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Viewpoint

Biohybrid Microrobots for Enhancing Adoptive Cell Transfers

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Cyborgs, or cybernetic organisms, are depicted in science fiction as characters that perform tasks that are too difficult or dangerous for humans. These beings represent a portmanteau of man and machine, typically possessing electrical or mechanical augmentations that enable superhuman abilities. Such enhancements include robotic appendages or infrared vision that give rise to increased strength, speed, agility, or intelligence. Through advances in microscale robotics and adoptive cell transfers, scientists have likewise begun to blur the lines between fiction and reality by creating cell-based biohybrid microrobots (Figure 1).

Microrobots refer to microscale particles that have the capacity to transduce energy from their environment or externally applied fields and locally dissipate that energy through mechanical reconfigurations or active locomotion. The use of microrobots in medicine has quickly gained popularity, particularly as autonomous drug delivery vehicles and biosensors.[1,2] As the field of active particles has matured, scientists have begun to create microrobots with new designs and compositions that enable actuation by various means, including acoustic fields, magnetic fields, light, and biochemical cues such as enzyme concentration or pH.[3] These microrobots move by harvesting and locally dissipating energy, allowing them to overcome biological barriers such as mucosa, endothelial cell linings, or the dense stroma of solid tumors. Most active particles are designed to deliver simple drugs such as small molecules (e.g., chemotherapeutic drugs) or macromolecules (e.g., antibodies, antigens, cytokines). The next frontier of this field is to use active particles to deliver living cells by focusing on situations where adoptive cell transfers currently fail to perform at their best.

Adoptive cell transfers (ACTs) describe the administration of living cells into patients as a therapy. ACTs have been used clinically for various indications, including cancer, infectious disease, and autoimmune disorders.[4] In most cases, the cells used in ACTs are derived from the immune system and are engineered to enhance the ability of the body to treat itself. A flagship example is chimeric antigen receptor (CAR) T cell therapy, whereby lymphocytes are genetically modified to express a CAR against a tumor-associated antigen (e.g., CD19 for B cell lymphoma).[5] A distinguishing feature of ACTs is that they are a living drug, in contrast to other treatments (e.g., chemotherapies). This characteristic allows cells to interact with specific tissues in a manner that is dynamic and potentially controllable. Another major advantage of ACTs is that they can be personalized to the patient of interest, allowing them to target and interact with a specific form of a disease to increase effectiveness and reduce side effects.

Engineers in the field of nanomedicine have increasingly shown interest in ACTs for two key reasons. First, due to the unique ability of cells to navigate the body and infiltrate specific tissues, ACTs have been employed to deliver nanoparticles to sites of interest with higher specificity compared to nanoparticles alone. By administering cells loaded or decorated with nanoparticles containing high-value drugs, these drugs can achieve higher concentrations in sites of interest, thereby enhancing therapeutic efficacies and reducing off-target toxicities. Second, in scenarios where cells encounter challenges in reaching or maintaining their presence at target sites, particles in the form of microrobots can improve the transport of cells. This is particularly useful for transporting engineered cells, such as transfected, gene-altered, or temporally stimulated cells. In the following sections, I discuss how these "cyborgs" or cellular biohybrid microrobots can improve the performances of adoptive cell transfers in a range of medical scenarios.

CELLS AS PARTICLE DELIVERY VEHICLES

For decades, researchers have developed nanoparticles to package drugs and contrast agents for systemic administration.[8] A handful of these nanoparticles have advanced to clinical trials for cancer treatment, wound healing, and medical imaging. However, many nanoparticle systems fail to advance to or beyond clinical trials due to poor biodistribution from a low accumulation in target tissues. In the case of cancer, a landmark meta-analysis published in 2016 found that only 0.7% of injected nanoparticles reach solid tumors.[9] This poor efficiency was consistent across a range of nanoparticle sizes, compositions, and surface modifications. This basic transport limitation has catalyzed interest in using immune cells as delivery vehicles (Figure 1a). Unlike nanoparticles, immune cells respond to inflammatory signals by way of chemotaxis. Immune cells express chemokine receptors that, when triggered by specific chemokines, can initiate a cascading mechanism within the cell to intravasate to the source (i.e., for positive chemotaxis) by rolling, crawling, and extravasating. These chemokines are

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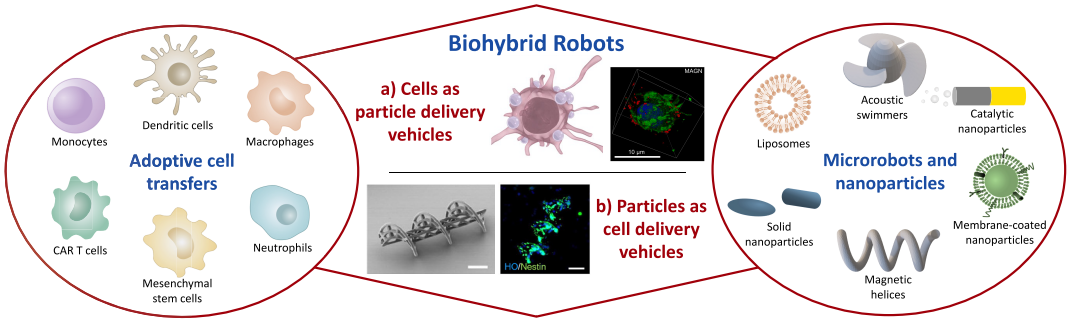

Figure 1. Cell-based biohybrid microrobots. Biohybrid robots incorporate adoptive cell transfers and particles. They are organized into two categories: (a) cells used as particle delivery vehicles and (b) particles used as cell delivery vehicles. An example of (a) is shown with a macrophage coated with nanosponge metal-phenolic network particles for treating metastatic cancer. Scale bar, 10 μm. Reproduced with permission from ref 6. Copyright 2023 The Authors. An example of (b) is shown with a helical microparticle for carrying mesenchymal stem cells. Scale bars, 40 μm. Reproduced with permission from ref 7. Copyright 2019 The Authors.

biochemically diverse, originating from different stimuli (e.g., cuts, wounds, infections) and attract specific populations of immune cells with distinct activation states.

Using cells as carriers for delivering nanoparticles to diseased tissues offers several advantages over administering nanoparticles alone. First, cells can be engineered to target specific tissues or organs in the body (e.g., tumors),[10,11] allowing for the improved delivery of nanoparticles to diseased sites. Second, cells can extend the circulation time of nanoparticles in the body and enhance their retention, improving treatment effectiveness. Third, delivering nanoparticles within cells can reduce their toxicity, as the cell membrane can act as a protective barrier against the nanoparticles interacting with healthy tissues. Last, cells can participate in the therapeutic effect. This was demonstrated by Samir Mitragotri's research group, where cellular backpacks on macrophages released IFN-γ to stimulate both the cells to which the backpacks were bound and neighboring cells in solid tumors.[12] Moreover, the use of cells to deliver nanoparticles can facilitate immunomodulation, as the cells themselves can modulate the immune microenvironment, thereby potentially enhancing the effectiveness of the nanoparticles.

While this field is still in its early stages, the potential for using chemotactic cells to transport therapeutic nanoparticles is promising. Researchers have already started investigating the use of cells for carrying magnetostrictive antennas, enabling wireless operation in applications such as remote sensing, modulation, and power-harvesting.[13] It is also worth noting that cells without inherent chemotactic abilities (e.g., red blood cells) can be used for delivering nanoparticles to areas such as lung metastases for systemic tumor suppression.[14]

MICROROBOTS AS CELL DELIVERY VEHICLES

In contrast to cells serving as delivery vehicles, microrobots are being explored as vehicles for transporting cells (Figure 1b).[15] While cells are excellent carriers in many situations, they face formidable challenges in others. For example, cellular chemotaxis may be hindered if the particle payload is sufficiently large. In such cases, microrobots can assist in providing greater mobility. Also, in applications where cells must cross challenging barriers, such as dense mucosa or the blood–brain barrier, microrobots can provide the necessary power to help cells through. Lastly, for applications that require delivery to an exact location, such as transfection or fertilization, microrobots can guide cells with precision at the single-particle level.

Microrobots have been used to aid the transport of various cell types for different physiological indications. One of the earliest examples, which has since been further developed, is the use of magnetic microhelicies by Oliver Schmidt's research group to transport sperm cells for *in vitro* fertilization.[16,17] This technique shows potential for improving the success rates of *in vitro* fertilization and enabling medically assisted fertilization *in vivo*. Other research groups have used microrobots to transport other types of cells, such as stem cells. For instance, Dong Sun's group has developed three-dimensional cages using two-photon lithography for transporting mesenchymal stem cells (MSCs), which could be beneficial for tissue regeneration.[23] Hongsoo Choi's group and others have demonstrated that magnetically actuated microrobots can transport hippocampal neural stem cells that differentiate into astrocytes, oligodendrocytes, and neurons.[7,18] Fei Peng's group has used magnetic helical hydrogel microrobots to transport immune cells such as classically activated (M1-like) macrophages[19] and T cells,[20] with the aim of enhancing the performance of cellular immunotherapies. Additionally, some research groups have explored the use of magnetotactic bacteria as cellular biohybrid robots for remote translocation and steering using magnetic fields.[21] Simone Schuerle's group has recently shown that magnetic fields can enhance the accumulation of magnetotactic bacteria in solid tumors, which could have important implications in cancer therapy.[22]

Biohybrid robots offer several benefits beyond remotely controlled navigation, including the ability to store and release drugs. This feature enables the optimized performance of cellular deliveries, especially for sensitive or delicate cells like stem cells that may be susceptible to adverse or unpredictable conditions in the body. Moreover, microrobots can deliver cells in a specific pattern or sequence, enabling precise orchestration of multicellular events over time, which is crucial for certain treatments. Furthermore, microrobots can enhance the migration of cells to specific sites within the body, which is important for cell-based therapies that require targeted migration to sites of injury or disease.[23,24]

OUTLOOK

Microrobots and adoptive cellular transfers (ACTs) independently hold promise for improving patient outcomes, but their combination offers an exciting approach to address major, unsolved challenges in medicine. Opportunities for continued development include (i) enhancing the accumulation of ACTs

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in target tissues, (ii) imparting spatiotemporal modulation of immune responses, (iii) monitoring the progression of treatment or disease with *in situ* biosensors, (iv) enhancing the performance of adoptive cell transfers by providing them with specific nutrients or other factors to promote biological functions, and (v) synergizing with other modalities such as chemotherapeutic agents, radiation therapy, and checkpoint inhibitors to augment established standards of care.

Challenges remain to advance biohybrid robots from concept-driven innovations to clinical revolutions. One consideration is host rejection, as autologous cell therapies (i.e., derived from the same patient) require time and financial resources for modification. Allogeneic approaches (i.e., using cells from donors that can be stored in a repository and transferred as needed) are promising alternatives but can result in host rejection. One solution is to deploy biohybrid robots immediately after chemotherapy or radiation, when the immune system is in a suppressed state. Alternatively, immunoprivileged cells like MSCs are promising candidates for biohybrid robots due to their ability to evade rejection and maintain chemotactic mobility. A second consideration is that most medical microrobots are powered by magnetic fields. Other forms of energization, especially those that are immediately compatible within the clinic (e.g., ultrasound), should be investigated.[25] Finally, the scale-up of biodegradable robots should be prioritized, as many examples in the literature use biocompatible materials that do not degrade on physiological time scales or require tedious fabrication methods. New studies in these areas will accelerate the translation of cell-based biohybrid microrobots into the clinic and maximize their impact.

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Notes

The author declares no competing financial interest.

Biography

C. Wyatt Shields, IV, is currently an Assistant Professor in the Department of Chemical and Biological Engineering at the University of Colorado (CU) Boulder. He obtained his Ph.D. from Duke University in 2016 and subsequently performed postdoctoral research at NC State University and Harvard University. Since joining the faculty at CU Boulder, he has received several research awards, including the NSF CAREER award, the ONR YIP award, and the NIH R35 MIRA. In 2022, he was named a Packard Fellow in Science and Engineering and a Pew Scholar in the Biomedical Sciences. The Shields lab is focused on developing field-responsive and active particle systems as vehicles for next-generation biosensing and drug delivery.

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