

## REVIEW ARTICLE

# Current Trends in Nanorobot Technology for Targeted Drug Delivery Systems



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**Abstract:** The development of nanorobotics marks a paradigm shift in precision medicine, offering unprecedented control over therapeutic interventions at the cellular and molecular levels. This review discusses about the nanorobotic technology, and its transformative potential in targeted drug delivery systems. Unlike passive nanocarriers, nanorobots are engineered as active agents capable of autonomous navigation, sensing, and actuation within complex biological microenvironments. The discussion encompasses the structural classification of these devices, ranging from biohybrid systems utilizing DNA, leukocytes, and sperm cells to synthetic architectures driven by exogenous fields or endogenous chemical fuels. Moreover, the integration of advanced fabrication techniques such as electron-beam lithography and bio-inspired assembly is analyzed in the context of optimizing biocompatibility and functionality. The clinical versatility of nanorobots is highlighted through their application in diverse medical fields, including oncology, cardiology, neurology, and endocrinology, where they facilitate site-specific cargo release and minimally invasive microsurgery. Despite these advancements, significant hurdles regarding scalability, immunogenicity, and regulatory guidelines remain. More research is required to bridge the gap between laboratory prototypes and viable clinical realities, indicating the role of artificial intelligence in improving targeting and therapeutic efficacy.

**Keywords:** Nanorobotics; Targeted Drug Delivery; Biohybrid Systems; Micro-pulsion; Precision Medicine

## 1. Introduction

Nanorobotics represents a transformative frontier at the intersection of nanotechnology, robotics, biomedical engineering, and materials science. It is defined as the design, fabrication, and control of functional devices with dimensions typically ranging from 1 to 100 nanometers, although functional assemblies often operate in the sub-micron to micron scale. Unlike traditional robotics, which deals with macroscopic electromechanical systems, nanorobotics involves the manipulation of matter at the molecular level to create intelligent machines capable of sensing, processing information, and actuating in response to environmental stimuli. This field has transitioned rapidly from theoretical conceptualizations to practical experimentation, driven by the urgent clinical need for therapeutic modalities that can overcome the biological barriers inherent in the human body [1].

The primary impetus for the development of medical nanorobots arises from the significant limitations of conventional pharmacotherapy. Traditional systemic drug administration often relies on passive diffusion and circulation, leading to a nonspecific distribution of therapeutic agents throughout the body. This "flooding" approach frequently results in suboptimal drug concentrations at the target site and severe cytotoxicity to healthy tissues, a challenge particularly acute in oncology where chemotherapeutic agents attack rapidly dividing cells indiscriminately. While first-generation nanomedicines, such as liposomes and polymeric nanoparticles, improved drug stability and bioavailability, they largely rely on passive targeting mechanisms like the Enhanced Permeability and Retention (EPR) effect. These passive carriers lack the ability to navigate against blood flow, penetrate dense tissue matrices, or respond dynamically to the heterogeneous physiological conditions of a disease state.

Nanorobots address these deficiencies by introducing the element of active agency. An ideal nanorobotic system is conceptualized as a "smart" device equipped with navigation, sensing, and actuation modules. These devices are engineered to propel themselves through biological fluids often non-Newtonian in nature to reach precise anatomical targets, such as a solid tumor core, a specific neuron, or a site of infection. Upon arrival, they can perform complex tasks: sensing local pH or enzymatic gradients, releasing a drug payload in a controlled burst, or even performing mechanical microsurgery on individual cells. This capability effectively realizes

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the "magic bullet" concept first proposed by Paul Ehrlich, but with a level of sophistication that allows for real-time interaction with the biological environment.

The architecture of a medical nanorobot is inherently multidisciplinary. It may integrate inorganic components (like gold or iron oxide nanoparticles for imaging and magnetic steering) with biological moieties (such as DNA strands for logic processing or antibodies for targeting). This hybrid approach allows scientists to leverage the durability of synthetic materials alongside the exquisite specificity of biological molecules. For instance, nanorobots can be designed to mimic the behavior of white blood cells, undergoing chemotaxis to locate pathogens, or to utilize the mechanical propulsion of flagellated bacteria.

However, the deployment of such devices requires rigorous adherence to design principles centered on safety and biocompatibility. A critical requirement is that the nanorobot must be non-immunogenic to avoid immediate clearance by the reticuloendothelial system (RES) before completing its mission. Moreover, the device must be biodegradable or excretable; once the drug is delivered or the task is complete, the nanorobot should break down into non-toxic byproducts that can be safely eliminated via renal or hepatic pathways. The current research is focused on optimizing these parameters, moving from simple cargo-towing nanostructures to fully autonomous systems capable of swarm behavior and collective decision-making [2].

## 2. Classification of Nanorobotic Systems

The structural diversity of nanorobots is largely categorized by their constituent materials and the integration of biological components. A prominent class of these devices is the biohybrid nanorobot, which synergizes synthetic nanomaterials with biological entities to leverage the innate motility and sensing capabilities of cells and molecules.

### 2.1. Biohybrid Nanorobots

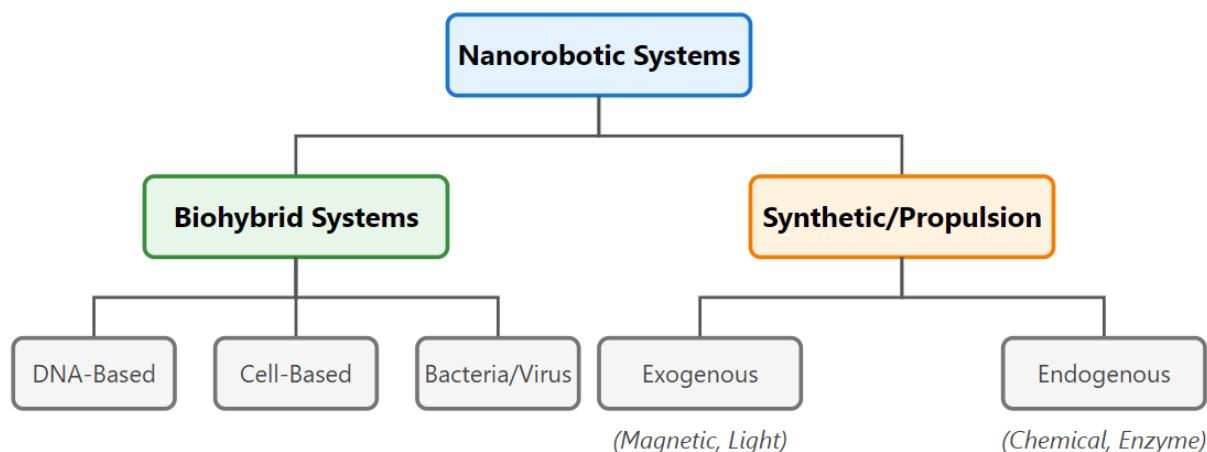
Biohybrid systems represent a frontier in nanorobotic design, combining artificial chassis such as inorganic polymers or metallic nanoparticles with biological actuators like DNA, enzymes, and live cells. This integration facilitates diverse functionalities, including microsurgery, single-cell manipulation, and enhanced tissue penetration [3].

#### 2.1.1. DNA-Based Architectures

DNA nanotechnology, particularly the DNA origami technique, has revolutionized the construction of programmable nanorobots. This method involves the controlled folding of single-stranded DNA molecules, stapled together by complementary oligonucleotides, to form distinct 2D and 3D nanostructures. These DNA assemblies can be functionalized with payloads and logic gates that respond to environmental triggers. For instance, researchers have developed biohybrid magnetic microrobots by conjugating DNA flagella to magnetic iron oxide particles. These constructs are particularly efficacious for precise cancer immunotherapy and vaccination, as the DNA structure can protect the immunogenic payload until it reaches the target site [4]. Recent advancements have demonstrated that equipping these DNA-based systems with magnetic iron oxide enhances their navigability under external magnetic fields, enabling efficient transport of vaccines and chemotherapeutics directly to tumor microenvironments [5, 6, 7].

**Table 1. Comparison of Biohybrid Nanorobotic Systems**

Biohybrid Type	Biological Component	Synthetic Component	Mechanism	Clinical Application
DNA-Based	DNA Origami / Oligonucleotides	Magnetic Iron Oxide / Gold Nanoparticles	Programmable molecular folding; shape-shifting triggers	Cancer immunotherapy; Targeted vaccine delivery; Logic-gated drug release
Immunobots (Macrophage-based)	Live Macrophages	Silica Nanoparticles / Magnetic Beads	Chemotaxis towards inflammation; Phagocytosis evasion	Solid tumor targeting; Active transport of chemotherapeutics
Neutrobots (Neutrophil-based)	Live Neutrophils	Drug-loaded Nanogels / Magnetic Nanoparticles	Trans-endothelial migration; Blood-Brain Barrier crossing	Glioblastoma treatment; Targeted delivery to brain tumors
Spermobots	Motile Sperm Cells	Magnetic Micro-harnesses / Drug-loaded caps	Flagellar propulsion; Rheotaxis (movement against flow)	Gynecological cancer therapy; Assisted fertilization; Genetic cargo transport



**Figure 1. Classification of Nanorobotic Systems**

### 2.1.2. Leukocyte and Neutrophil-Based Systems

Leveraging the body's own immune cells as carriers offers a biomimetic strategy to bypass the mononuclear phagocyte system (MPS), a common barrier for synthetic nanoparticles. Macrophage-based biohybrids, often termed "immunobots," utilize the inherent chemotactic ability of macrophages to migrate toward inflammation and tumor sites. Researchers can enhance their targeting capabilities through magnetic activation by loading these cells with silica or magnetic particles allowing for the delivery of high concentrations of anticancer agents [8]. Similarly, neutrophils have been engineered into "neurobots" by encapsulating drug-loaded nanostructures. These biohybrids can cross the blood-brain barrier to treat malignant gliomas, utilizing the natural ability of neutrophils to traverse endothelial barriers in response to inflammatory cytokines. This "Trojan horse" strategy protects the therapeutic cargo from degradation and immune clearance while ensuring deep tissue penetration [9, 10, 11].

### 2.1.3. Sperm-Templated Systems

Sperm cells possess a powerful natural propulsion system via their flagella, making them excellent candidates for biohybrid micromotors. "Spermbots" are created by coupling motile sperm cells with synthetic magnetic harnesses or drug-loaded microstructures. These devices exploit the sperm's rheotaxis (movement against flow) and thigmotaxis (movement along boundaries) to navigate complex physiological environments. Applications of spermbots extend beyond artificial insemination to include the targeted delivery of hydrophilic drugs and genetic material to gynecological cancers, providing a propulsion efficiency that is difficult to replicate with purely synthetic motors [12, 13].

## 3. Propulsion Mechanisms and Power Sources

The locomotion of nanorobots within the viscous, low-Reynolds-number environment of biological fluids requires efficient propulsion mechanisms. These are broadly classified based on the origin of the energy source: exogenous (external) and endogenous (internal).

### 3.1. Exogenous Propulsion Strategies

Exogenous systems rely on external energy fields to drive the nanorobot, offering the advantage of indefinite operation time without fuel depletion, provided the external source is active [14].

#### 3.1.1. Magnetic Field Actuation

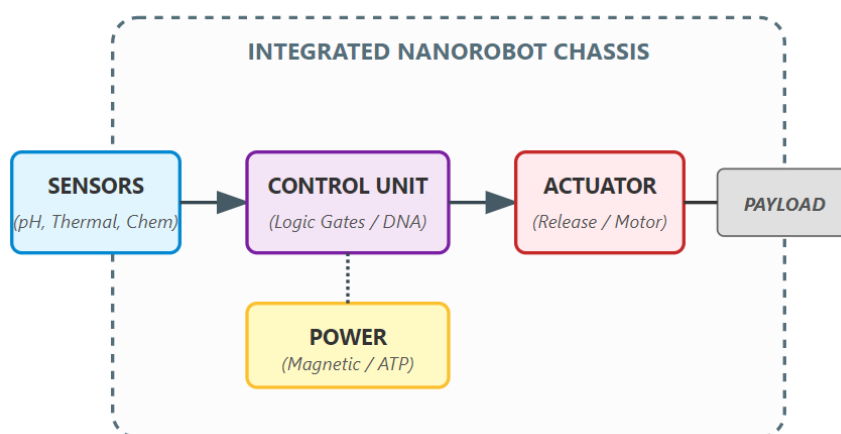
Magnetic propulsion is one of the most promising techniques due to the deep tissue penetration and safety of low-frequency magnetic fields. Nanorobots embedded with ferromagnetic or paramagnetic materials can be steered and propelled by oscillating or rotating magnetic gradients. This non-contact actuation method allows for precise navigation through the vascular network to the site of drug administration without requiring onboard fuel [15].

**Table 2. Classification of Nanorobot Propulsion Mechanisms**

Power Source Category	Propulsion Mechanism	Energy Source / Fuel	Advantages	Limitations
Exogenous (External)	Magnetic Actuation	Oscillating/Rotating Magnetic Fields	Deep tissue penetration; No onboard fuel needed; Precise control	Requires bulky external equipment; Distance-dependent field strength
	Ultrasound	Acoustic Waves	Strong adjustability; Enhances tissue permeability (sonoporation)	Potential for tissue heating; Limited by bone/gas interfaces
	Optical (Light)	Visible/NIR Light	High spatial resolution; Remote activation	Limited tissue penetration depth (especially visible light)
Endogenous (Internal)	Chemical Catalysis	Urea / Hydrogen Peroxide	Autonomous operation; High speed	Toxicity of fuels (e.g., H <sub>2</sub> O <sub>2</sub> ); Byproduct accumulation
	Enzymatic	Glucose / ATP	Biocompatible; Uses physiological fuels	Reaction rate depends on substrate concentration (e.g., blood glucose levels)

### 3.1.2. Optical and Ultrasonic Propulsion

Light-driven nanorobots utilize mechanisms such as photocatalysis or photothermal effects to convert light energy into mechanical motion. Upon irradiation, asymmetric chemical reactions or thermal gradients are generated, propelling the device. However, tissue penetration depth remains a limitation for visible light. Conversely, ultrasound propulsion offers deeper penetration and strong adjustability. Acoustic waves can propel nanorobots toward target tissues, such as tumors, and have been shown to enhance the cellular uptake of drugs via sonoporation effects [15].

**Figure 2. Nanorobot Functional Architecture**

## 3.2. Endogenous Propulsion Systems

Endogenous nanorobots harvest energy directly from the biological environment, utilizing fluids and biochemicals present in the body as fuel.

### 3.2.1. Chemical Catalysis

Chemically powered nanomotors often rely on the decomposition of abundant biological molecules. For example, urease-powered nanobots convert urea into ammonium and bicarbonate ions. The rapid diffusion of these ions creates a local concentration gradient and electric field, driving the particle through self-electrophoresis or diffusiophoresis. Similarly, glucose-fueled systems utilize glucose oxidase to catalyze the oxidation of glucose into D-glucono-1,5-lactone and hydrogen peroxide, generating propulsive force [16].

### 3.2.2. Enzymatic Propulsion

Enzyme-functionalized nanorobots represent a highly biocompatible approach to propulsion. Oxidoreductase enzymes, such as catalase and glucose oxidase, serve as catalytic engines. The enzymatic breakdown of substrates releases chemical energy, often in the form of oxygen bubbles or ionic gradients, which propels the nanorobot. For instance, the decomposition of hydrogen peroxide by catalase into water and oxygen generates recoil forces that drive the motion. This "chemical swimming" allows for autonomous navigation in glucose-rich or urea-rich physiological environments [17]

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## 4. Principles and Fabrication Methods

The transition of nanorobots from theoretical constructs to functional biomedical devices necessitates the adoption of rigorous design principles and advanced fabrication strategies. These methodologies must address the dichotomy between structural robustness required for navigation and the soft compliance necessary for biological interaction.

### 4.1. Bio-inspired and Deterministic Models

Contemporary design paradigms increasingly favor bio-inspiration, drawing from the mechanical efficiency observed in natural systems. Recent investigations highlight the utility of soft network composite materials, which mimic the elasticity and adaptability of biological tissues. These materials allow nanorobots to undergo reversible deformation when traversing narrow capillaries or cellular junctions, minimizing endothelial damage. Engineers can create devices that maintain electronic functionality even under significant mechanical strain by integrating deterministic designs with soft electronics, a critical attribute for long-term in vivo monitoring [18]. Moreover, the micro-architecture of the nanorobot chassis specifically porosity and pore size plays a pivotal role in cargo loading and release kinetics. Research into three-dimensional scaffolds for tissue engineering suggests that manipulating nanoscale porosity can control the diffusion rates of therapeutic agents, thereby enabling sustained release profiles essential for chronic disease management [19].

### 4.2. Integration of Artificial Intelligence in Design

The complexity of nanoscale interactions has spurred the integration of artificial intelligence (AI) and machine learning (ML) into the design process. AI algorithms are currently employed to simulate protein folding and molecular docking, predicting the optimal structural configurations for nanorobots before physical fabrication. These computational methods facilitate the directed evolution of protein-based components, optimizing them for specific functional requirements such as enhanced receptor binding affinity or enzymatic stability in serum [20, 21].

### 4.3. Advanced Fabrication Techniques

The fabrication of nanorobots relies on a suite of high-precision manufacturing techniques, each suited to specific material classes and resolution requirements.

#### 4.3.1. Lithographic and Etching Techniques

Electron-beam lithography (EBL) remains a gold standard for defining nanoscale features with high resolution. It is extensively used to pattern polymer and metal components for analyte sensing and analyzing cellular dynamics [22]. For silicon-based architectures, chemical etching provides a subtractive manufacturing route capable of producing ultra-high aspect ratio structures essential for X-ray imaging detectors and spectrum detection systems [23].

#### 4.3.2. Bio-fabrication and Self-assembly

To enhance biocompatibility, bottom-up approaches such as molecular self-assembly are utilized. This technique exploits the natural tendency of lipids, peptides, and block copolymers to organize into stable nanostructures such as micelles and vesicles under thermodynamic equilibrium. Self-assembled peptide hydrogels are particularly notable for their ability to form nanofibrous networks that mimic the extracellular matrix, serving as excellent candidates for drug delivery vehicles [24, 27]. Additionally, the sol-gel process allows for the synthesis of silica-based nanorobots with tunable mesoporosity, providing high surface area reservoirs for drug encapsulation [28].

#### 4.3.3. Additive Manufacturing

For larger-scale or flexible components, inkjet printing offers a versatile solution. This method enables the deposition of conductive inks and biomaterials onto flexible substrates, facilitating the production of wearable sensors and flexible electronics that can interface with nanorobotic systems [25]. Similarly, electrospinning is employed to generate continuous nanofibers, creating porous scaffolds that support tissue regeneration and cell growth [26].

**Table 3. Advanced Fabrication Techniques for Nanorobots**

Fabrication Technique	Suitable Materials	Resolution / Scale	Applications
Electron-Beam Lithography (EBL)	Polymers, Metals (Gold, Nickel)	High Resolution (<10 nm)	Analyte sensing arrays; Study of cellular dynamics; Precise patterning
Chemical Etching	Silicon, Silicon Dioxide	Micron to Sub-micron	Ultra-high aspect ratio structures; X-ray imaging detectors
Self-Assembly	Lipids, Peptides, DNA	Molecular Scale	Drug delivery vehicles (micelles, liposomes); Biocompatible scaffolds
Inkjet Printing	Conductive Inks, Biomaterials	Micro-scale (>20 $\mu\text{m}$ )	Flexible electronics; Wearable sensors; Rapid prototyping
Electrospinning	Polymers (PLGA, Collagen)	Nanofiber scale	Tissue engineering scaffolds; Nerve regeneration guides

## 5. Biomedical and Clinical Applications

The functional versatility of nanorobots enables their deployment across a wide spectrum of medical disciplines, moving beyond simple drug transport to active intervention and tissue repair.

### 5.1. Endocrinology and Metabolic Monitoring

In the management of diabetes mellitus, nanorobots offer a non-invasive alternative to traditional blood glucose monitoring. These devices can be engineered to function as autonomous "chemostats" circulating in the bloodstream. Upon detecting glucose levels exceeding a physiological threshold, they can release insulin or alert the patient via an external interface. This continuous monitoring capability allows for real-time regulation of blood sugar, significantly reducing the morbidity associated with hypo- and hyperglycemic episodes [29].

### 5.2. Cardiovascular Interventions

Cardiovascular disease management stands to benefit significantly from nanorobotic interventions. Nanorobots are being explored for the treatment of atherosclerosis, where they function by physically identifying and reducing atherosclerotic plaque. These devices can be loaded with lipid-lowering agents, such as statins (e.g., simvastatin, lovastatin), and programmed to target inflamed endothelial regions. Nanorobots minimize systemic side effects like myopathy while maximizing the therapeutic impact on the arterial blockage by delivering these agents locally to the plaque site.

### 5.3. Orthopedics and Regenerative Medicine

In orthopedics, nanorobots facilitate the reconstruction of bone tissue through the precise assembly of mineralized nanoparticles. Utilizing ultrasound-guided navigation, nanorobots can transport bone-like hydroxyapatite particles to fracture sites or areas of osteoporosis. Once at the target, they arrange these particles to mimic the natural hierarchical structure of bone, accelerating the healing process and improving the mechanical integration of the new tissue.

### 5.4. Neurology and Nerve Regeneration

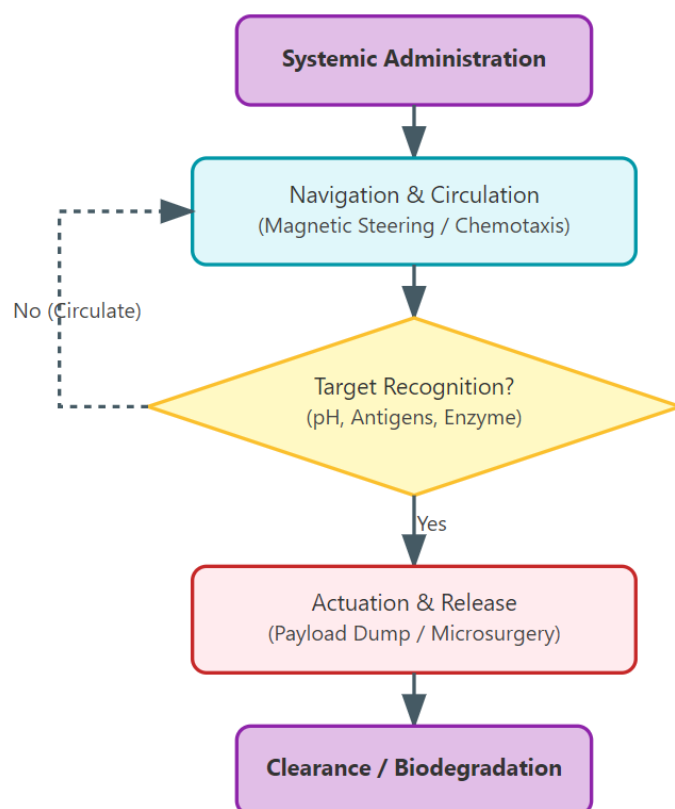
The repair of the central nervous system represents one of the most challenging frontiers in medicine. Nanorobotic systems incorporating peptide amphiphiles have demonstrated profound potential in nerve regeneration. As pioneered by researchers Stupp and Kessler, these self-assembling nanofibers can form scaffolds that mimic the extracellular matrix of the spinal cord. The nanorobots present bioactive amino acid sequences that inhibit scar tissue (glial scar) formation and promote the outgrowth of axons. Efficacy studies in murine models of spinal cord injury have documented significant functional recovery, suggesting a promising avenue for treating paralysis and neurodegenerative disorders.

**Table 4. Clinical Applications of Nanorobotic Systems in Medical Field**

Medical Discipline	Nanorobot Function	Therapeutic Target / Goal	Example Payload / Action
Oncology	Active Targeting & Release	Solid Tumors / Metastatic Cells	Doxorubicin, siRNA, Thermal ablation
Cardiology	Plaque Detection & Ablation	Atherosclerosis / Thrombosis	Statins (Simvastatin), Thrombolytics
Endocrinology	Continuous Monitoring (Chemostat)	Diabetes Management	Insulin release triggered by glucose levels
Neurology	Neural Scaffolding	Spinal Cord Injury / Neurodegeneration	Peptide amphiphiles for axon growth
Infectious Disease	Pathogen Recognition	Bacterial Infections / Biofilms	Antibiotics, Silver nanoparticles
Orthopedics	Mineral Assembly	Bone Fractures / Osteoporosis	Hydroxyapatite nanoparticles for bone repair

### 5.5. Precision Oncology

Targeted cancer therapy remains the primary driver of nanorobotic research. The objective is to achieve a "search and destroy" capability that spares healthy tissue. Oncological nanorobots are typically equipped with three core modules: nanosensors for detecting tumor-specific biomarkers (e.g., overexpressed surface receptors), a cargo bay containing high-potency chemotherapeutics, and a release mechanism triggered by the tumor microenvironment (e.g., acidic pH). This architecture ensures that cytotoxic drugs are released exclusively in the vicinity of malignant cells, drastically reducing systemic toxicity [30].

**Figure 3. Targeted nanorobotic drug delivery system**

### 5.6. Infectious Disease and Immunology

Nanorobots offer a novel approach to combating antibiotic-resistant pathogens. Overcoming resistance mechanisms like biofilm formation by identifying and adhering to bacteria, they can deliver concentrated antibiotics directly to the infection site. Moreover,

in vaccinology, nanorobots can function as adjuvants and delivery vehicles, transporting antigens directly to antigen-presenting cells to elicit a robust and specific immune response.

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## 6. Challenges and Limitations

Despite the promising therapeutic potential, several critical barriers impede the clinical translation of nanorobotic technologies.

### 6.1. Fabrication and Scalability

The transition from laboratory-scale synthesis to industrial mass production poses a significant bottleneck. Many biohybrid and synthetic nanorobots are currently fabricated using complex, low-throughput methods such as optical tweezers or manual assembly, which are economically unfeasible for widespread pharmaceutical application. Developing scalable manufacturing techniques that maintain the precise nanoscale features and functionality of these devices is a prerequisite for commercial viability [31].

### 6.2. Biocompatibility and Environmental Interaction

The interaction between nanorobots and the biological environment is complex and often unpredictable. The formation of a "protein corona" the adsorption of plasma proteins onto the nanorobot surface can alter its physicochemical properties, masking targeting ligands and affecting biodistribution. Moreover, the long-term toxicity of synthetic propulsion materials and the potential immunogenicity of biohybrid components require extensive toxicological profiling to ensure patient safety [32].

### 6.3. Control Systems

Achieving precise real-time control over nanorobot swarms in deep tissues remains a technical challenge. While magnetic actuation is effective, it requires bulky external equipment. Autonomous navigation systems must surmount the chaotic fluid dynamics of blood flow and the physical barriers of the extracellular matrix. Developing feedback mechanisms that allow nanorobots to communicate their location and status to the external operator is essential for monitored therapy [33].

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## 7. Conclusion

Nanorobotic technology represents a revolutionary advancement in the field of biomedicine, offering the potential to transform the diagnosis and treatment of complex diseases. These devices address the fundamental limitations of conventional systemic therapies by enabling precise, molecular-level interventions. The convergence of materials science, robotics, and molecular biology has yielded innovative propulsion and targeting strategies, exemplified by DNA-based and cell-mimicking biohybrids. However, the path to clinical reality is obstructed by challenges in scalability, biocompatibility, and control. Research must prioritize the development of biodegradable materials, autonomous navigation algorithms powered by artificial intelligence, and scalable manufacturing processes.

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