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PERSPECTIVE

Microrobots for Biomedicine: Unsolved Challenges and Opportunities for Translation

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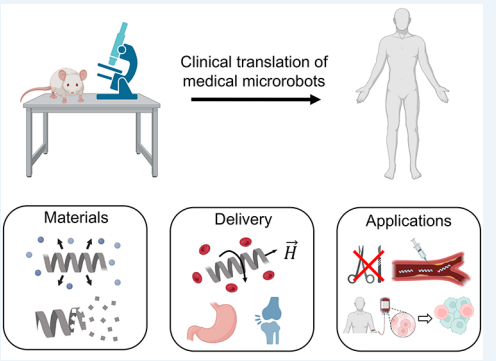
ABSTRACT: **Microrobots are being explored for biomedical applications, such as drug delivery, biological cargo transport, and minimally invasive surgery. However, current efforts largely focus on proof-of-concept studies with nontranslatable materials through a "*design-and-apply*" approach, limiting the potential for clinical adaptation. While these proof-of-concept studies have been key to advancing microrobot technologies, we believe that the distinguishing capabilities of microrobots will be most readily brought to patient bedsides through a "*design-by-problem*" approach, which involves focusing on unsolved problems to inform the design of microrobots with practical capabilities. As outlined below, we propose that the clinical translation of microrobots will be accelerated by a judicious choice of target applications, improved delivery considerations, and the rational selection of translation-ready biomaterials, ultimately reducing patient burden and enhancing the efficacy of therapeutic drugs for difficult-to-treat diseases.**



INTRODUCTION

Microrobots are micron-sized objects that carry out programmable actions such as sensing,[1] object manipulation,[2] and enhanced navigation[3] when powered by external fields or environmental sources. Common strategies to power microrobots include external fields, such as magnetic,[4] acoustic,[5] and electric fields,[6] and environmental sources, such as chemical reactions[7−9] and biological signals.[10] Due to their programmable action, the small size of microrobots enables their use in traditionally difficult-to-reach environments, such as blood vessels, cavities, and confined porous media (i.e., cortical bone,[11] mucus,[12] and extracellular matrix[13]) found within the human body. Moreover, forces acting on microrobots powered by external fields are significantly greater than those acting on nanoparticles, allowing them to reach target sites effectively.[14−16] This bestows microrobots the potential to revolutionize minimally invasive medicine and the targeted delivery of therapeutic agents.

Despite the immense promise of medical microrobots, there has been limited translation of these technologies from the lab bench to preclinical or clinical settings. We believe this is because the community has primarily focused on a small portion of the major challenges associated with this emerging technology, shying away from the more practical challenges required to move microrobots to clinical settings. It is often claimed that increased robot intelligence, more advanced materials, and higher resolution imaging are the key challenges that remain. However, designing microrobots that address these issues promotes the development of laboratory-specific toolboxes for problems that may not necessarily address the actual clinical needs. More importantly, this focus lends itself toward continued proof-of-concept studies, such as demonstrating enhanced maneuverability, resulting in technologies that are not practical in clinical scenarios (e.g., remote surgery, *in situ* sensing, and biopsy collection).

While there is utility in proof-of-concept studies that advance our knowledge, highlight the functionality of medical microrobots, and provide solid groundwork for future advancements, we believe that the key to clinical translation is shifting our collective focus toward addressing disease states that lack efficacious treatments. This requires (i) shifting scientific effort to address more realistic biomedical applications, (ii) developing application-specific microrobot delivery requirements, and (iii) using materials with the necessary properties (e.g., degradation, clearance, and immune interactions) for clinical feasibility. Finally, each of these steps must be accompanied by earlier and more frequent communication

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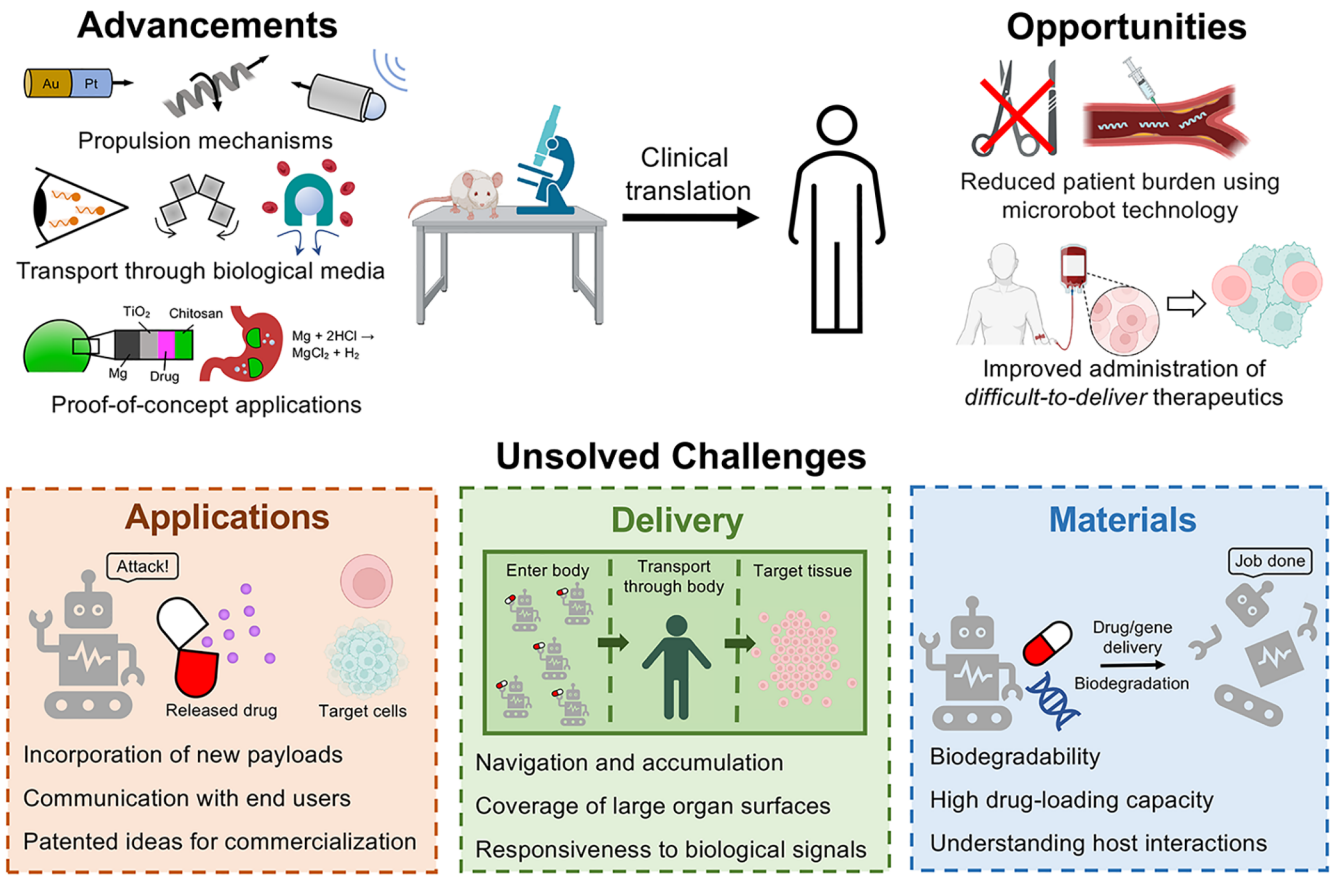

Figure 1. Advancements, opportunities, and unsolved challenges for the clinical translation of medical microrobots. Some parts of this figure were made with BioRender.

with clinicians and end users to help shepherd medical microrobots from the lab to the bedside and improve current treatment outcomes.

In this Perspective, we outline what we identify as the most important advancements, opportunities, and unsolved challenges in three different aspects of translating microrobots from proof-of-concept studies to clinical applications (Figure 1). First, we articulate which biomedical applications are most ready for microrobots, focusing on use cases that can be tested in biologically relevant environments and take advantage of the strengths of microrobots for ailments that currently lack effective treatments. Second, we discuss the negative consequences of prioritizing studies that focus on single particle locomotion instead of improving the localization or dispersion of microrobots *in vivo*. Lastly, we detail how advances in materials chemistry from the drug delivery community can be used to accelerate the clinical translation of microrobots.

APPLICATIONS

The revolutionary capabilities of microrobots have sparked a flurry of scientific research aimed at pushing the boundaries of biomedical research. Advancements in propulsion science, materials engineering, and fluid mechanics has enabled engineers and scientists to create microrobots with a suite of functionalities.[17−24] Such functions include transporting living cells and other biological cargo, moving through complex heterogeneous biological media, providing targeted and controlled drug delivery,[26,27] offering switchable control over modes of locomotion,[28,29] and enabling *in vivo* imaging.[30] These advancements have fueled proof-of-concept studies in areas such as ocular drug delivery,[14] *in vitro* fertilization,[25] root canal prevention,[31] and tumor treatment,[4] among others. Additionally, some theoretical and experimental studies have shown the propulsion of microrobots in non-Newtonian environments to highlight their potential for use *in vivo*.[15,32]

Despite this, most of the medical microrobots developed to date have focused on proof-of-concept applications under controlled benchtop conditions while claiming improbable applications. We believe the origins of these limitations for translation are due to the "*design-and-apply*" approach that is commonly employed, which focuses on the fabrication and propulsion of microrobots under nonphysiological settings. This approach highlights only the potential for microrobots; it seldom solves a practical and unmet clinical need. Thus, to go beyond the bench toward useful applications in humans, we propound that medical microrobots must be developed using a "*design-by-problem*" approach (Figure 2).

To apply a "*design-by-problem*" approach, microrobots should first and foremost be designed to solve biomedical problems that lack effective options and can be overcome by leveraging the specific strengths of the microrobots. For example, to use microrobots for cancer treatment, they must carry therapeutic agents and penetrate the tumor stroma and cellular junctions.[33] This capability is difficult to achieve with traditional nanoparticles alone. While nanoparticles have shown utility in biomedicine as therapeutic delivery vehicles,[34−37] they rely on passive diffusion or circulation for

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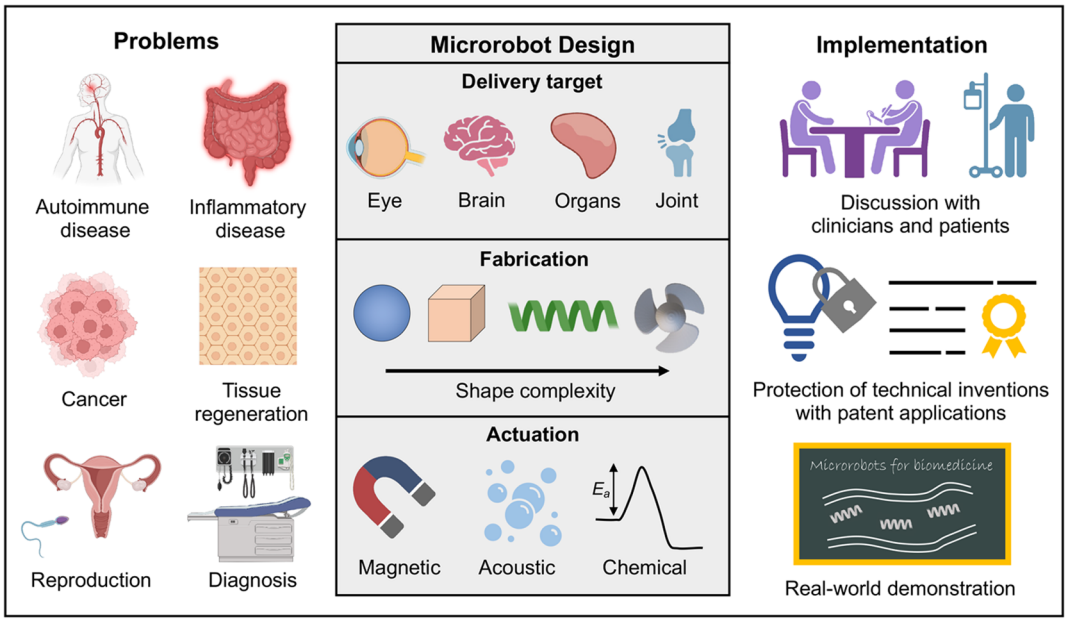

Figure 2. Medical microrobots design approach for real-world applications. Some parts of this figure were made with BioRender.

transport, subjecting them to both physical and biological barriers that limit their delivery efficiency to places like solid tumors (i.e., only ≈0.7% of systemically injected nanoparticles reach solid tumors).[38] Thus, designing microrobots with specific transport capabilities will be necessary for many biomedical applications to avoid biological filters. Moreover, once microrobots enter *in vivo* environments, the adsorption of macromolecules on their surfaces leads to protein corona formation that may influence their propulsion, interactions with target cells, degradation, or internalization by phagocytes.[39] Therefore, a tailored microrobot design to maintain stability and function after *in vivo* administration should be addressed. While judicious material choices can be employed to offset this issue, transport and actuation mechanisms that may be inhibited by such biological interactions should be avoided. This illustrates the need for greater communication across research disciplines; for example, collaboration between materials scientists, physicists, and immunologists would promote an understanding of the limitations associated with multiple aspects of microrobot design. For synergistic problem solving to occur, researchers must be willing to communicate the strengths and limitations of their approaches across disciplines both frequently and candidly such that collaborations can be more easily forged.

Another challenge for the clinical translation of medical microrobots is to drive propulsion at high Reynolds numbers. Intravenous injection of microrobots will initially result in convection-dominated transport, yet most proof-of-concept studies are performed at low Reynolds numbers.[40] Thus, the route of administration should be carefully considered to avoid navigation in areas of fast flow, such as the cardiovascular system. These considerations should also inform the intended application of medical microrobots. For example, microsurgery or remote biopsy may be heavily impacted by flow conditions that make precise control difficult. When considering the administration of medical microrobots in clinical settings, the methods used should avoid exposure to regions with high fluid flows when possible as this may result in limited control over where the microrobots accumulate. Some promising focus areas we identify include creating microrobots with a high drug loading capacity,[41] controlling drug release rates *in vivo*,[42] maximizing microrobot retention time,[43] and selecting administration routes with minimal travel requirements.[44]

DELIVERY

The delivery and transport of microrobots are other key aspects of their potential use in biomedical applications (Figure 3). Microrobots must be delivered to the correct area in the body, with the correct number density, at the correct time. This task is complicated by the complexity of the biological environments that microrobots may encounter. During transport, microrobots must often move through tortuous networks filled with complex fluids, penetrate biological tissues, and respond to interactions from other micron-sized objects such as cells.[45−47] These challenges have compelled researchers to focus on building single microrobots that can move through increasingly complex environments with high resolution. However, such capabilities are far less useful when the clinical application involves driving thousands to millions of robots through tortuous 3D pathways within the body.

In this respect, several microrobots have been proposed to offer high resolution maneuverability in complex environments.[15,28,48−51] While this problem is interesting from a fundamental perspective and will enable future studies on directing the motions of multiple microrobots, single microparticle maneuverability in a complex physiological environment is not applicable to most biomedical tasks. Applications such as medical catheterization, stent placement, and clot clearance do require precise single particle manipulation;[52,53] however, many proposed applications such as remote biopsy, surgery, and sensing are likely infeasible given the current capabilities of microrobots, meaning that a focus on such applications will only hinder clinical translatability. To motivate translatable efforts, we believe that a greater emphasis should be placed on their use in drug delivery, an application that will more readily bring microrobots to the bedside and eventually lead to other applications.

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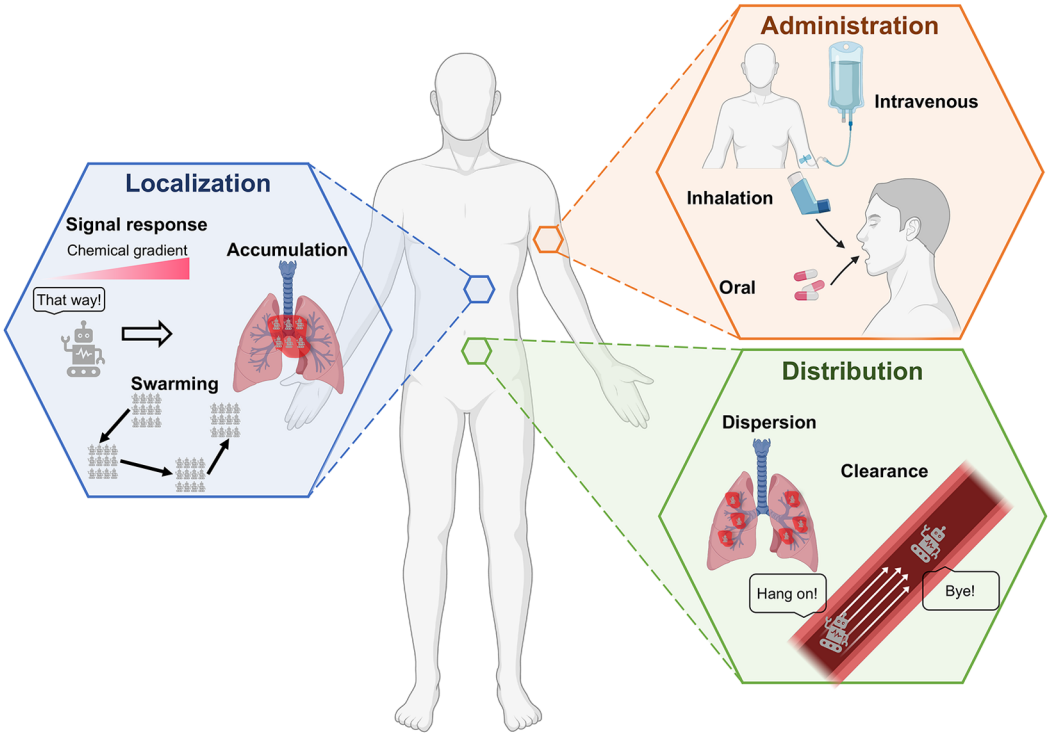

Figure 3. Considerations and strategies for the delivery of microrobots *in vivo*. Some parts of this figure were made with BioRender.

The delivery of therapeutic payloads takes advantage of the ability of microrobots to enhance the localization and release of drugs. In this way, an ideal microrobot system for drug delivery must be able to (i) migrate to the region of interest with high specificity and (ii) disperse itself within that region. These functionalities are nontrivial. First, the transport of multiple microrobots to the desired region must be considered. Similar to single microrobot transport, biological barriers, complex fluids, and innate clearance mechanisms make it difficult to maneuver to and sustain many microrobots within a region of interest. Additionally, there is often the challenge of determining where the region of interest is located (e.g., the precise location of a neoplastic tumor). One promising mechanism to address this challenge is using microrobots that can home into the regions of interest by responding to inherent chemical signals such as chemokines. Alternatively, to circumvent these issues, researchers could address medical ailments that reside in well-defined regions of the body, where microrobots have proven transport capabilities. This could include the gastrointestinal tract,[54] reproductive system,[25] bladder,[43] lungs,[55,56] and eye.[14] These environments are all easily accessible through noninvasive means, enabling facile dispatching.

Despite the challenges associated with using microrobots to deliver drugs, opportunities are plentiful and careful implementation could create drug delivery systems that greatly improve patient outcomes. One exciting opportunity is in the development of microrobots that can respond to signals released from target areas in the body by creating cell-microrobot complexes.[4,57] These complexes take advantage of the chemotactic capabilities of cells and may enhance the localization of microrobots at target sites. Another promising opportunity to accelerate the therapeutic efficacy of microrobots is the use of robotic swarms.[55,58−60] Swarming allows for the localized movement of large amounts of microrobots, which could improve both imaging capabilities and payload delivery.[61] One final opportunity is to engineer microrobots that remain at target sites by utilizing microrobots with high surface areas,[62] adhesive surface coatings,[63] or responsiveness to stimuli to promote robust physical interactions with target tissues,[43,64] to better tolerate biological clearance mechanisms, such as strong fluid flow.[43,64,65]

We also believe that there is an opportunity to show that microrobots perform in a manner superior to traditional micro- or nanoparticles in drug delivery, something that has not yet been adequately investigated by the community. By showing that microrobots can accumulate at target sites better than traditional (nonactive) particle systems and provide better mechanisms for controlling the release of drugs within those target sites, microrobots may be poised as a top contender for particle-based drug delivery systems.

MATERIALS

The persistence of microrobots at target sites depends on the method of administration and their final delivery location. Use of microrobots in areas that involve direct clearance mechanisms (e.g., the bladder, where microrobots attached to the epithelial lining can be shed and excreted through urination,[43] or the lungs, where coughing or mucociliary action can eject microrobots through the trachea[66]) allows for use of materials that are biocompatible but not biodegradable.[43,67] In contrast, applications in regions where microrobots cannot be reliably cleared by phagocytosis or excretion (e.g., solid tumors, where microrobots can be trapped to dense tissue microstructures, or in the bloodstream, where large microrobots cannot undergo digestion in phagosomes or kidney filtration) are common.[68−71] In these systems, nonbiodegradable microrobots are unusable. Despite the necessity of biodegradability for many biomedical applications, current

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Table 1. Biodegradable Polymers for Microrobot Fabrication

material	degradation	immune effects	FDA approval	fabrication methods	notes
Poly(lactic-co-glycolic acid) [PLGA]	Bulk hydrolysis 1−6 months	Inert	Yes	Emulsion, molding	Degradation rate controlled by LA to GA ratio[85,86]
Poly(β-amino ester) [PBAE]	Surface, then bulk, hydrolysis 1−2 years; 1−45 days modified	Inert	No	Emulsion, molding, photolithography	Acrylate modification necessary for photocuring; suitable for gene delivery due to positive charges[74,87]
Polyhydroxyalkanoate [PHA]	Surface hydrolysis and enzyme-mediated degradation 6 months to 2 years	Minimally inflammatory	Yes (poly[4-hydroxybutyrate] only)	Emulsion, molding	Produced by bacterial fermentation[88−90]
Polycaprolactone [PCL]	Bulk or surface hydrolysis (end-group dependent) 1−2 years	Inert	Yes (without modifications)	Emulsion, molding, photolithography	Methylacrylate modification necessary for photocuring[91,92]
Poly(glycerol sebacate) [PGS]	Surface hydrolysis 2 months	Minimally inflammatory	Yes (reactants [glycerol, sebacic acid-containing polymers] only)	Emulsion, molding, photolithography	Acrylate modification necessary for photocuring[93−96]
Polydioxanone [PDS]	Bulk hydrolysis 1−6 months	Minimally anti-inflammatory	Yes	Emulsion, molding	Commonly used as a copolymer[97,98]

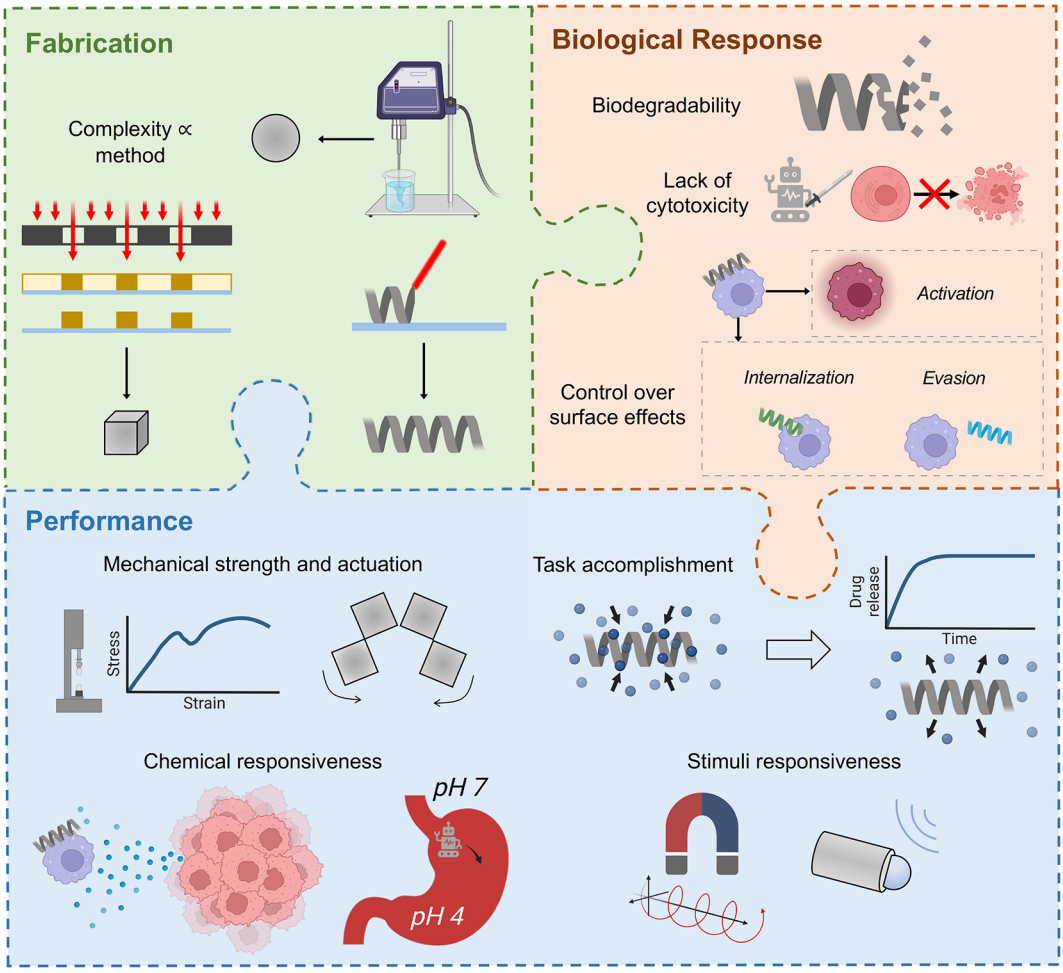

Figure 4. Considerations for selecting or designing materials for microrobots. Some parts of this figure were made with BioRender.

efforts continue to focus on designing proof-of-concept microrobots with nonbiodegradable components, limiting their potential for *in vivo* testing. While proof-of-concept studies are useful for establishing feasibility, a greater emphasis must be placed on moving past such systems developed with nonbiodegradable materials and toward *in vivo* testing with translation-ready biomaterials.

Innovations in drug delivery systems over the last several decades provide a foundation for implementing biodegradable materials into microrobots. Using drug delivery materials that have already been clinically investigated (e.g., polyesters, phospholipids, polysaccharides) will allow for accelerated translation due to FDA approval and the wealth of supporting literature.[72] However, fabrication techniques compatible with most of the materials used for drug delivery tend to limit the

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ACS Nano XXXX, XXX, XXX−XXX

complexity of particles that can be fabricated (e.g., spheres, discs, or ellipsoids).[57,73] Particle designs that can undergo complex transport, such as helices or particles with well-defined cavities, require the use of high-resolution lithography. Therefore, there is a critical need for simple, robust, and tunable materials that are biodegradable and photocurable.[74]

Alternatively, multistep fabrication techniques such as molding/templating can be implemented to formulate microrobots from nonphotocurable materials. Molding allows for the use of nonbiodegradable materials to form negative shapes with high complexity, followed by backfilling with the desired biodegradable material. This approach may enable the rapid use of biodegradable materials that are nonphotocurable, but it requires careful consideration of solvents and often has limited throughput compared to lithographic methods.[75−78] One notable exception is the particle replication in nonwetting templates (PRINT) method, a high-throughput fabrication process for generating complex particles for drug delivery, which demonstrates the potential for clinical translation of molding methods.[79] While molding is a highly enabling process for the use of many common drug delivery materials, the need for photocurable drug delivery materials remains due to the resolution, reliability, and scalability of lithographic techniques. A comprehensive review of modern fabrication techniques can be found elsewhere.[80]

Hydrogels with photocurable linkers have been widely used for implants and in tissue engineering, and there are some examples of their successful use in microrobotics.[19,81−83] However, applications of microrobots made from hydrogels are limited due to the swelling and relatively low mechanical strength of hydrogels. Given the challenge of designing biodegradable materials that enable complex task performance, we list a handful of synthetic polymers from the drug delivery and tissue engineering communities that are promising for making microrobots due to their history of use, biodegradation, hydrophobicity, and photocurable properties (Table 1). Natural materials such as polysaccharides, lipids, and extracellular matrix proteins, while also promising for the clinical translation of microrobots, have been described elsewhere.[72,84]

In addition to these bulk materials, care must be taken to ensure that stimuli-responsive moieties used in microrobots (e.g., magnetic handles or catalytic patches) are biodegradable or at least biocompatible, such as using iron oxide for imparting magnetic responsiveness instead of cobalt.[99,100] Materials considerations for the fabrication, biological response, and performance of microrobots are summarized in Figure 4.

We anticipate that drug, gene, and cell delivery will be one of the earliest opportunities for translating microrobots. As such, the physical properties of the drug and manner by which it is incorporated into the microrobot are critical materials consideration. Drug loading capacity of small molecules, proteins, and nucleic acids in common drug delivery systems have been described elsewhere.[101] Hydrophobic small molecules are one of the simplest therapeutic modalities to incorporate due to their stability in organic solvents and compatibility with many types of polymers; however, gene delivery, although more difficult, is an increasingly important therapeutic strategy that should be investigated for a range of disease types that are not treatable by other methods.[102] For example, delivery of genes requires physical insertion into cells, making nonviral gene delivery a suitable target application for microrobots due to the potential for actuation-guided gene insertion.[103] As such, strategies for transporting and delivering genes by microrobots should be prioritized.

For both cell delivery and other applications, exploiting materials immunogenicity may be a way to confer advantageous immune responses without the use of drugs or synergistically with drug release. Both the materials used for fabricating microrobots and their degradation products may provide some degree of immunomodulation, such as a proinflammatory response, which may be useful in treating diseases, such as cancer. Often, immune activation is avoided (e.g., by inert surface coatings),[81] where the aim is to prevent unwanted immune activation or premature clearance of microrobots. Instead, judicious materials selection may enable control over immune cell activation for a therapeutic benefit; a similar approach has been demonstrated through the use of cell membrane particle coatings.[69] This design choice may allow for the use of a wider range of materials that were previously avoided due to unwanted immune effects. The opportunity for drug and gene delivery, as well as therapeutic material−cell interactions, should be leveraged to design medical microrobots with multiple therapeutic functionalities.

CONCLUSION

Microrobots are a budding technology with the potential to mold the future of minimally invasive medicine and drug delivery. Recent work has illustrated the potential of microrobots to accomplish challenging biomedical tasks such as targeted drug release, cell transport, and advanced imaging. Despite the competencies of microrobots, limited effort has been made to facilitate their translation to the bedside. This is due to the "*design-and-apply*" approach often taken, where *in vitro* proof-of-concept studies have been favored over deliberate pushes to preclinical and clinical trials through *in vivo* studies with translational materials. This can be overcome by applying a "*design-by-problem*" approach instead, wherein the intrinsic capabilities of microrobots are used to enhance the efficacy of treatments for diseases that currently lack effective treatment options. To accomplish this, researchers should prioritize feasible applications, consider the dispersion of microrobots *in vivo*, and use material advancements from the drug delivery community to prepare translation-ready microrobots. One hurdle that may inhibit the adoption of a "*design-by-problem*" approach is a lack of funding sources and incentives to motivate researchers in basic science and clinical settings to take on developmental challenges that are often considered incremental by funding agencies, academic institutions, and research journals. This might be alleviated by increased partnership with industry, wherein both monetary support and the motivation to translate technologies to patients will be more readily available. Microrobots designed with these principles will have numerous advantages that will support their clinical translation and may result in their widespread adoption in targeted drug delivery, *in vivo* imaging, and a collage of other applications.

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Notes

The authors declare no competing financial interest.

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ACS Nano XXXX, XXX, XXX−XXX