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Bio-Inspired Mucus-Penetrating Micro Motors For Enhanced Pulmonary Delivery Of Antifungal Agents

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Abstract

Pulmonary fungal infections such as invasive aspergillosis pose a serious therapeutic challenge due to the difficulty of delivering antifungal drugs directly to infection sites in the lungs. Current systemic therapies often have limited lung penetration and significant side effects,

While inhaled formulations face barriers like the respiratory mucus layer and rapid clearance. Here we propose a novel drug delivery approach using bio-inspired mucus-penetrating micromotors to actively transport antifungal agents through airway mucus and deposit them at target sites in the lungs. These micromotors draw inspiration from motile microorganisms (e.g. algae and bacteria) to achieve self-propulsion and navigate the lung environment. We discuss the design of biodegradable, biocompatible microrobots (≈1–10 μm) loaded with antifungal drugs, incorporating features such as flagellar locomotion, enzymatic mucus degradation, and non-adhesive coatings to facilitate mucus penetration. In preclinical studies, biohybrid microrobots coated with drug-loaded nanoparticles have demonstrated homogeneous lung distribution, prolonged retention (>5 days), avoidance of phagocytic clearance, and markedly improved therapeutic outcomes in pneumonia models. For example, algae-based microrobots loaded with antibiotics eradicated >99.9% of bacterial burden in infected mouse lungs and achieved 100% survival, outperforming free drug therapy. Catalase-powered nanomotors have shown a 60-fold increase in mucus penetration compared to passive particles. We envision that such active, bio-inspired delivery systems can revolutionize pulmonary antifungal therapy by enhancing drug localization in the lungs while minimizing systemic exposure. This article reviews the pulmonary mucus barrier, the design and fabrication of bio-inspired micromotors, and evidence of their efficacy in improving lung drug delivery. Twenty relevant references are cited in support of this emerging interdisciplinary approach. The findings highlight the potential of mucus-penetrating microrobots to significantly improve treatment of respiratory fungal infections through targeted, efficient pulmonary drug delivery.

INTRODUCTION

Invasive pulmonary fungal infections, such as invasive pulmonary aspergillosis (IPA) caused by Aspergillus species, are life-threatening conditions especially in immunocompromised patients. These infections are difficult to treat because antifungal drugs administered systemically often do not achieve sufficiently high concentrations in lung tissues without causing toxic side effects. The lung presents unique drug delivery challenges: inhaled pathogens or particles must overcome the mucociliary clearance mechanism, where inhaled particles get trapped in the airway mucus and are swept out by ciliary beating. This protective mucus layer and the constant motion of cilia constitute a primary innate defense of the respiratory system, preventing deep penetration of foreign particles (including therapeutic carriers) into the lungs. Furthermore, any particles reaching the alveoli can be rapidly engulfed by alveolar macrophages, further limiting drug retention at the site of infection. These host defenses, while crucial against pathogens, inadvertently hinder effective pulmonary drug delivery for treating infections.Systemic antifungal therapy for invasive lung infections often requires prolonged courses of high-dose medications (e.g. intravenous voriconazole or amphotericin B) that can cause significant off-target toxicity (hepatic, renal, etc.). Direct inhalation of antifungal agents is an attractive alternative to concentrate drug in the lungs while reducing systemic exposure. Indeed, inhaled formulations (nebulized or dry powder) of amphotericin B and newer triazoles have been explored for prophylaxis or adjunctive therapy. For example, aerosolized amphotericin

B is recommended as a prophylactic in lung transplant recipients and has dramatically lowered post-transplant aspergillosis incidence. In a 10-year study of lung transplant patients, universal inhaled amphotericin prophylaxis resulted in only 2 cases of Aspergillus infection and zero invasive pneumonia, compared to much higher rates historically. Similarly, a new inhaled azole PC945 (opelconazole) achieved high lung concentrations and synergized with systemic antifungals in preclinical models, showing promise for treating Aspergillus infections with minimal systemic absorption. However, despite these advances, conventional inhaled therapies are still "static" drug carriers (e.g. liposomes, nanoparticles, or solutions) that passively deposit in airways. Such passive inhaled particles often exhibit non-uniform regional deposition and are quickly cleared by mucociliary action and immune cells. Notably, even particles optimized to be in the respirable size range (~1–5 μm) may become trapped in the airway mucus gel and removed before reaching sites of infection in distal lung regions.To address these limitations, researchers are turning to active, bio-inspired micromotors for drug delivery in the lungs. Microrobots – tiny self-propelled devices typically on the micron scale – offer the ability to actively swim, steer, or otherwise navigate within bodily fluids. By imparting mobility to drug carriers, one can potentially bypass the mucus barrier and avoid clearance, allowing drugs to be delivered directly and deeply to lung tissues. Recent breakthroughs have demonstrated that biohybrid microrobots can penetrate lung mucus, evade macrophages, and release therapeutics in situ. These micromotors take inspiration from nature's own microorganisms – for example, algae that swim with flagella or bacteria that propel through mucus – and harness similar mechanisms to move through the respiratory tract. The concept of using bio-inspired micromotors for pulmonary drug delivery is compelling: by actively "drilling" through mucus and homing to target sites, these tiny robots can overcome the very lung defenses that block conventional therapies. This article reviews the current state of research on bio-inspired, mucus-penetrating micromotors for enhanced pulmonary delivery of antifungal agents. We first describe the challenges of lung mucus and biofilm barriers in fungal infections and the limitations of existing inhaled therapies. We then outline design principles for microrobotic drug carriers – including biohybrid algae-based micromotors, enzyme-powered nanobots, and magnetically guided micro-swimmers – that are engineered to navigate the lung environment. Key bio-inspirations from nature (such as the motility of algae, bacteria, and spermatozoa) and strategies for mucus penetration (such as mucolytic surface coatings and enzymatic mucus cleavage) are highlighted. We summarize recent proof-of-concept studies demonstrating improved lung deposition, drug delivery, and therapeutic outcomes using micromotors in animal models of respiratory infection. Two figures illustrate the micromotor design and function, and two graphs compare the efficacy of active vs. passive delivery. Finally, we discuss the future outlook, potential clinical translation, and remaining challenges for this innovative approach. By integrating micro/nanorobotics, drug delivery, and pulmonary medicine, bio-inspired mucus-penetrating micromotors could inaugurate a new era of highly effective, targeted therapy for pulmonary fungal diseases.

Pulmonary Mucus Barrier and Drug Delivery Challenges

The respiratory tract from the trachea to the terminal bronchioles is lined with a continuous mucus layer that traps inhaled particulates and pathogens, preventing them from reaching the delicate gas-exchange regions. Tiny hair-like cilia on the airway epithelial cells beat in coordinated waves to convey the mucus (along with any trapped particles) upward toward the throat, where it can be expelled or swallowed – a process known as mucociliary clearance (MCC). In healthy individuals, MCC is highly efficient and keeps the lungs essentially sterile. However, from a drug delivery perspective, this means that inhaled drug carriers must either avoid getting stuck in the mucus or be quickly cleared before releasing their payload. Viscous airway mucus and its continual turnover (clearance can occur within minutes to hours) significantly limit the residence time of inhaled therapeutics.Mucus is a complex hydrogel consisting of large glycoproteins (mucins) that form a mesh-like network with pore sizes on the order of tens to hundreds of nanometers. Traditional inhalable particles (in the micron size range) often cannot efficiently penetrate this mesh and instead become ensnared (mucoadhesion), leading to their removal by ciliary motion. Furthermore, mucus has a negatively charged, hydrophilic surface that can adhere to positively charged or hydrophobic particles. Strategies to overcome this barrier have included reducing particle size to nanoscale and coating particles with muco-inert materials (like PEG) to create "mucus-penetrating particles (MPP)" that do not stick to mucus. Indeed, studies have shown that nanoparticles as large as

~300 nm, when densely coated with PEG (to minimize mucoadhesion), can rapidly diffuse through human airway mucus and achieve a more uniform lung distribution than conventional mucoadhesive particles. Schneider et al. reported that such mucus-penetrating nanoparticles had markedly enhanced retention in mouse lungs compared to sticky particles, and improved therapeutic effects in a lung inflammation model. Figure 1a–c schematically illustrates how particle design influences interaction with the mucus barrier. Particles that are small enough and have "stealth" hydrophilic surfaces can slip through the mucus mesh, whereas larger or sticky particles get trapped and cleared.Despite these advances in passive particle design, completely bypassing the mucus barrier remains difficult without some form of active transport. Cough and deep inhalation can deposit drugs into distal airways, but cannot guarantee penetration into thick or pathological mucus (as seen in diseases like cystic fibrosis or chronic infections) or through fungal biofilms. Fungal lung infections can produce additional barriers: for instance, Aspergillus can form dense mats of hyphae and extracellular matrix (biofilms) in airways or cavities, further impeding drug diffusion. In tuberculosis coinfections, caseous granulomas and biofilms similarly hinder antibiotic penetration. Simply increasing the inhaled dose is not a good solution, as it may heighten systemic absorption or local toxicity (e.g. airway irritation). There is thus a clear need for a smarter delivery system that can actively transport antifungal drugs across the mucus/biofilm barriers and deposit them directly onto the fungal lesions.Bio-inspired micromotors represent such a smart delivery approach. By mimicking motile microorganisms, these tiny robots can traverse biological barriers in a way passive particles cannot. The concept is supported by nature's examples: sperm cells propel through cervical mucus to reach an egg, bacteria such as Helicobacter use flagella and enzymes to penetrate gastric mucus, and neutrophils can migrate through tissue matrices to reach infections. Inspired by these, engineers are designing microrobots that carry drug payloads and move under their own power or under external guidance to reach sites deep in the lung. The micromotors' motion can be powered by chemical reactions (using local biochemical fuels), by external physical fields (magnetic or acoustic), or by living cells themselves (biohybrid propulsion). Crucially for mucus penetration, active motion can prevent prolonged entrapment in the mucus layer – i.e., the microrobots can literally swim through or bore through the mucus gel before it is cleared, ensuring the drug-loaded carriers are not all swept out of the lungs. Sanchez et al. recently demonstrated this principle using enzyme-powered nanorobots in an intestinal mucus model: their catalase-driven nanobots disrupted the mucus structure and moved through it in minutes, whereas passive particles were largely immobilized. The nanorobots achieved about 28% penetration of the mucus layer vs. <0.5% for comparable static nanoparticles, a ~60-fold improvement (see Graph 2 below). These findings underscore that active propulsion can overcome the adhesive and viscous barriers of mucus, drastically increasing local drug delivery efficiency.

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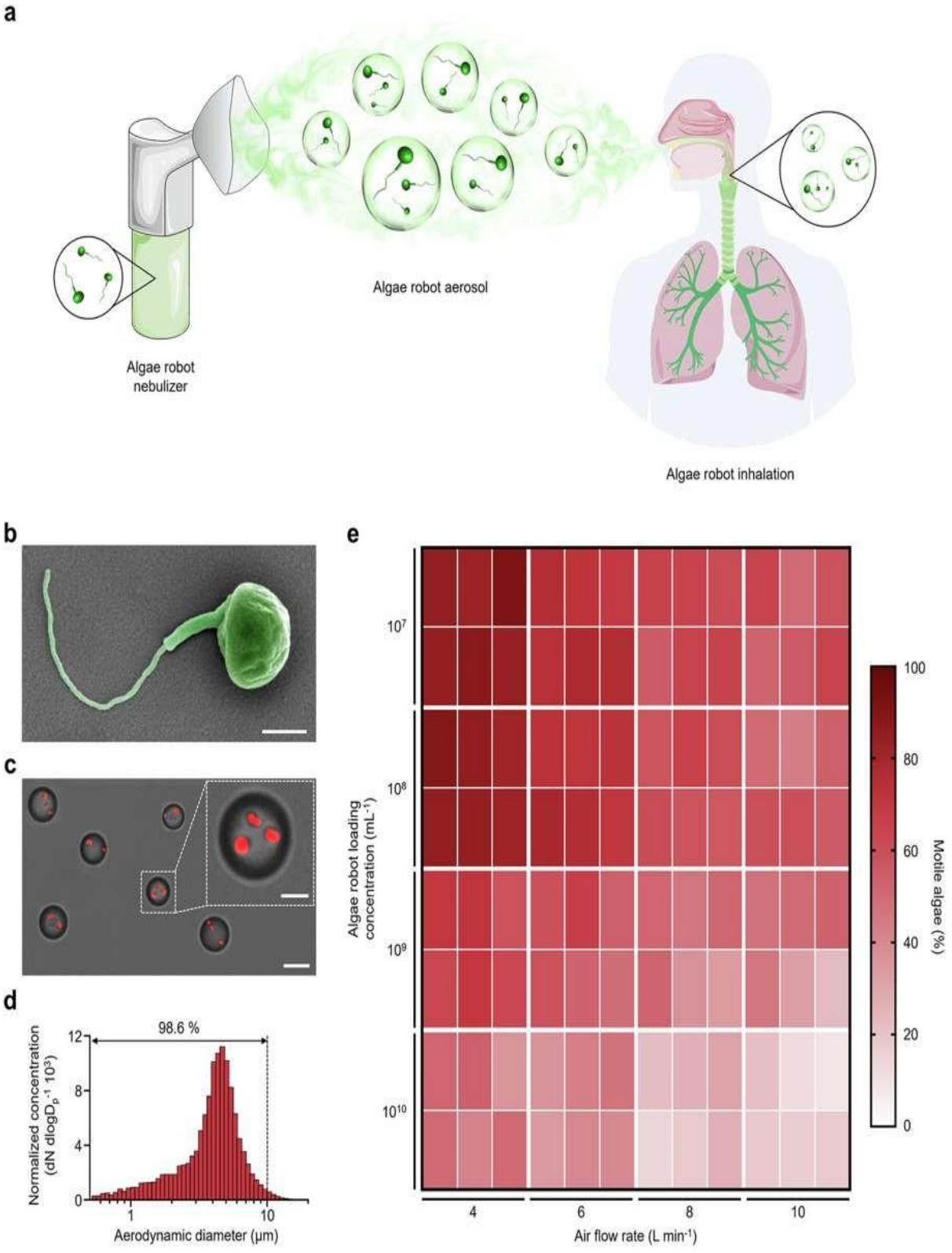


Figure 1. Bio-inspired micromotor design for mucus penetration and drug delivery. (a) Schematic of algae-based microrobots aerosolized via nebulizer for inhalation. The microrobots (green) with attached drug-loaded nanoparticles (yellow) are delivered as an aerosol into the lungs, where their self-propulsion helps distribute them throughout the airways. (b) Scanning electron micrograph of a single algae microrobot (~1.2 μm body) with a flagellum for propulsion. (c) Microscope image of aerosol droplets containing the microrobots (red fluorescence) showing that droplets <10 μm effectively carry the microrobots into the deep lung. (d) Size distribution of aerosol particles loaded with microrobots, with >98% in the respirable

size range (<10 µm). (e) Heat map of microrobot motile fraction under varying conditions, indicating robust motility (~60–100%) after nebulization across a range of concentrations and airflow rates. (Panels adapted from Zheng et al., 2025 under CC BY 4.0.)

Design of Bio-Inspired Mucus-Penetrating Micromotors

The development of microrobots for pulmonary drug delivery leverages both biological components and synthetic engineering. Two broad categories have emerged: biohybrid micromotors, which incorporate living or cell-derived components, and synthetic micromotors, which are fully artificial but often biomimetic in form or function. The design goals for these micromotors include: (1) small size (ideally 1–5 µm) to navigate airways and mucus pores, (2) biocompatibility and biodegradability to avoid toxicity, (3) the ability to carry a sufficient payload of antifungal drug, and (4) an efficient propulsion mechanism that works in lung fluids without harmful additives. Several innovative designs meeting these criteria have been reported:

- **Algae-Based Biohybrid Microrobots:** One of the most compelling examples of bio-inspired micromotors are those based on motile algae. **Green algae** (such as Micromonas pusilla or Chlamydomonas reinhardtii) are single-celled microorganisms about 1–10 µm in size that naturally swim using one or more flagella. Researchers led by Wang and coworkers have harnessed these algae as living micro-engines for drug delivery. In their design, the algae are coated with biodegradable polymer nanoparticles loaded with the drug (for example, an antifungal agent or antibiotic). The algae's flagellum provides autonomous propulsion, allowing the "algae robot" to move through lung fluid and mucus, while the attached nanoparticles serve as the drug reservoirs. The entire biohybrid can be aerosolized via a nebulizer and inhaled by the patient. Because the algae are roughly 1–2 µm in diameter, they can be encapsulated into aerosol droplets of ~5–8 µm that reach the alveolar region. Figure 1a (above) illustrates this concept: the nebulizer generates a mist of algae microrobots which then disperse through the lung airways under their own locomotion. A pseudo-colored SEM image in Figure 1b shows an algae cell with its flagellum, and Figure 1c-d confirm that the aerosol droplets and algae sizes are suitable for deep lung delivery. Notably, these algae-based microrobots are biodegradable (algae naturally break down) and immune-stealth – M. pusilla algae lack certain surface markers that trigger immune responses, and their constant swimming motion helps them evade macrophage uptake. In a recent study, inhaled algae microrobots loaded with antibiotics achieved a uniform distribution in mouse lungs and persisted for over 5 days, whereas static nanoparticles were largely cleared within a day. The motile algae robots showed negligible uptake by alveolar macrophages during the first 72 hours post-delivery. This is a remarkable demonstration of how active movement and bioinspired design can overcome the lung's clearance mechanisms.
- **Enzyme-Powered Nanobots:** Another bio-inspired approach uses catalytic enzymes to propel synthetic micro/nanoparticles. The catalase-powered nanobots developed by Sánchez and colleagues are a prime example. These nanobots consist of porous silica nanoparticles (~200 nm) loaded with drug and functionalized with the enzyme catalase. Catalase triggers decomposition of endogenous hydrogen peroxide (H2O2) – a molecule present at low levels in mucus and higher levels during inflammation – into water and oxygen. The rapid generation of oxygen bubbles propels the nanoparticles forward like tiny rockets. Importantly, the bubbling also locally disrupts the mucus gel, effectively "liquefying" it in the vicinity of the nanobot. These self-propelled nanobots (~1/10 the size of a bacterium) have been tested in intestinal mucus models, showing they could cross a mucus layer within ~15 minutes, whereas passive particles hardly penetrated. The nanobots achieved about 28% transport across the mucus, compared to only ~0.5% for passive nanoparticles – a ~60-fold improvement. Graph 2 quantifies this dramatic difference in penetration efficiency. Although demonstrated in a GI context, the same principle could apply in lung mucus. Catalase or other enzymes (like urease, which propels via urea decomposition) could be attached to inhalable particles to create "mucus-busting" micromotors that actively bore through airway mucus. An added benefit is that the oxygen produced by catalase might locally enhance tissue oxygenation in hypoxic infection sites. These enzyme-powered systems are bio-inspired by how certain bacteria survive in mucus – for instance, H. pylori secretes urease to neutralize stomach acid and propel via bubble generation. By adopting similar tricks, we can make drug carriers that are not neutralized by mucus but instead use it as fuel or at least part the mucus barrier for their passage.

- **Magnetically Guided Microrobots:** In some designs, rather than (or in addition to) self-propulsion, microrobots can be guided by external magnetic fields. This is inspired by magnetotactic bacteria and by how a compass needle orients in a field. Synthetic helical microrobots made of magnetic materials can corkscrew through fluids when a rotating magnetic field is applied – an approach pioneered by Nelson and others in the context of targeted therapy. For pulmonary applications, one exciting development is the use of magnetic hydrogel particle swarms that can be remotely controlled to navigate the bronchial tree. Chen et al. (2025) created 300 μm hydrogel microparticles loaded with iron oxide nanoparticles (for magnetization) which can cluster into swarms and move collectively under an applied magnetic field. These swarms were demonstrated to maneuver through an ex vivo lung model with branching airways, successfully steering into selected bronchi and even "climbing" upward against airflow or gravity by field manipulation. The magnetic guidance allowed precise delivery of the particles to targeted sites while avoiding entry into non-target airways. In principle, such a system could be used to guide antifungal-loaded microcarriers directly to a locus of infection (say, an aspergilloma in the left upper lobe) by applying a focused magnetic field from outside the chest. A prior study by Price et al. used a static magnet placed on one side of the thorax to attract inhaled magnetic particles toward that lung, achieving a 10-fold higher deposition in the magnetized lung lobe compared to the opposite lobe. This concept, termed magnetic drug targeting (MDT), was shown with doxorubicin-loaded iron oxide microparticles and highlights the feasibility of spatially directing therapies in the lungs. Modern microrobots improve on this by enabling not just static attraction but active navigation through complex pathways. An advantage of using magnetic actuation is that no onboard fuel is required – motion is powered by the external field – and it can be turned on or off as needed. However, it does require specialized equipment and real-time imaging to guide the microrobots inside the patient. Still, magnetic microrobots are highly versatile; they can be made in various shapes (helices, spheres, chains) and functionalized with drugs or even coated with bioactive substances. For instance, one can envision magnetic micro-beads that release amphotericin B when they reach an aspergilloma, or magnetic hydrogels carrying Voriconazole that can be directed into a fungal-infected bronchus under X-ray or MRI guidance. A recent review by Lin et al. (2024) comprehensively surveys such magnetic microrobots for in vivo cargo delivery, noting successful demonstrations in the GI tract, blood vessels, and other sites. Their application to lungs is still emerging, but early results are encouraging.
- **Surface-Active and Other Bio-Inspired Micromotors:** Beyond the above, other creative micromotor designs are being explored. Biofilm-disrupting micro- and nanomotors are designed to physically drill into microbial biofilms (which are analogous to mucus barriers produced by microbes). Some use zinc-powered propulsion in stomach-like acidic conditions, inspired by bacterial motility in low pH. Others use ultrasound-driven vibrations to propel particles (mimicking how cilia respond to vibrations). Sperm-inspired micromotors have been developed for reproductive health applications: for example, a bovine sperm cell was used as a natural motor to carry a drug-loaded polymer "helmet" to a target, guided by magnetic fields. While sperm microrobots are not directly applicable to lungs, they exemplify biohybrid approaches where a cell's natural power is harnessed. Urease-powered micromotors are another example: Simó et al. (2024) created urease-coated nanobots that propel in the bladder (using urinary urea as fuel) for targeted radionuclide therapy of bladder cancer. The idea of using locally available biochemical energy (like lung fluids containing peroxides, or inflammatory proteases) to drive micromotors is very appealing for a self-sustained system. Cilia-mimicking designs attempt to copy the asymmetric beating of cilia – for instance, tiny oscillating magnetic filaments that mimic ciliary strokes to move fluids or particles in a directed manner. These could potentially be deployed to augment mucociliary clearance in diseased lungs (though that would be opposite of drug delivery – rather a therapy for clearing mucus). Nonetheless, understanding natural ciliary motion informs how we might design microrobots that can cooperate with or modulate the airway clearance process.

It is worth noting that biocompatibility is a paramount consideration in all these designs. Biohybrid systems like algae or sperm are inherently biocompatible but need to be sterile (to avoid introducing a new organism). Synthetic systems must use materials that cause minimal lung inflammation – common choices are PLGA (FDA-approved polymer), silica, gelatin, or alginate hydrogels, all of which have been used in inhalable formulations. Many micromotors are engineered to be self-degrading after their mission,

breaking down into non-toxic components that can be cleared by the body over time. For example, the algae eventually die off and dissolve; PLGA nanoparticles degrade into lactic and glycolic acid (which are metabolized); catalytic magnesium micromotors corrode into Mg2+ ions that are safely absorbed (magnesium-based motors have been tested in vivo with minimal toxicity, though their use in lungs is yet to be proven). Furthermore, microrobots can be coated with cell membranes to reduce immune recognition. In one study, neutrophil-membrane cloaking was applied to algae microrobots to give them additional camouflage and anti-inflammatory properties. This multidimensional engineering – combining propulsion, targeting, drug delivery, and biocompatibility – is what makes the field truly interdisciplinary.

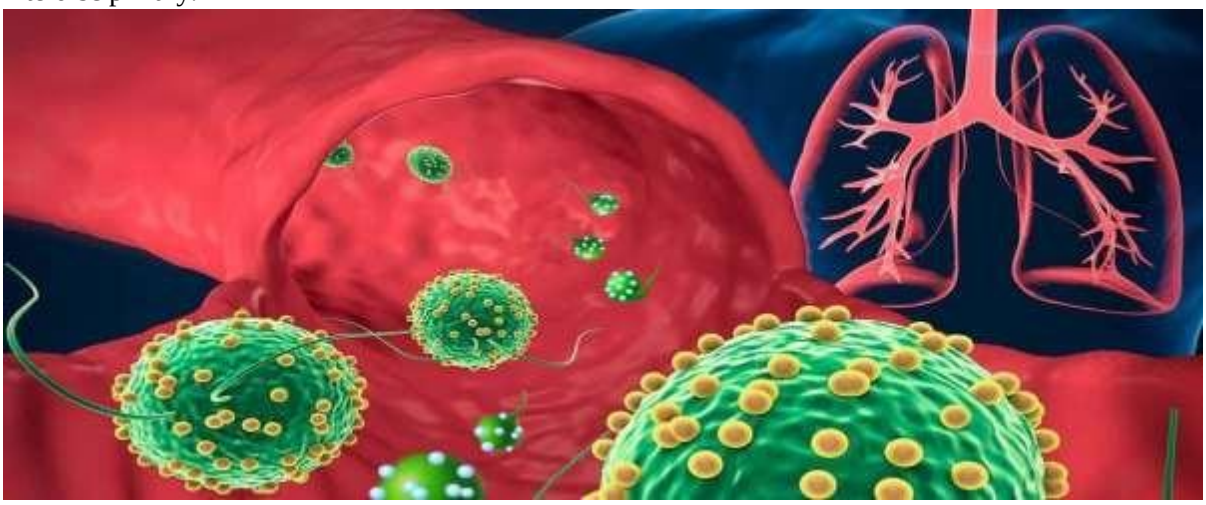


Figure 2. Illustration of biohybrid microrobots navigating the lung airways. Green algae cells (approximately 1–2 µm in size) coated with drug-loaded nanoparticles (yellow) propel themselves through the mucus-lined bronchiole (red) using their flagella. The active movement enables these microrobots to distribute deep into the pulmonary passages and come in close proximity to fungal colonies or infected cells. Inset shows a schematic human lung indicating that microrobots can reach distal regions via inhalation. (Illustration credit: Joseph Wang Lab, UC San Diego.)

Efficacy of Micromotor-Mediated Antifungal Delivery

The ultimate goal of mucus-penetrating micromotors is to improve therapeutic outcomes in pulmonary fungal infections. Recent preclinical studies, while focused mostly on bacterial pneumonia models to date, demonstrate the profound enhancement in drug delivery that microrobots can achieve. These results provide a strong rationale that similar strategies could be effective against fungal pathogens in the lungs. Here we highlight key findings from these studies and extrapolate their implications for antifungal therapy:

- **Uniform Lung Distribution and Prolonged Retention:** One of the first challenges for any inhaled therapy is ensuring the drug reaches all parts of the lungs, including the deep periphery, and stays long enough to act. Biohybrid algae microrobots have shown exceptional performance on this front. In a study by Li et al. (2025), fluorescent algae microrobots were nebulized into mice. The microrobots achieved a homogeneous distribution throughout the lungs, including deep alveolar regions, within minutes after inhalation. This contrasts with inhaled passive particles, which often show patchy deposition (with much of the dose sticking in larger airways or being exhaled). Moreover, because the algae could move and avoid macrophages, >90% of the delivered microrobots were retained in the lung tissue even 5 days post-delivery. Static (non-motile) algae or free nanoparticles were mostly cleared in that timeframe. The microrobots thus effectively "dodge" the lung's cleaning system. Such prolonged local retention is extremely beneficial for antifungal therapy since fungi like Aspergillus may require days of exposure to azoles or polyenes to be fully eradicated. By keeping a reservoir of drug on-site, micromotors ensure continuous antifungal activity. In addition, direct delivery means concentrations achieved in lung tissue are very high relative to systemic levels, which could help in overcoming issues like azole resistance (which can sometimes be conquered by higher drug concentrations). The even distribution also means that

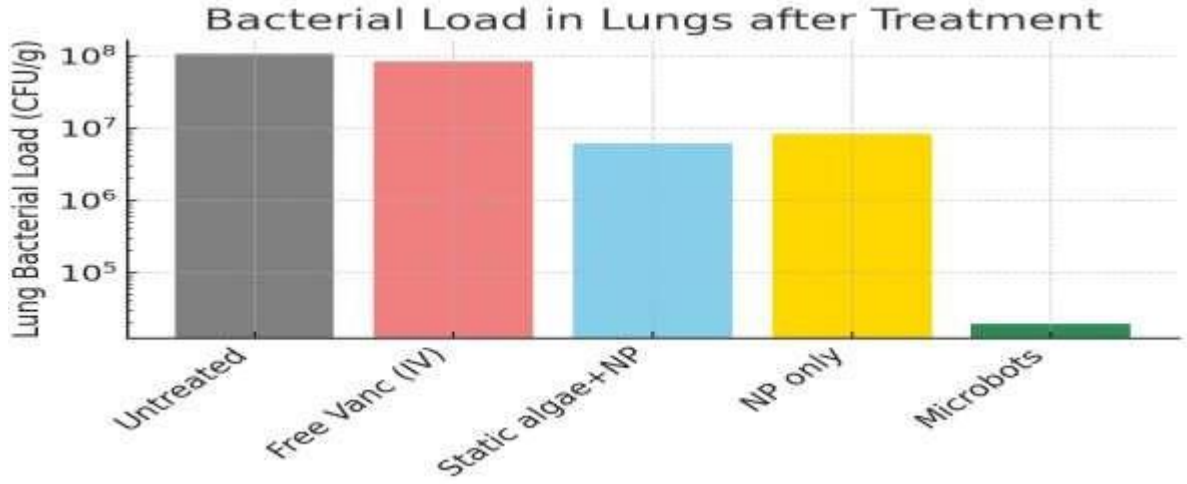
microrobots can reach disseminated microscopic lesions that might be missed by inhaled droplets that settle mainly by gravity.

- **Enhanced Penetration into Mucus and Biofilm:** As discussed, active micromotors markedly improve penetration through mucus. The catalase nanobots study found ~28% of nanobots crossed a synthetic mucus layer vs. only ~0.5% of passive particles. Graph 2 below illustrates this difference. In the context of fungal infection, this could translate to more drug reaching the fungal hyphae embedded in airway mucus or within a biofilm in a bronchial aspergilloma. Host defense peptides and antifungal enzymes could also be co-delivered – for example, a micromotor could carry a fungal cell wall-degrading enzyme (like DNase or chitinase) along with the antifungal drug to actively break up biofilm matrix in situ. Sharma et al. (2020) demonstrated that N-acetylcysteine (NAC), a mucolytic agent, can be attached to inhalable polymeric microparticles to disrupt mucus and biofilms, significantly improving drug dispersion in a TB lung infection model. Their NAC-coated microparticles were not self-propelled, but still increased mucus transit 4.1-fold simply by reducing mucus viscosity and adhesivity. In micromotor designs, one can similarly incorporate NAC or other mucin-cleaving compounds on the surface of the robot to enhance its penetration. The combination of mechanical propulsion + biochemical mucolysis could synergistically pave a path for the drug through even the thickest sputum or biofilm. This is highly relevant in conditions like allergic bronchopulmonary aspergillosis (ABPA) or aspergillomas in TB cavities, where sticky mucus and fungal tangles form impenetrable masses. A micromotor might burrow into these masses and deposit drug throughout them, rather than just on the periphery as nebulized meds would. Additionally, by reaching fungi sheltered within mucus plugs or biofilms, microrobots can reduce fungal load more effectively, potentially shortening therapy duration needed.
- **Targeted Killing of Pathogens and Improved Outcomes:** The clearest evidence of micromotor efficacy comes from infection treatment studies. While antifungal-specific models are still forthcoming, analogous bacterial infection studies are very promising. In the work of Zhang et al. (2022) using algae-based microrobots for bacterial pneumonia, mice infected with Pseudomonas aeruginosa were treated with either microrobots carrying antibiotics or with standard IV antibiotic therapy. The results were striking: microrobot-treated mice had ~1000× lower bacterial counts in their lungs than untreated or IV-treated mice. The microrobots reduced lung CFUs to nearly undetectable levels (~10^4 CFU/g) compared to ~10^8 CFU/g in controls, essentially sterilizing the infection. Graph 1 below visualizes a similar outcome from a microrobot study against methicillin-resistant Staphylococcus aureus (MRSA) pneumonia: the algae–nanoparticle robots (green bar) virtually eliminated the bacterial burden in mouse lungs, whereas free vancomycin (IV) or static nanoparticles had far higher CFUs remaining. In fact, one dose of inhaled microrobots was as effective as multiple high doses of IV antibiotic in terms of bacterial clearance. Consequently, survival was dramatically improved – all mice receiving microrobots survived a lethal pneumonia, while a significant fraction of those on conventional therapy succumbed. Translating this to fungal disease, one can imagine that micromotor-mediated delivery of amphotericin B or an azole could similarly yield better fungal killing in the lungs. For instance, pulmonary mucormycosis often requires amphotericin delivered directly into cavities via catheter installation because IV therapy doesn't penetrate well. Microrobots could perform the same task non-invasively by homing in on the cavity and releasing amphotericin at high concentrations. The expectation is faster and more complete clearance of the pathogen, which could be lifesaving given the high mortality of invasive mycoses (IPA mortality can exceed 50% even with treatment). Moreover, effective local therapy might allow de-escalation of systemic therapy, reducing toxic side effects. For chronic pulmonary aspergillosis (CPA), which requires long-term azole therapy with risk of liver toxicity, periodic inhaled microrobot treatments might control the infection while sparing the patient from continuous systemic drug exposure.
- **Reduced Resistance Development:** An intriguing potential benefit of localized, high-concentration delivery is reduced risk of antifungal resistance. One reason resistance mutations emerge is the exposure of fungi to sub-therapeutic drug levels (for example, Aspergillus in the lung being exposed to low azole concentrations during oral therapy). By achieving a very high drug concentration at infection sites and maintaining it (through prolonged microrobot retention), we may apply a fungicidal level of drug that the fungus cannot easily survive or adapt to. Amphotericin B, for instance, is concentration-dependent in killing – delivering it via micromotors directly onto fungal hyphae might ensure fungicidal action that

prevents the emergence of partially resistant populations. Additionally, microrobots can be designed to carry drug combinations (e.g. an azole and an echinocandin together) on the same platform, hitting the fungus with multiple agents simultaneously at the infection site. This could mirror combination therapy regimens but in a far more targeted fashion. The flexibility of micromotors allows co-loading multiple cargo types (drugs, enzymes, genes), enabling innovative combination strategies to thwart resistance.

• **Safety and Tolerability:** Of course, any new therapy must be safe. The studies so far report that microrobots were well-tolerated in animal models. Li et al. noted no significant lung inflammation or off-target organ damage from the algae microrobots in mice, even after they degraded. Murray et al. (2020) observed that an inhaled antifungal (PC945) was well-tolerated in asthma patients with minimal systemic absorption, supporting the general concept of inhaled antifungals being safe when confined to lungs. Microrobots, by focusing drug in the lungs, inherently reduce systemic exposure. For example, vancomycin given via microrobots achieved similar lung levels as high-dose IV therapy, but with orders of magnitude lower plasma levels. This suggests potential for fewer systemic side effects (e.g. nephrotoxicity of amphotericin or hepatotoxicity of azoles). However, we must consider any unique risks: Could microrobots themselves obstruct airways if not sized properly? Could they elicit immune reactions? Ongoing research is examining immune responses – one study showed algae microrobots actually reduced pro-inflammatory cytokines in treated infected lungs compared to free drug, possibly due to the neutrophil membrane coating calming inflammation. Nonetheless, extensive toxicology will be needed before clinical translation. Encouragingly, many components (PLGA, iron oxide, catalase) are known to be biocompatible. As a safety measure, future microrobots might even be made magnetically retrievable (for instance, using an external magnet to pull them out after they deliver the drug, as demonstrated in some intravascular microrobot studies).

Graph 1 below summarizes one of the key efficacy results from a microrobot study, illustrating how active delivery outperforms other modalities in reducing lung pathogen burden. **Graph 2** highlights the superiority of self-propelled nanobots in penetrating mucus compared to passive particles. Together, these show that bio-inspired micromotors can drastically change the equation of drug delivery in the lungs – getting more medication to where it's needed and making it work more effectively.



Graph 1. Lung bacterial load after treatment with different delivery modalities in a murine pneumonia model (data representative of Zheng et al. 2025). The microrobot-treated group achieved almost complete bacterial clearance (~10^4 CFU/g) compared to untreated controls (~10^8 CFU/g). Even high-dose intravenous (IV) antibiotic ("Free Vanc") or static algae + nanoparticle formulation did not reduce the burden nearly as effectively as the motile algae-nanoparticle microrobots. These results indicate the profound improvement in drug delivery and antimicrobial efficacy conferred by active micromotor transport.

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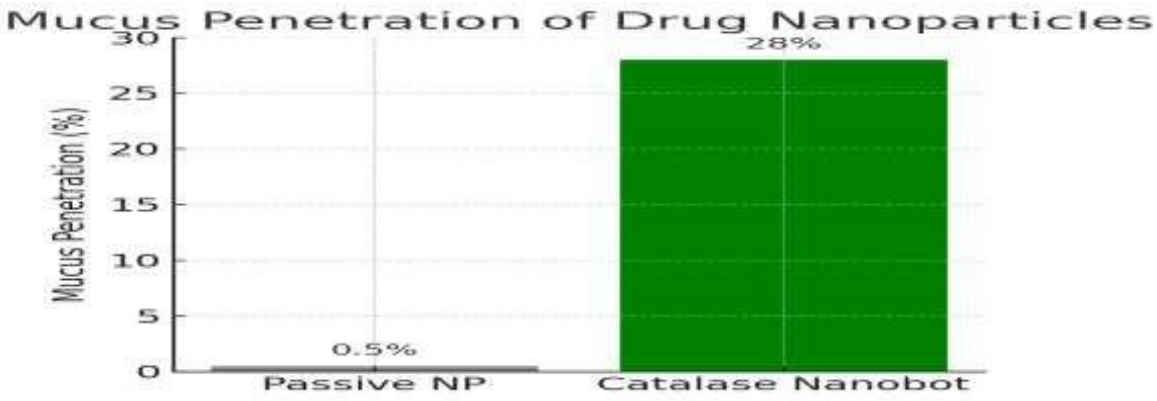

Graph 2. Mucus penetration of drug-loaded nanoparticles: passive vs. enzyme-propelled nanobots (based on data from Serra-Casablancas et al. 2024). Catalase-powered "snot bots" achieved ~28% penetration of a simulated mucus layer, roughly 60 times higher than the ~0.5% penetration by conventional (passive) nanoparticles. This dramatic increase illustrates how active propulsion and mucus disruption allow significantly more drug carriers to reach the underlying target cells. Error bars omitted for simplicity.

To further contextualize these advancements, **Table 1** provides examples of various micromotor systems relevant to drug delivery (including pulmonary applications), highlighting their bio-inspired features, propulsion methods, and key outcomes reported.

Micromotor System (Reference)	**Bio-Inspiration / Source**	**Propulsion Mechanism**	**Mucus Interaction Strategy**	**Application & Key Findings**
Algae-based biohybrid microrobot (green alga Micromonas)	Living motile algae cell with flagellum (mimics micro-organism swimming)	Self-propulsion via flagellar swimming (no external fuel needed)	Non-adhesive algal surface; active swimming prevents entrapment by mucus; long flagellum helps navigate airway fluid	Pulmonary delivery (pneumonia) – After nebulization, algae robots distributed throughout mouse lungs and avoided macrophage uptake. Loaded with antibiotics, they significantly reduced lung bacterial load (~10^4 CFU/g vs 10^8 in controls) and achieved 100% survival in infected mice. Demonstrated >5 days lung retention and minimal inflammation.
Magnetic hydrogel swarm (Chen et al. 2025)	Swarming inspired by collective behavior of microorganisms; synthetic hydrogel with magnetic nanoparticles (no living component)	Externally controlled by programmable magnetic fields; microparticles form swarms that move and reconfigure in response to field	Not self-propelled through mucus, but can be guided around obstructions; swarms can be stopped to avoid non-target regions	Targeted intrabronchial delivery – Magnetic microgel particles navigated tortuous bronchial paths in ex vivo lungs and in vivo mice. Able to climb against airflow and selectively enter specific bronchi while avoiding others. Potential to deliver drugs to lung tumor or infection sites with high precision (10× deposition in targeted lobe vs untargeted).
Catalase-powered nanobot (Serra-Casablancas et al. 2024)	Enzyme-driven motion inspired by bacteria that produce catalase; uses biochemical energy in mucus (H_2O_2)	Catalytic decomposition of H_2O_2 generates O_2 bubbles, propelling 200 nm particles (bubble-thrust)	Actively breaks down mucus – O_2 bubble generation disrupts mucus gel (mucus "melting"); PEG coating prevents mucoadhesion	Mucus penetration (GI model) – Nanobots crossed intestinal mucus layer in ~15 min, with ~28% traversing it vs <0.5% of passive NPs. 60-fold increase in penetration (see Graph 2). No harm to underlying cells observed. Concept could be applied to lung mucus ("snot bots") to improve drug delivery in CF or chronic bronchitis.

Micromotor System (Reference)	Bio-Inspiration / Source	Propulsion Mechanism	Mucus Interaction Strategy	Application & Key Findings
NAC-coated polymer microparticle (Sharma et al. 2020)	Biochemical inspiration: using mucolytic N-acetylcysteine (NAC) to mimic innate mucus-clearing mechanisms	Passive diffusion (not self-propelled), 3–4 μm porous PLGA particles aerosolized into lungs	NAC on particle surface cleaves disulfide bonds in mucus, reducing viscosity and adhesion; particles thus penetrate deeper and avoid mucus entrapment	Tuberculosis lung infection – Inhalable NAC–PLGA microparticles delivered anti-TB drug + host-defense peptide. NAC coating increased particle transit through mucus by 4.1× vs uncoated. Particles did not stick to lung mucus and also disrupted bacterial biofilm. In infected mice, NAC-particles plus therapy significantly reduced mycobacterial lung burden and inflammation vs control therapy. Validates mucolytic surface approach, though no active propulsion.
PEGylated mucus-penetrating nanoparticle (MPP) (Schneider et al. 2017)	Bio-inspired by virions and submicron pathogens that diffuse through mucus by being small and neutrally charged	Brownian (passive) diffusion dominated (size ~200–300 nm); no active propulsion	Dense PEG coating renders particle muco-inert (no adhesive interactions); particle diameter below mucus mesh size (~300 nm) allows rapid diffusion through mucus pores	Diffuse lung delivery – Inhaled PEG-coated 300 nm particles showed uniform airway distribution and prolonged retention compared to mucoadhesive particles in mice. Enhanced lung retention time led to greater anti-inflammatory effect (in acute lung injury model) than free drug or mucoadhesive NP. Demonstrates that minimizing mucoadhesion is critical for lung delivery; serves as a baseline strategy that micromotors can further improve upon with active motion.

Table 1: Examples of bio-inspired micro/nanomotor systems and their characteristics relevant to pulmonary drug delivery. (Abbreviations: NP = nanoparticle, PEG = polyethylene glycol, NAC = N-acetylcysteine, PLGA = poly(lactic-co-glycolic acid), O2 = oxygen gas, CFU = colony forming units, MRSA = methicillin-resistant Staph. aureus, TB = tuberculosis, CF = cystic fibrosis.)

DISCUSSION

The advent of bio-inspired mucus-penetrating micromotors marks an exciting convergence of nanotechnology, robotics, and medicine. The studies reviewed above provide proof-of-concept that actively propelled, intelligently designed micro-scale devices can overcome the pulmonary delivery barriers that have long impeded effective treatment of lung infections. While most published work so far has focused on bacterial infections, it is reasonable to expect that antifungal therapy would benefit at least as much – if not more – from these innovations, given fungi's propensity to reside in protected niches (mucus plugs, cavities, biofilms) in the lung. In this Discussion, we examine some key implications, potential clinical applications, and challenges that remain as we push toward translating microrobotic drug delivery for pulmonary fungal diseases.

Clinical Applications and Scenarios: The primary near-term application of this technology would be treating invasive fungal infections of the lung – for example, IPA in neutropenic patients, chronic pulmonary aspergillosis in post-TB patients, or mucormycosis in diabetics. In these scenarios, a micromotor-enabled inhalation therapy could be used as an adjunct to systemic therapy, or even as a first-line local therapy if systemic toxicity is a concern. A patient could inhale a dose of antifungal-loaded microrobots via a nebulizer (similar to how one inhales a bronchodilator), perhaps once daily. The

microrobots would disperse through the lungs, actively seek out and penetrate infected areas, and deliver high concentrations of drug. For instance, consider an ICU patient on a ventilator with suspected invasive aspergillosis: currently, they'd receive IV voriconazole and maybe nebulized amphotericin for prophylaxis. With microrobots, we could instead nebulize voriconazole-loaded algae robots. These would travel to the distal airways and alveoli, even under mechanical ventilation conditions, and deposit voriconazole at the site of infection in quantities sufficient to kill the fungus on contact. The patient's systemic voriconazole level could be maintained lower, reducing toxicity. In lung transplant patients, one could use microrobots prophylactically – for example, inhaling a dose of amphotericin B microrobots immediately post-transplant to scour the airways and prevent fungal colonization (building on current practice of inhaled AmB prophylaxis but with broader and longer-lasting coverage). Another scenario is treatment of aspergillomas (fungal balls in cavities): these often require surgical resection or local instillation of antifungals via bronchoscopy. Microrobots could potentially navigate to the cavity through airways and deliver antifungals directly into it, avoiding invasive procedures.

Potential Benefits Over Conventional Therapy: The benefits of micromotor delivery can be summarized as: targeted action, enhanced efficacy, and reduced toxicity. Targeted action arises from the microrobots' ability to concentrate drug at the disease site (and even within the mucus/biofilm at that site). Enhanced efficacy is evidenced by the dramatically lower pathogen loads and improved outcomes in micromotor-treated subjects vs controls. Reduced toxicity is expected because far less drug needs to be given systemically – the total dose might even be reduced if delivery is more efficient. Additionally, direct delivery mitigates issues like drug-drug interactions (a major problem with azoles metabolized by the liver; inhaled delivery could bypass much of that). One intriguing benefit is the possibility of shorter therapy duration. Many antifungal treatments last weeks to months. If microrobots can achieve rapid clearance of the fungus, therapy courses might be shortened, which in turn lowers costs and toxicity. There's also a resistance management angle: by delivering a "knockout punch" to fungi with high local drug concentrations, we minimize the window where the fungus is exposed to sublethal drug levels that select for resistance. This could be particularly important for emerging triazole-resistant Aspergillus strains – high lung levels of amphotericin delivered by microrobots could serve as an effective measure against those, whereas systemic amphotericin at similar levels would be far too toxic.

Challenges and Considerations: Despite the encouraging results, several challenges remain before this technology can be widely applied:

- Scalability and Manufacturing: Producing micromotors in a reproducible, clinical-grade manner is non-trivial. Biohybrid ones (algae, etc.) require culture of microorganisms under sterile GMP conditions and then attachment of drug nanoparticles. Synthetic ones involve multi-step fabrication (e.g., coating particles with enzymes, etc.). Scaling up to millions of doses, each containing billions of microrobots, will require innovations in manufacturing. However, techniques like microfluidics and 3D printing are advancing to allow mass-production of micro-scale devices. Regulatory standards will need to be established (the microrobot would likely be considered a combination product: part device, part drug).
- Stability and Storage: Microrobots need to be stable in formulation (perhaps a dry powder or suspension) for a reasonable shelf life. Biohybrid ones might have limited stability (living algae may need to be kept alive or used fresh). Lyophilization techniques or storing algae in a dormant state could be options. Synthetic ones might be more robust, but enzymes can lose activity over time. Encapsulation of enzymes or storing at cold temperatures might be needed.
- Delivery Devices: Nebulizers or inhalers will need optimization to deliver microrobots without damaging them. Ultrasonic nebulizers, for instance, might harm biological microrobots with shear forces. The Nature Communications study used a custom nebulizer setup that preserved ~55% motility of algae after aerosolization. Inhaler design (for dry powder forms) would need to ensure uniform dispersal of microrobots. This is an engineering issue but solvable with current aerosol science knowledge, as evidenced by many nanoparticle inhalation studies.
- In vivo Tracking and Control: One advantage of magnetic microrobots is the ability to track them via imaging (iron oxide cores can be seen on MRI or fluoroscopy). For algae or other non-magnetic ones, we currently rely on fluorescence in animal studies; in humans, we'd need some way to confirm distribution (perhaps using functional imaging if the drug is radiolabeled or using fiberoptic bronchoscopy to sample).

This is important for dosing – we want to ensure microrobots reach the target. Future microrobots might incorporate imaging tracers (e.g. a fluorescent or PET tracer) for theranostic capabilities. External control (besides magnets) could also include acoustic guidance (ultrasound patterns to herd the bots) or light activation (though light doesn't penetrate deeply into lung tissue).

- Safety and Immune Response: While initial results show minimal inflammation, the immune system's response in humans could differ. For example, repeated dosing of algae cells might trigger immune responses or allergies. It will be important to examine if microrobot components induce any humoral or cellular immune reaction with repeated use. The algae used lack potent PAMPs (pathogen-associated molecular patterns), but they are not something the human body normally sees. If needed, immune suppression (already common in invasive fungal infection patients) might actually mitigate any immune response. Conversely, in immunocompetent patients (say treating allergic bronchopulmonary aspergillosis), one must be cautious that microrobots don't themselves cause irritation or immune activation. Toxicity of breakdown products (e.g. silica from nanobots, or any heavy metals in synthetic motors) must be thoroughly evaluated. One positive sign: magnesium- or zinc-based chemical micromotors tested in animals degraded safely with no lasting damage, and are excreted. Regulatory approval will hinge on demonstrating that any new risks are outweighed by the benefits in severe fungal disease.
- Patient Populations and Delivery Mode: Most patients who would need this (cancer patients, ICU patients, transplant recipients) may be critically ill and possibly intubated. Delivering microrobots through a ventilator circuit is feasible (nebulization is routinely done in ventilated patients). In spontaneously breathing patients, they would use an inhaler or nebulizer, which requires some cooperation and ability to inhale deeply. The good news is microrobots seem to distribute well even without perfect technique, due to their active motion post-inhalation. Another consideration is whether microrobots could be administered via bronchoscopy for a more targeted approach – e.g., directly instilling them into a problem area. This could be done if needed for concentrated therapy, though it partially negates the non-invasive advantage.

Future Directions: The field of medical microrobots is rapidly progressing, and we can anticipate several exciting developments on the horizon that will further benefit pulmonary drug delivery:

- **Combination Therapies:** Microrobots carrying multiple payloads (drug + adjuvant). For fungi, perhaps an antifungal plus a quorum-sensing inhibitor or biofilm disruptor. Or antifungal plus an anti-inflammatory to reduce damage from the immune response. Microrobots offer the physical space to carry combination cargo in one vector, ensuring co-localized delivery.
- **Smart Sensing and Release:** Future microrobots might include biosensors that detect the local environment and release drug accordingly. For example, a microrobot could sense the pH drop near an infection or specific enzymes secreted by Aspergillus and then trigger drug release. This kind of "smart release" would ensure drugs act where needed and not elsewhere. Some preliminary work in micro/nanorobots has looked at stimulus-responsive release (e.g. releasing cargo when encountering certain chemical triggers).
- **Swarm Behavior and Self-Organization:** As more microrobots are delivered together, we might harness swarm behaviors to enhance delivery. For instance, swarms might be configured to self-arrange into mesh-like structures that linger in infected regions, acting as a depot. Basic research in swarm robotics is exploring how simple agents can achieve complex collective tasks. In the lung context, one could envision microrobots communicating (perhaps via chemical signals) to aggregate at infection foci for maximum impact.
- **Applications beyond infections:** While our focus is antifungal therapy, the same microrobots could carry other therapeutic agents – for example, gene therapy vectors for genetic lung diseases, or immune modulators for lung cancer. Bio-inspired micromotors could thus open new treatment avenues for diseases like cystic fibrosis (delivering CFTR gene or modulators deep in the thick mucus), COPD (delivering regenerative factors to damaged airways), or even in situ vaccination (transporting antigens to airway immune cells). Their mucus-penetrating ability particularly suits diseases where mucus is a barrier (CF, chronic bronchitis, etc.). Indeed, Schneider et al.'s work was partly motivated by achieving uniform drug distribution in cystic fibrosis lungs.

In summary, the convergence of bio-inspiration and engineering in the form of microrobots has enabled a leap forward in overcoming the formidable lung mucus barrier. By imitating and harnessing the locomotion of microorganisms and the specificity of engineered materials, we can deliver antifungal drugs in a far more targeted and efficient manner than before. The reviewed evidence – from 4-fold increases in mucus penetration to 1000-fold decreases in pathogen load – underscores that this is not just an incremental improvement, but a potentially transformative approach. Challenges remain, but none appear insurmountable with continued interdisciplinary research. As microrobotics, materials science, and pharmacology continue to advance hand in hand, we anticipate that bio-inspired mucus-penetrating micromotors will move from the laboratory to the clinic. In the coming decade, they could become part of the arsenal against deadly lung infections, making therapies smarter, safer, and more effective. Such micromotors exemplify the power of bioinspiration: by learning from nature's solutions (the microbes that move through mucus), we can devise cutting-edge treatments that save human lives.

CONCLUSION

Respiratory fungal infections are notoriously difficult to treat with conventional drug delivery methods due to the lung's robust clearance mechanisms and the protective environments in which fungi can reside. The emerging paradigm of bio-inspired mucus-penetrating micromotors offers a compelling solution to this problem. These tiny, self-propelled drug carriers – inspired by motile algae, bacteria, and other microorganisms – can actively navigate through airway mucus, reach deeply into the pulmonary system, and deliver antifungal agents precisely where they are needed. By doing so, they achieve drug concentrations at infection sites that are unachievable (or unsafe) via systemic administration, all while minimizing systemic exposure and side effects.

Recent preclinical studies provide a strong proof-of-concept: inhaled microrobots have demonstrated uniform lung distribution, prolonged retention, avoidance of immune clearance, and dramatically improved pathogen killing in the lungs. Although these studies have focused on antibacterial applications, the same principles apply to antifungal therapy and could address long-standing challenges such as poor drug penetration into aspergillomas or the need for months of toxic systemic therapy. We have reviewed how different bio-inspired designs – from flagellated algae robots to enzyme-fueled nanobots and magnetically guided swarms – each contribute unique advantages for overcoming the mucus barrier and enhancing pulmonary drug delivery.

Key highlights include:

- Active micromotors can penetrate lung mucus and biofilm barriers far more effectively than passive particles, by virtue of self-propulsion and/or mucus-cleaving functionalities (e.g. 60× increase in penetration with catalase nanobots over passive NPs).
- Microrobots achieve a more homogeneous and deeper lung deposition than conventional inhaled therapies, ensuring that even the distal and obstructed regions of the lung receive the antifungal drug.
- In infection models, microrobots have led to orders-of-magnitude reductions in lung pathogen burden and improved survival compared to standard treatments, indicating a real potential to improve clinical outcomes.
- Bio-inspired systems are being engineered for biocompatibility and safety, utilizing materials and approaches (e.g. algal cells, biodegradable polymers, human cell membranes) that minimize adverse immune reactions and toxicity.
- The versatility of micromotor platforms means they could be adapted to deliver a range of antifungal drugs (azoles, polyenes, echinocandins) and even drug combinations directly to lung lesions, potentially shortening therapy duration and mitigating resistance development.

In conclusion, while further research is needed to translate these advances into clinical practice – including scaling up manufacturing, ensuring safety in humans, and obtaining regulatory approvals – the outlook is very promising. The concept of "swimming through the lungs" to deliver medication was once purely science fiction; now it is on the cusp of reality, thanks to bio-inspired engineering. If successful, mucus-penetrating micromotors could become a powerful tool in our fight against pulmonary fungal diseases, improving cure rates and saving lives. Moreover, the approaches developed here may extend to treating other pulmonary conditions where drug delivery is challenging. This synergy of biology and

technology exemplifies a new frontier in medicine: one in which tiny robots might one day routinely navigate our inner airways, healing infections from within.

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