temperature. This targeted approach ensures that drugs are delivered only when needed, further reducing the potential for side effects.

4.2 Advancements in biodegradable materials

Developing MXene formulations that degrade predictably within the body will enable controlled drug release, thereby improving treatment outcomes. Researchers are likely to explore combinations of MXenes with other biodegradable polymers or natural materials to achieve desired degradation profiles and biocompatibility. Notably, multifunctional microrobots will become a focal point for future research. Integrating various therapeutic modalities—such as chemotherapy, photothermal therapy, and even gene therapy—into a single microrobot could enhance the treatment efficacy.

4.3 Responsive materials

Future designs may incorporate responsive materials that activate under specific stimuli, allowing for tailored therapeutic responses to the tumor microenvironment.[109] The integration of responsive materials in MXene-based microrobots enhances their adaptability and functionality in biomedical applications. By utilizing hydrogels, shape-memory polymers, stimuli-responsive nanoparticles, and electroactive materials, these microrobots can perform targeted drug delivery, navigate complex biological environments, and respond intelligently to stimuli.[13] One of the most exciting categories of smart materials is shape-memory polymers (SMPs).[110] These materials can "remember" a predefined shape and revert to it when exposed to specific stimuli, such as heat or light. By integrating SMPs with MXene microrobots, researchers can design systems that change shape to navigate through intricate biological environments. For instance, a microrobot could compress to pass through narrow blood vessels and then expand to deliver a drug payload once it reaches its target site. Moreover, hydrogels are another promising smart responsive material. These hydrogels can swell or shrink in response to changes in pH, temperature, or ionic strength. When used in MXene microrobots, hydrogels can provide controlled drug release mechanisms. For instance, a hydrogel layer surrounding a microrobot could release therapeutic agents when it encounters the acidic environment typical of tumor tissues, enhancing targeted drug delivery while minimizing systemic side effects.[111] Notably, incorporating piezoelectric materials into MXene-based microrobots can enable them to convert mechanical energy from their environment into electrical signals.[112] This capability allows for the development of self-powered systems that can perform tasks without needing external power sources. For instance, these microrobots could harness the motion of body fluids to generate energy for on-demand drug release or monitoring functions.[45,113] Furthermore, stimuli-responsive nanoparticles can be embedded within MXene microrobots to enhance their functionality. These nanoparticles can react to various external factors, such as magnetic fields or ultrasound, allowing for precise control over the microrobots' movements. By utilizing magnetic fields, researchers can guide the microrobots to specific locations within the body while simultaneously triggering drug release through localized heating or other mechanisms. Additionally, MXenes themselves exhibit unique electrical and thermal properties, making them ideal candidates for responsive materials.[114] For instance, changes in temperature can alter the conductivity of MXenes, enabling real-time monitoring of environmental conditions or the detection of specific biological markers. This feature can be crucial for applications in diagnostics, where timely responses to physiological changes are necessary.[115]

4.4 Advanced imaging techniques

The incorporation of advanced imaging techniques will also be pivotal wherein studies may employ imaging modalities such as fluorescence, photoacoustic, or magnetic resonance imaging to monitor the movement and therapeutic effects of

MXene-based microrobots in real-time. Imaging technologies play a crucial role in enabling real-time monitoring, navigation, and diagnostics, thereby improving the overall efficacy of these innovative microrobots. One of the most promising imaging techniques is fluorescence imaging.[116] By functionalizing MXene microrobots with fluorescent dyes or tags, researchers can track their movement and interactions within biological systems. This capability allows for the visualization of microrobots as they navigate through tissues, providing valuable insights into their targeting efficiency and therapeutic effects. Moreover, fluorescence imaging can be combined with multiplexing techniques, enabling the simultaneous monitoring of multiple biomarkers or therapeutic agents. Another cutting-edge technique is magnetic resonance imaging (MRI). The inherent magnetic properties of MXenes make them suitable for enhancing MRI contrast.[117] By incorporating MXene-based microrobots into MRI systems, clinicians can obtain high-resolution images of targeted tissues or tumors. This application not only improves diagnostic accuracy but also aids in tracking microrobots during drug delivery procedures. The ability to visualize microrobot behavior in real time is critical for optimizing treatment strategies. Additionally, ultrasound imaging is gaining traction as a non-invasive technique for monitoring MXene microrobots. By using ultrasound contrast agents that can be integrated with MXenes, researchers can achieve high-resolution imaging of microrobot movement within the body. This technique offers several advantages, including real-time monitoring and the ability to provide functional information about blood flow or tissue perfusion, which is invaluable during therapeutic interventions. Moreover, photoacoustic imaging, which combines the high spatial resolution of optical imaging with the tissue penetration capabilities of ultrasound, is another exciting avenue.[118] MXene-based microrobots can be designed to absorb specific wavelengths of light, generating ultrasound signals when illuminated. This approach allows for precise localization of microrobots and can provide information about their interactions with biological environments, such as cellular uptake or drug release dynamics. Notably, the incorporation of imaging capabilities directly into MXene microrobots is an emerging trend. By embedding miniaturized imaging sensors, such as micro cameras or optical fibers, researchers can create self-monitoring microrobots capable of assessing their environment in real-time. This advancement could lead to autonomous systems that adapt their behavior based on the data collected during their operation.

4.5 The integration of intelligent systems

The integration of intelligent systems into MXene-based microrobots represents a transformative shift in their functionality and applicability. This convergence of advanced materials and smart technologies opens a plethora of opportunities, especially in the biomedical field. Incorporating artificial intelligence (AI) into microrobots enhances their autonomous decision-making capabilities.[119] Imagine a MXene microrobot programmed to navigate through the bloodstream, identifying and targeting specific cells or tissues. With AI algorithms, these microrobots can learn from their environment. They can adapt their strategies based on real-time data, ensuring efficient drug delivery or precise diagnostics. This adaptability is crucial for dynamic biological systems where conditions can change rapidly.

Machine learning techniques can optimize the operational performance of MXene microrobots. Machine learning algorithms (including deep learning and reinforcement learning) enable these microrobots to analyze sensor data in real time and adapt their movement on the fly. For instance, deep learning models can allow a microrobot to automatically identify and track specific targets in the body (such as a tumor or clot), which in turn enhances swarm coordination and environmental monitoring during a mission. By analyzing large datasets of biological interactions, these systems can predict the most effective paths for drug delivery or the best conditions for sensing. In dynamic biological environments like the bloodstream, AI-driven control helps the robot adjust to changing conditions (*e.g.*, blood flow or obstacles), ensuring it stays on course toward the intended site and delivers its therapeutic payload with high precision. Recent studies underscore how effective these AI navigation systems can be – using model-free reinforcement learning, microrobots have learned optimal paths through complex fluid channels, achieving near-100% success rates in reaching random target locations autonomously. This level of intelligent control is crucial for targeted drug delivery, as it minimizes off-target wandering and maximizes the time the robot spends at the disease site. This predictive capability allows for more precise and personalized medical interventions, ultimately improving patient outcomes. In addition, the integration of sensor technologies is a game changer. AI-based navigation also brings a degree of adaptive autonomy that outperforms purely manual or pre-programmed control. Sensors embedded within MXene microrobots can monitor physiological parameters, such as temperature, pH, or biomarker levels. MXene microrobots can be programmed to "sense and respond", altering their course or behavior based on local cues (such as chemical gradients or tissue boundaries). This real-time data collection enables continuous health monitoring, providing valuable insights for early disease detection. For instance, a microrobot could sense elevated glucose levels in diabetic patients, triggering insulin release precisely when needed. Comparative studies with other AI-integrated microrobot platforms show that this trend is not limited to MXene systems – magnetic helical swimmers, biohybrid bacteria-based robots, and others have all benefited from machine learning control for tasks like obstacle avoidance and path planning. What sets MXene-based microrobots apart is that they can merge this AI-driven intelligence with the unique material advantages of MXenes (such as their conductivity and stimuli-responsiveness, discussed below), resulting in an especially robust platform. Furthermore, communication capabilities can enhance the functionality of these microrobots. By enabling inter-robot communication, multiple microrobots can collaborate to achieve complex tasks. For instance, a swarm of MXene microrobots could work together to map out tumor locations or deliver a coordinated drug payload, maximizing treatment efficacy. However, challenges exist in the

integration process. Developing robust algorithms that ensure reliable performance in unpredictable biological environments is essential. Additionally, ensuring the security of data collected by these intelligent systems is paramount, especially in sensitive medical applications. This could also help in producing new types of MXene based microbots for the aim of treating other types of disease. For instance, microbots could offer a novel approach to treating diseases of the brain and nervous system by providing a way to cross biological barriers and deliver drugs to precise locations. One major challenge in neurology is effectively delivering therapeutics across the blood–brain barrier (BBB). Tiny robots, guided by magnetic fields or acoustic waves, could navigate through blood vessels and even penetrate the BBB to deliver neuropharmaceuticals. MXene microrobots could be functionalized to seek out pathological protein aggregates or inflamed neural tissue, opening possibilities for treating neurodegenerative conditions like Alzheimer's or Parkinson's disease. By ferrying medications or gene therapy vectors directly to affected neurons, these robots might enhance treatment efficacy while limiting systemic side effects, which is especially valuable in the delicate context of the brain. In cardiovascular medicine, microrobots could transform how we treat conditions like thrombosis, atherosclerosis, or heart failure. Because they can navigate through even the smallest blood vessels, microrobots are ideal for seeking out and treating problems within the circulatory system. The photothermal feature of MXene along with its ability to carry anti-clotting drug could be used in future research for opening the blocked coronary artery. The precision of such devices promises to reduce damage to healthy tissue and avoid the risks of large systemic drug doses. They could also be applied for the treatment of different types of infected diseases through selectively attached to the infection part, penetrating into the biofilm, and destroying the microbial contamination. The small size and maneuverability of MXene-based microrobots make them attractive for regenerative therapies and microsurgical procedures. They could offer real-time imaging to ensure the payload is delivered to exactly the right spot, and perhaps even create a favorable microenvironment (through localized heating or electrical stimulation) to promote cell engraftment. As for minimally invasive surgeries, microrobots could take on tasks that currently require complex surgical navigation. For instance, in endoscopic surgery a microrobot could leave the endoscope channel to navigate a small cavity or vessel on its own, guided by an external magnetic field and onboard AI, to perform a micro-scale intervention – such as excising a tiny tumor fragment, cauterizing a bleeding micro-vessel, or taking a biopsy from deep within an organ. MXene-based robots, with their multifunctionality, would allow the same device to cut (using a laser activated by the MXene photothermal effect), visualize (by providing contrast for imaging), and cauterize or disinfect (by heating) all at once. Although these scenarios remain conceptual for now, but they highlight the expansive potential of MXene microrobots beyond oncology, ranging from targeted drug and cell delivery in degenerative diseases to serving as autonomous surgical tools that could access regions of the body that surgeons cannot easily reach today.

4.6 Advancements in targeting strategies

Researchers are expected to investigate novel targeting ligands or surface modifications that improve the affinity of microrobots for cancer cells. One significant development is the use of biomolecular recognition elements. By functionalizing MXene surfaces with antibodies, peptides, or nucleic acids, researchers can create microrobots that specifically target disease markers, such as cancer cells or pathogens.[120,121] This selective binding increases the likelihood of effective drug delivery, reducing off-target effects and enhancing therapeutic outcomes. For instance, MXene-based systems coated with antibodies against a tumor-specific antigen can navigate through the bloodstream and selectively bind to cancer cells, delivering a payload directly to the site of action.[122] Additionally, the incorporation of pH-sensitive or enzyme-responsive elements further refines targeting strategies. MXene-based microrobots can be designed to release therapeutic agents in response to the unique microenvironment of diseased tissues. For instance, the acidic pH typical of tumor sites can trigger the release of drugs from microrobots, ensuring that treatment is administered precisely where it is needed while sparing healthy tissues.[123] Moreover, researchers are exploring the application of magnetic targeting.[123] MXene microrobots, being magnetic, can be guided through the body using external magnetic fields. This approach allows for real-time navigation and positioning of microrobots, ensuring they reach specific locations within the body. By combining magnetic targeting with biomolecular recognition, the efficiency of drug delivery can be significantly improved. The development of "smart" microrobots that can respond to multiple stimuli is another exciting advancement. These microrobots can be engineered to not only detect specific biomarkers but also respond to changes in temperature, light, or other environmental factors. This multifaceted approach allows for enhanced precision in targeting and treatment delivery, adapting to the dynamic nature of biological environments.[124,125] Future studies should be conducted on the incorporation of imaging capabilities into MXene-based microrobots to enhance targeting strategies. By integrating optical or ultrasound imaging technologies, these microrobots can provide real-time feedback on their location and interactions within the body. This capability enables clinicians to monitor treatment progress and make necessary adjustments in real time, optimizing therapeutic outcomes.

5. Conclusion

MXene-based microrobots represent a groundbreaking advancement in the domains of targeted drug delivery and synergistic chemo-photothermal therapy. Their unique properties, comprising excellent biocompatibility, photothermal conversion efficiency, and biodegradability, position them as promising candidates for innovative cancer treatments. Recent advancements in nanomaterial integration, such as the use of novel composites and coatings, have shown promising results

in enhancing the therapeutic effects of MXene-based microrobots. These developments underscore the potential of these microrobots to advance cancer treatment by providing targeted, efficient, and personalized therapies. However, several lingering challenges ought to be addressed to facilitate their successful clinical application. Key concerns include cytotoxicity, where the long-term effects of MXenes on biological systems require thorough investigation; biodegradation, necessitating the development of controlled degradation profiles that align with therapeutic needs; and the scalability of production, which must ensure consistent performance for clinical use. Furthermore, the integration of multifunctionalities into these microrobots poses engineering challenges, as does achieving high targeting precision in complex biological environments. Additional explorations on biocompatibility and toxicity will guide the optimization of these materials for safe and effective usage in patients. The development of biodegradable formulations will enable controlled drug release, while advancements in multifunctional microrobot designs will allow for the simultaneous delivery of various therapeutic modalities. Improved targeting strategies and the incorporation of advanced imaging techniques will further enhance the precision of these innovative devices, enabling real-time monitoring of treatment efficacy. Notably, the clinical translation of MXene-based microrobots for targeted drug delivery and synergistic therapies is fraught with challenges ranging from regulatory hurdles to manufacturing scalability and patient variability.

Author contributions

Siavash Iravani: supervision, conceptualization, writing – review & editing, drafted section 1, 2.2., and 2.3; Atefeh Zarepour: writing – review & editing, drafted section 2.1; Arezoo Khosravi: visualization, writing – review & editing, drafted section 2.1; Rajender S. Varma: writing – review & editing, drafted section 2, 2.3, and part of section 2.1; Ali Zarrabi: supervision, writing – review & editing, drafted section 2.1.

Data availability

No data was used for the research described in the article.

Conflicts of interest

Author(s) declare no conflict of interest.

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