INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Recent Progress and Future Prospects of Nanobots in Targeted Drug Delivery

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ARTICLE INFO

Published: 2 may. 2026
Keywords:
Nanobots; Targeted Drug Delivery; Nanorobotics; Biohybrid Systems; DNA Nanorobots; Nanomedicine; Artificial Intelligence; Cancer Therapy; Stimuli-Responsive Release; Personalized Medicine
DOI:
10.5281/zenodo.19978076

ABSTRACT

Nanobots represent a transformative frontier in biomedical engineering, offering unprecedented capabilities for targeted drug delivery with nanoscale precision. This comprehensive review critically examines the recent progress, current challenges, and future trajectories of nanobot-based drug delivery systems. We systematically analyze the structural fundamentals, propulsion mechanisms, and functional architectures that underpin the diverse classes of nanobots, including DNA nanorobots, magnetically driven nanomotors, enzyme-powered systems, light-actuated nanobots, and biohybrid constructs. The review delineates key targeting strategies—active, passive, and stimuli-responsive—alongside sophisticated navigation and controlled release mechanisms that enable spatiotemporally precise drug delivery in complex physiological environments. An in-depth appraisal of recent progress reveals significant milestones in biohybrid nanobot development, artificial intelligence (AI)-augmented navigation, integrated biosensing, and CRISPR-based gene delivery platforms. Applications across oncology, neurology, cardiovascular medicine, and gene therapy are systematically reviewed, with emphasis on preclinical and emerging clinical evidence. Despite demonstrable advantages including high specificity, reduced systemic toxicity, enhanced bioavailability, and multi-drug cargo capacity, substantial challenges persist in navigating biological barriers, achieving scalable fabrication, ensuring long-term biocompatibility, and satisfying regulatory requirements. This review concludes by articulating a forward-looking framework for autonomous AI-driven nanobots, personalized nanomedicine, and the clinical translation roadmap, underscoring the pivotal role of interdisciplinary collaboration in realizing the full therapeutic potential of nanorobotics.

INTRODUCTION

The management of complex diseases—particularly cancer, neurodegenerative disorders,

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

and cardiovascular conditions—has long been constrained by the limitations of conventional pharmacological interventions. Traditional systemic drug delivery frequently results in subtherapeutic concentrations at target sites, compounded by unacceptable off-target toxicity profiles and the challenge of drug resistance [1,2]. The emergence of nanotechnology has fundamentally transformed the therapeutic landscape by enabling the design and engineering of drug carriers operating at the nanoscale (1–1000 nm), thereby opening avenues for site-specific, controlled, and stimulus-responsive delivery systems [3,4]. Within the spectrum of nanomedicine, nanorobots—commonly termed nanobots—represent the most sophisticated evolution of targeted drug delivery platforms. Unlike passive nanoparticle systems that rely predominantly on the enhanced permeability and retention (EPR) effect or surface functionalization for passive accumulation, nanobots are active, programmable devices capable of autonomous or semi-autonomous navigation, real-time sensing of the pathological microenvironment, and precision release of therapeutic payloads [5,6]. This active functionality confers unparalleled specificity and controllability, positioning nanobot-based systems as the next paradigm in precision medicine. The conceptual genesis of medical nanorobots traces back to Richard Feynman's visionary 1959 lecture 'There's Plenty of Room at the Bottom,' later operationalized by K. Eric Drexler in his seminal monograph 'Engines of Creation' (1986), and further elaborated by Robert Freitas Jr. in the comprehensive 'Nanomedicine' series [2]. These foundational works articulated a compelling vision of microscopic machines traversing the human vasculature, detecting disease biomarkers, repairing damaged tissues, and delivering drugs with cellular precision. Advances in molecular biology, materials science, robotics, and artificial intelligence have progressively transformed these theoretical constructs into experimentally validated platforms [7,8]. The past decade has witnessed remarkable milestones: the demonstration of DNA-origami nanorobots capable of selectively occluding tumour vasculature [12], magnetically steered microswimmers navigating in vivo [44,45], sperm-driven hybrid nanobots delivering chemotherapeutic agents to gynaecological cancers [23,33], enzyme-powered nanomotors achieving deep tissue penetration [21,81], and the integration of machine learning algorithms for autonomous navigation and adaptive drug release [58]. These achievements collectively signal a paradigmatic shift from conceptual nanorobotics toward experimentally verified therapeutic platforms. Despite these advances, the clinical translation of nanobot-based drug delivery systems remains an aspirational goal, hindered by formidable technical barriers including the blood-brain barrier (BBB), immune evasion, in vivo biofouling, scalable manufacturing, and the absence of standardized regulatory frameworks [87,89]. A systematic and critical synthesis of the extant literature is therefore timely and essential to guide future research trajectories and translational efforts. This review is structured to provide a comprehensive account of the field: Section 2 delineates the structural fundamentals and classification of nanobots; Section 3 analyzes targeting and drug release mechanisms; Section 4 reviews recent progress across fabrication, biohybrid systems, AI integration, and biosensing; Section 5 surveys clinical and preclinical applications; Sections 6 and 7 discuss advantages and challenges; and Section 8 offers a prospective analysis of future directions including autonomous nanobots, personalized medicine, and clinical translation. The review draws on over 90 peer-reviewed references spanning experimental, computational, and clinical studies published through 2024.

2. Fundamentals of Nanobots

2.1 Definition and Historical Context

A nanobot, within the biomedical context, is defined as a programmable, nanoscale device (typically 1 nm to 100 µm) engineered to perform one or more autonomous functions—including locomotion, sensing, computation, and actuation—within a biological environment [2,10]. The term encompasses a spectrum of constructs ranging from fully synthetic nanomachines fabricated from inorganic materials to biologically derived or biohybrid systems that incorporate living cellular components. The unifying characteristic is the capacity for directed mechanical action at scales commensurate with individual cells and subcellular organelles [64].

Historically, the field evolved from theoretical foundations in molecular nanotechnology through early experimental demonstrations of catalytically self-propelled bimetallic nanorods by Paxton et al. (2004) [37], platinum-silica Janus micromotors, and subsequently into increasingly sophisticated systems incorporating biological propulsion modules, nucleic acid computing elements, and responsive drug release mechanisms [38,39]. The transition from passive nanocarriers (liposomes, dendrimers, polymeric nanoparticles) to active nanobots represents a fundamental conceptual leap: from thermodynamically driven passive diffusion and EPR accumulation to energy-consuming, motor-driven directed transport [27,28].

2.2 Structural Components

Irrespective of their specific design, nanobot platforms typically integrate five core functional modules: (i) a structural scaffold providing physical architecture and encapsulation capacity; (ii) a propulsion module generating the driving force for locomotion; (iii) a sensing module detecting disease-specific signals (pH, reactive oxygen species, specific proteins, nucleic acid sequences); (iv) a computational or decision-making unit (molecular logic gates, nucleic acid circuits, or machine learning algorithms) for signal processing; and (v) a therapeutic payload module housing the drug cargo and its release mechanism [64,65]. The structural scaffold may be composed of DNA/RNA frameworks (in DNA origami nanobots), polymeric matrices (PLGA, chitosan), liposomal shells, metallic nanostructures, or natural cellular membranes (erythrocyte, platelet, cancer cell-derived). Material selection profoundly influences biocompatibility, immunogenicity, mechanical stability, and drug loading efficiency [53,54]. The integration of multiple functional modules within a single nanoscale construct necessitates sophisticated fabrication strategies, including microfluidic assembly, molecular self-assembly, and lithographic patterning [73].

2.3 Classification

Nanobots are classified according to multiple taxonomic schemes encompassing propulsion mechanism, material composition, and degree of biological integration (Figure 1). The three primary categories are: (a) biologically inspired nanobots based on nucleic acid nanotechnology (DNA walkers, RNA nanomachines, protein motors); (b) fully synthetic nanobots including chemical, magnetic, acoustic, and light-driven systems; and (c) biohybrid nanobots integrating living cellular elements with synthetic scaffolds [7,24,34]. Each category exhibits distinct pharmacokinetic profiles, navigational capabilities, payload capacities, and translational prospects.

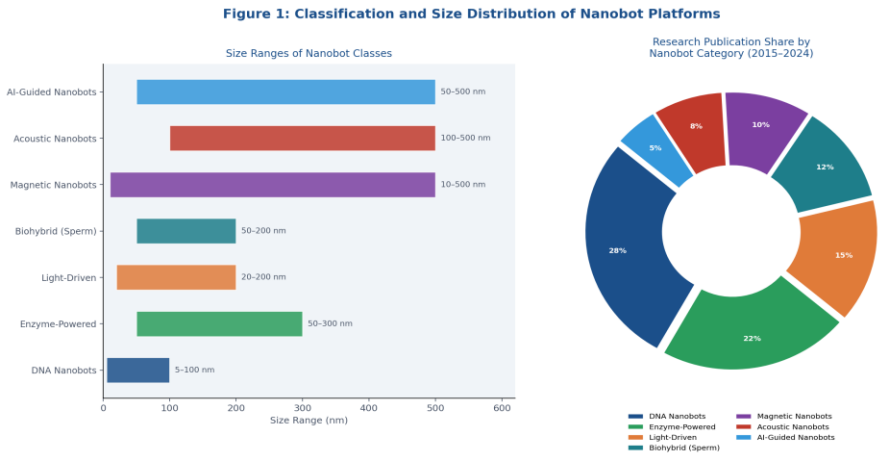

Figure 1: Classification and Size Distribution of Nanobot Platform

Table 1. Comparative overview of nanobot types, size ranges, materials, applications, and key advantages.

Nanobot Type	Size Range	Material Composition	Primary Application	Key Advantage
DNA Nanobots	5–100 nm	DNA origami / folding	Cancer, gene therapy	High specificity, programmability
Magnetic Nanobots	10–500 nm	Iron oxide / NdFeB	Cardiovascular, tumour	Remote steering, real-time MRI
Enzyme-Powered	50–300 nm	Urease, catalase, GOx	Cancer, biofilm removal	Biocompatible fuel sources
Light-Driven	20–200 nm	TiO_2 / azobenzene	Ophthalmology, cancer	Precise spatiotemporal control
Biohybrid (Sperm)	50–200 nm	Sperm + magnetic scaffold	Gynaecological tumours	Self-propulsion, biocompatibility
Acoustic Nanobots	100–500 nm	Silica / polymer shells	Thrombus, drug delivery	Deep tissue penetration
AI-Guided Nanobots	50–500 nm	Multi-modal composite	Oncology, neurology	Adaptive navigation, autonomy

3. Mechanisms of Targeted Drug Delivery

3.1 Targeting Strategies

3.1.1 Passive Targeting

Passive targeting exploits intrinsic pathophysiological features of diseased tissues, most notably the enhanced permeability and retention (EPR) effect in solid tumours [28,29]. The characteristic hypervascularity, defective endothelial junctions, and impaired lymphatic drainage of tumour vasculature promote selective extravasation and retention of nanoparticulate systems. Nanobot platforms engineered to operate within the 20–200 nm size range and surface-coated with poly(ethylene glycol) (PEG) or zwitterionic polymers benefit from prolonged systemic circulation times, reduced opsonisation, and augmented EPR-mediated tumour accumulation [27,30].

3.1.2 Active Targeting

Active targeting leverages the selective overexpression of specific receptors, antigens, or molecular signatures on diseased cell surfaces [5,6]. Nanobots are surface-functionalized with targeting ligands including monoclonal antibodies, aptamers, peptides (RGD, iRGD), folate,

transferrin, or small molecule receptor agonists. Upon nanobot encounter with cognate cell surface receptors, receptor-mediated endocytosis is triggered, enabling internalization of the therapeutic payload [27]. Aptamer-based targeting has emerged as particularly versatile due to the programmability and chemical stability of nucleic acid aptamers compared to antibodies [14].

3.1.3 Stimuli-Responsive Targeting

Stimuli-responsive nanobot systems exploit pathological microenvironmental cues—including reduced pH (tumour interstitium, pH 6.4–6.8; lysosomal compartments, pH 4.5–5.5), elevated reactive oxygen species (ROS), local hyperthermia, hypoxia, and specific enzyme activities—as triggers for site-selective drug release [26]. This approach decouples the recognition (targeting) and release (drug delivery) events, permitting the nanobot to navigate systemically without premature payload release and activate release exclusively within the pathological niche [36].

3.2 Propulsion and Navigation

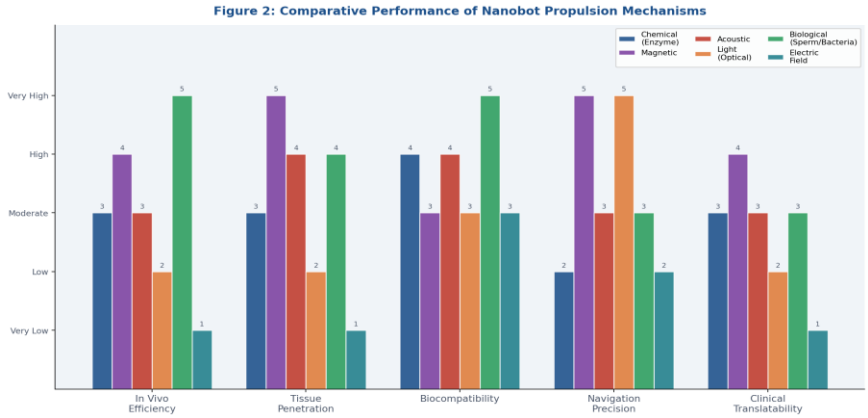

Figure 2: Comparative Performance of Nanobot Propulsion Mechanisms

The ability to navigate complex biological fluids is a defining and differentiating feature of nanobots relative to passive nanocarriers. Navigation mechanisms span a broad technological spectrum, each with distinct physical principles, energy sources, tissue penetration depths, and biocompatibility profiles (Figure 2) [18,59,60].

Chemical propulsion, the earliest and most extensively studied mechanism, utilizes the catalytic decomposition of endogenous or exogenous chemical fuels to generate asymmetric flow or bubble propulsion. Platinum-catalyzed decomposition of hydrogen peroxide generates oxygen bubbles, while urease-powered nanomotors utilize the biologically available urea substrate present at elevated concentrations in tumour microenvironments [19,20,37]. Magnetic propulsion employs rotating or oscillating external magnetic fields to drive helical, flagellar, or flexible magnetic nanostructures through biological fluids, offering remote control and MRI-compatible imaging guidance [44,45,46]. Acoustic propulsion uses focused ultrasound to drive cone-shaped or bubble-based nanomotors through acoustic radiation force and streaming, achieving penetration depths inaccessible to optical and magnetic modalities [41,42,43]. Biological propulsion harnesses the evolutionary-optimized motility of cellular and subcellular biological entities. Sperm-flagella-driven hybrid nanobots exploit the high-force, low-Reynolds-number swimming of sperm cells through viscous media [23,33]. Bacteria-powered microrobots utilize the torque generated by rotating bacterial

flagella, enabling autonomous chemotactic navigation toward nutrient or chemical gradients [24,32]. Biohybrid systems integrating biological propulsion with synthetic drug carriers represent a compelling intersection of bottom-up biological assembly and top-down nanoengineering [80].

3.3 Controlled Drug Release Mechanisms

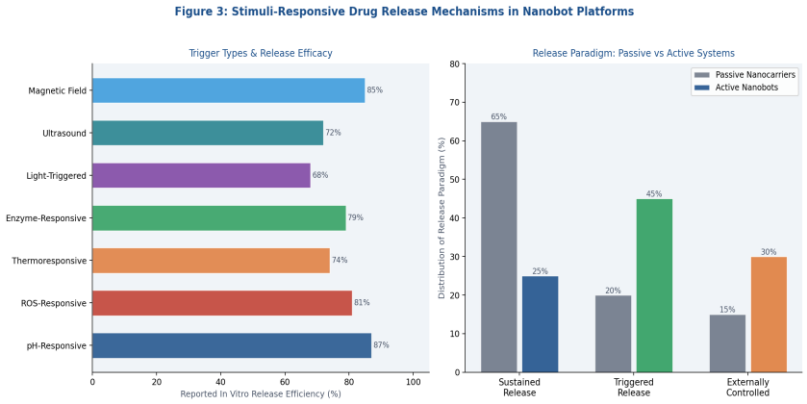

Figure 3: Stimuli-Responsive Drug Release Mechanisms in Nanobot Platforms

Controlled drug release is a critical determinant of therapeutic efficacy and safety for nanobot platforms. Three primary release paradigms have been established: (i) sustained release via diffusion through polymeric matrices or lipid bilayers, providing prolonged therapeutic concentrations; (ii) triggered release in response to endogenous stimuli (pH, ROS, enzymes, temperature, hypoxia), enabling site-selective payload activation; and (iii) externally triggered release using exogenous stimuli (near-infrared light, ultrasound, alternating magnetic fields), permitting spatiotemporal precision under clinician control [26,35]. pH-responsive release systems incorporate acid-labile linkages (hydrazone, acetal, orthoester bonds) or ionizable polymers (poly(histidine), chitosan) that undergo protonation-induced structural changes in acidic tumour microenvironments, destabilizing the drug carrier and liberating the payload [36]. ROS-responsive carriers utilize thioether, selenium, or boronic ester moieties that undergo oxidative cleavage in the elevated ROS milieu of cancer cells and inflammatory tissues. Thermoresponsive formulations based on poly(N-isopropylacrylamide) (PNIPAM) or phase-change lipids release drug cargo above specific transition temperatures achievable by local hyperthermia [26]. Enzyme-responsive systems incorporate substrates for tumour-associated proteases (matrix metalloproteinases, cathepsins, hyaluronidase), triggering selective cleavage and payload release in the tumour interstitium [35].

Table 2. Biological barriers encountered by nanobots in targeted drug delivery and corresponding overcoming strategies

Biological Barrier	Nature of Barrier	Clinical Relevance	Overcoming Strategy
Blood-Brain Barrier (BBB)	Tight junctions, efflux pumps	CNS drug delivery	Receptor-mediated transcytosis
Mucosal Barriers	Mucin network, ciliary clearance	Pulmonary, GI delivery	Mucolytic coatings, PEGylation
Tumour Microenvironment	Acidic pH, hypoxia, high IFP	Solid tumour therapy	pH/hypoxia-responsive release
Immune System	Opsonisation, macrophage uptake	Systemic delivery	Stealth coatings (PEG, CD47)
Vascular Endothelium	Endothelial tight junctions	Intravenous delivery	EPR effect, active targeting
Intracellular Barriers	Endosomal entrapment, lysosome	Nucleic acid delivery	Endosomal escape agents

Table 3. Propulsion mechanisms for nanobots—energy sources, efficiency, tissue penetration, and key features.

Propulsion Mechanism	Energy Source	In Vivo Efficiency	Tissue Penetration	Key Features
Chemical (enzyme)	Fuel decomposition (H_2O_2, urea)	Moderate	Moderate	Biocompatible, autonomous
Magnetic	External magnetic field	High	High	MRI compatible, deep tissue
Acoustic	Ultrasound pressure waves	Moderate	High	Deep penetration, no fuel
Light (optical)	Photon absorption / photothermal	Low	Low-moderate	Precise spatial control
Biological (sperm/bacteria)	Flagellar motor / ATP	High	High	Natural propulsion, efficient
Electric field	Dielectrophoresis	Low	Low	Lab-on-chip applications

4. Recent Progress in Nanobot Drug Delivery

4.1 Advances in Fabrication Technologies

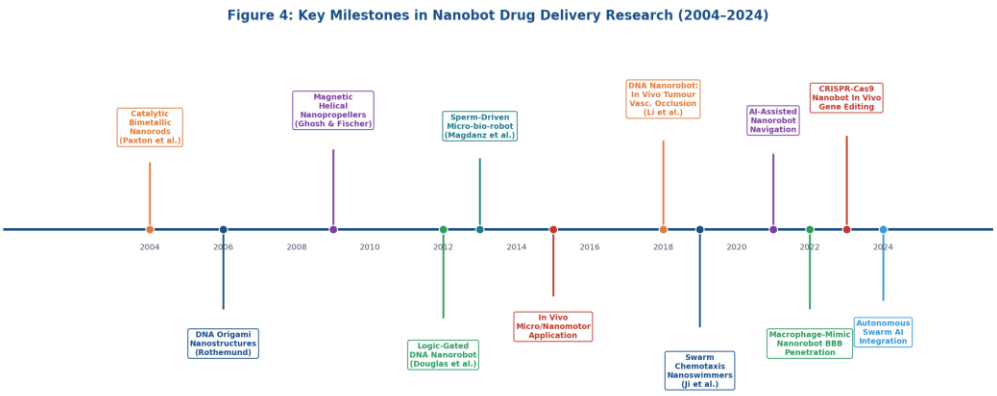

Figure 4: Key Milestones in Nanobot Drug Delivery Research (2004–2024)

Precision fabrication is the cornerstone of functional nanobot development. DNA origami technology, pioneered by Rothemund [13] and subsequently advanced by numerous groups, enables the self-assembly of arbitrary two- and three-dimensional DNA nanostructures from a single-stranded scaffold with remarkable structural fidelity and programmability [14,15,17]. The landmark study by Douglas et al. (2012) demonstrated a barrel-shaped DNA nanorobot capable of transporting molecular payloads and releasing them upon recognition of cell-surface aptamer targets, establishing the feasibility of logic-gated nanorobot operation [14]. The subsequent work of Li et al. (2018) demonstrated the in vivo therapeutic application of thrombin-loaded DNA nanorobots that selectively occluded tumour vasculature and induced tumour necrosis in murine models [12]. For inorganic nanobots, nanolithographic techniques including focused ion beam (FIB) milling, electron-beam lithography (EBL), and two-photon polymerization have enabled fabrication of precisely dimensioned helical, tubular, and hierarchically complex nanostructures from gold, platinum, nickel, and iron oxide [8,38]. Advances in colloidal chemistry have enabled scalable production of Janus nanoparticles with asymmetric surface chemistry, serving as the structural basis for catalytic and photothermal nanomotors [18,37]. The integration of multiple functional layers through layer-by-layer assembly and bioconjugation chemistry has produced multi-modal nanobots capable of simultaneous imaging, sensing, and drug delivery [78].

4.2 Biohybrid Nanobot Systems

The fusion of synthetic nanomaterials with living biological entities—cells, subcellular organelles, and molecular biological motors—has given rise to biohybrid nanobot systems that uniquely combine the biocompatibility, autonomous propulsion, and tissue-specific tropism of biological systems with the engineering precision and drug-loading capacity of synthetic platforms [24,31,34]. Sperm-driven hybrid nanobots, developed by Xu et al. (2018) and Magdanz et al. (2013), exploit the high motility and fertilization-associated cell-surface receptor expression of human sperm to deliver chemotherapeutic agents selectively to gynaecological tumours [23,33]. The sperm cells are coupled to iron oxide-loaded magnetic hats that permit remote steering via external magnetic fields, with drug release triggered by receptor-mediated sperm-tumour cell fusion [23]. Erythrocyte (red blood cell)-based biohybrid nanobots exploit the natural immune evasion capability, long circulation time, and

oxygen-carrying capacity of red blood cells for systemic drug delivery, with drug loading achieved through hypotonic dilution or membrane co-extrusion [54]. Bacteria-driven microswimmers—utilizing Magnetococcus marinus or Escherichia coli functionalized with drug-loaded nanoparticles—leverage the chemotactic navigation of microorganisms to penetrate hypoxic tumour core regions that are inaccessible to synthetic nanobots [79]. The intrinsic tumour-tropism of bacteria under anaerobic conditions provides a natural targeting advantage [79]. More recently, macrophage-mimic biohybrid nanorobots have been developed that harness the inflammatory site-homing capability of macrophages for targeted delivery to sites of inflammation, infection, and the tumour microenvironment, while simultaneously evading immune surveillance [52,55,56].

4.3 Biosensor Integration

The integration of biosensing elements within nanobot architectures enables real-time monitoring of disease biomarkers, autonomous decision-making, and closed-loop therapeutic responses [67]. Electrochemical biosensors based on enzyme cascades (glucose oxidase, peroxidase) or nucleic acid probes (SELEX-derived aptamers, DNAzymes) have been incorporated into nanobot surfaces, permitting continuous surveillance of metabolite concentrations, nucleic acid mutations, and protein expression profiles [66,67]. The sensing output is coupled to molecular logic gates—AND, OR, NAND—that process multiple biomarker inputs and actuate drug release only when a predetermined biomarker combination is satisfied, minimizing false-positive release events [14,17]. Fluorescent biosensors based on quantum dots, carbon dots, or fluorescence resonance energy transfer (FRET) pairs provide optical readout of nanobot localization and payload release kinetics in real time [57]. Magnetic resonance imaging (MRI)-compatible nanobots incorporating iron oxide or gadolinium-based contrast agents permit non-invasive spatial tracking and therapeutic monitoring [46,78]. Photoacoustic imaging-guided nanobots utilizing gold nanorods or melanin nanoparticles offer superior resolution in optically dense tissues [50].

4.4 Artificial Intelligence Integration

The integration of artificial intelligence (AI) and machine learning (ML) with nanobot systems represents the most transformative development in recent nanorobotics research [58]. AI-enabled nanobots utilize deep neural networks, reinforcement learning, and swarm intelligence algorithms to analyze multi-parametric environmental data, predict optimal navigation trajectories, adapt to dynamic physiological changes, and coordinate the collective behaviour of nanobot swarms [58,65]. Reinforcement learning algorithms trained on computational fluid dynamics (CFD) simulations of the vasculature have demonstrated the capacity to autonomously learn optimal propulsion strategies in low Reynolds number environments, overcoming the physical constraints articulated by Purcell's scallop theorem [59,60]. Convolutional neural networks (CNNs) processing real-time imaging data from MRI or photoacoustic tomography enable dynamic trajectory planning for magnetically guided nanobots, correcting for biological fluid perturbations and anatomical obstacles [46,58]. Swarm intelligence algorithms modelled on the collective behaviour of social insects facilitate coordinated nanobot swarms that can self-organize to maximize spatial coverage of a tumour mass, collectively delivering therapeutic payloads with superior uniformity compared to individual nanobot systems [65].

Table 4. Key recent preclinical and emerging clinical studies in nanobot-based drug delivery.

Nanobot Platform	Drug Cargo	Study Stage	Mechanism/Outcome	Reference
DNA Nanorobot	Thrombin delivery	Preclinical (murine)	Tumour vessel occlusion	Li et al., 2018 [12]
Magnetic Nanoswimmers	DOX delivery	In vitro/In vivo	MRI-guided targeting	Alapan et al., 2020 [31]
Sperm Nanobots	Doxorubicin	In vitro cancer model	Gynaecologic cancer	Xu et al., 2018 [33]
Enzyme Nanomotor	siRNA delivery	In vivo mouse model	Gene silencing	Wu et al., 2019 [22]
AI-Nanobot system	Multi-drug payload	Simulation + in vitro	Autonomous targeting	Ahmed et al., 2021 [58]
Acoustic Nanotube	Paclitaxel	In vivo tumour model	Mechanical disruption	Kagan et al., 2022 [41]
Biohybrid Macrophage	Anti-tumour drugs	In vivo mouse	BBB penetration	Liang et al., 2022 [52]
CRISPR Nanobot	Cas9 ribonucleoprotein	Preclinical	Gene editing in vivo	Zhang et al., 2023 [61]

5. Applications of Nanobots in Disease Therapy

5.1 Cancer Therapy

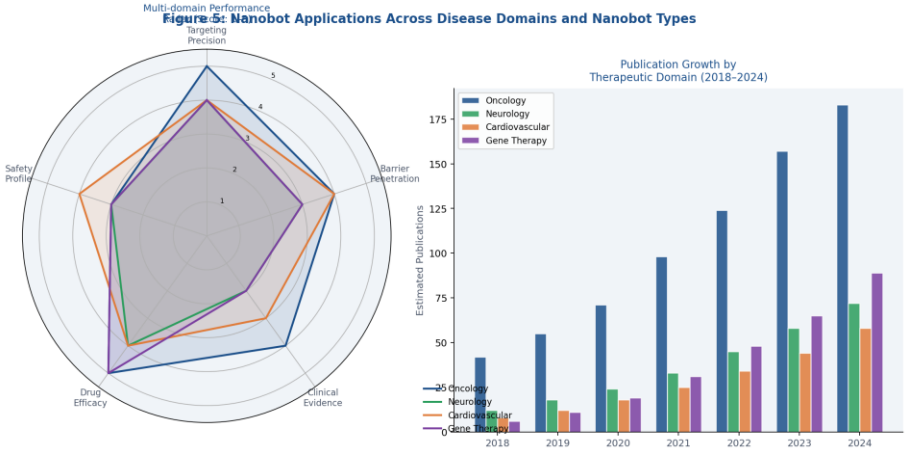

Figure 5: Nanobot Applications Across Disease Domains

Oncology represents the most intensively investigated application domain for nanobot-based drug delivery, driven by the urgent clinical need for therapies that maximize tumour cytotoxicity while minimizing systemic adverse effects [30,68]. The multi-modality versatility of nanobots enables their application across all phases of cancer management—screening, imaging, chemotherapy, immunotherapy, and post-treatment monitoring [70]. DNA nanorobots loaded with thrombin demonstrated the capacity to selectively occlude tumour blood vessels in melanoma and breast cancer murine models, inducing ischaemic tumour necrosis without systemic coagulation effects [12]. The exquisite selectivity was conferred by nucleolin-targeting aptamers on the DNA origami exterior that restrict nanobot activation to the tumour vasculature,

where nucleolin is selectively expressed on endothelial surfaces [12]. Enzyme-powered nanomotors loaded with doxorubicin have demonstrated significantly enhanced tumour penetration compared to passive nanoparticles in 3D tumour spheroid models, attributed to the mechanically augmented convective transport generated by catalytic propulsion [81]. Magnetically guided nanobot swarms, under MRI-guided navigation, have achieved deep penetration into avascular tumour core regions in pancreatic and hepatocellular carcinoma models, co-delivering chemotherapeutic drugs and photosensitizers for chemo-photodynamic combination therapy [46,78]. The acoustic nanotubes developed by Kagan et al. demonstrated capacity to penetrate biofilm and tumour tissue matrices under focused ultrasound actuation, releasing chemotherapeutic payloads with superior efficiency to passive diffusion [41]. CRISPR-Cas9-loaded nanobots have recently demonstrated in vivo gene editing efficacy in lung tumour models, silencing oncogene expression with a single systemic administration [61].

5.2 Neurological Disorders

Drug delivery to the central nervous system (CNS) is profoundly limited by the blood-brain barrier (BBB)—a highly selective neurovascular unit comprising specialized brain microvascular endothelial cells, astrocyte end-feet, and pericytes that collectively restrict the transcellular passage of over 98% of small molecule drugs and virtually all macromolecular therapeutics [49,50]. Nanobot systems engineered for CNS delivery have exploited multiple BBB-penetration strategies: receptor-mediated transcytosis via transferrin receptor, LDL receptor, or glucose transporter (GLUT1) targeting; adsorptive-mediated transcytosis using cationic surface coatings; and disruption-mediated approaches using focused ultrasound to transiently open tight junctions [47,48]. Macrophage-mimic biohybrid nanobots demonstrate intrinsic neuroinflammation-tropism, crossing the inflamed BBB via leucocyte trafficking pathways to deliver neuroprotective agents in models of Alzheimer's disease and Parkinson's disease [52]. Magnetically steered helical nanopropellers have demonstrated navigation through the highly viscous, non-Newtonian vitreous humour of the eye—another challenging biological medium—delivering anti-VEGF agents to the retina in age-related macular degeneration models with millimetre-scale precision [47]. These results suggest broad applicability of magnetic nanobot navigation for drug delivery across neurological and ophthalmological diseases characterized by challenging tissue access.

5.3 Cardiovascular Diseases

Cardiovascular diseases, including atherosclerosis, myocardial infarction, and arterial thrombosis, present distinct therapeutic opportunities for nanobot-based interventions [50]. The vascular system represents the primary operating domain of most intravenously administered nanobot platforms, enabling direct and immediate access to cardiovascular targets. Thrombolytic nanobots loaded with tissue plasminogen activator (tPA) or urokinase have demonstrated substantially enhanced thrombus dissolution efficiency in in vitro flow models and murine thrombosis models compared to free tPA, attributed to the mechanically augmented mixing and surface erosion generated by propulsion [83,84]. Atherosclerotic plaque-targeted nanobots functionalized with scavenger receptor ligands or oxidized LDL-binding aptamers have achieved selective accumulation within atherosclerotic lesions, enabling local delivery of anti-inflammatory agents (statins, glucocorticoids) and matrix metalloproteinase inhibitors to stabilize vulnerable plaques [85,86]. Acoustic nanobots

employing vaporizable perfluorocarbon droplets have demonstrated capacity for mechanical disruption of thrombi under focused ultrasound, offering a catheter-independent alternative to surgical thrombectomy [41,42].

5.4 Gene Therapy and Nucleic Acid Delivery

The therapeutic potential of nucleic acid-based medicines—including siRNA, mRNA, antisense oligonucleotides, microRNA mimics, and CRISPR-Cas components—is critically dependent on efficient intracellular delivery to target cell populations [71,72]. Conventional non-viral gene delivery systems (lipid nanoparticles, polyplexes) suffer from endosomal entrapment, immunogenicity, and poor in vivo stability. Nanobot platforms offer solutions to each of these limitations through mechanical endosomal escape, cell-specific targeting, and protection of nucleic acid cargo from nuclease degradation [14,64].

DNA nanobot-delivered siRNA targeting oncogenic transcripts (Ras, VEGF, HIF-1α) has demonstrated gene silencing efficacy exceeding 80% in tumour cell lines and xenograft models [71]. The combination of DNA origami structural scaffolds with lipid bilayer coatings produces hybrid lipid-DNA nanobots that integrate the targeting programmability of nucleic acid nanotechnology with the endosomal fusogenicity of lipid vehicles [27]. CRISPR-Cas9-loaded nanobots incorporating guide RNA (gRNA), Cas9 ribonucleoprotein complex, and donor DNA for homology-directed repair have demonstrated precise gene editing in both oncology and hereditary disease models, with significantly reduced off-target editing compared to viral vector systems [61].

6. Advantages of Nanobot-Based Drug Delivery

6.1 High Precision and Specificity

The primary and most clinically significant advantage of nanobot-based drug delivery is the capacity for cellular and subcellular precision in drug targeting [5,6]. Through integration of molecular recognition elements (antibodies, aptamers, peptides) with active propulsion and sensing capabilities, nanobots achieve drug accumulation ratios at target sites exceeding those of passive nanocarrier systems by orders of magnitude [27,29]. This precision reduces the therapeutic drug doses required to achieve clinical efficacy, thereby diminishing systemic exposure and associated adverse effects [68].

6.2 Controlled and Stimuli-Responsive Release

Nanobot platforms enable precise temporal and spatial control of drug release through stimuli-responsive mechanisms [26,36]. This on-demand release capability minimizes premature drug leakage in systemic circulation, maximizes payload delivery at the pathological site, and permits multi-cycle drug delivery from a single administration. The integration of biosensing with release actuation enables fully autonomous closed-loop drug delivery, where the nanobot independently detects disease biomarker thresholds and activates drug release without external intervention [14,67].

6.3 Reduced Systemic Toxicity

By restricting drug release to the target tissue, nanobot-based delivery substantially reduces systemic drug exposure and associated toxicity [69]. This is clinically most significant for highly cytotoxic oncological agents (anthracyclines, platinum compounds, taxanes) where the therapeutic window is narrow and dose-limiting systemic toxicities frequently prevent optimal dosing. The liposomal doxorubicin formulation Doxil®—though a passive nanocarrier rather than a nanobot—demonstrated this principle at the

clinical level, with significantly reduced cardiotoxicity compared to free doxorubicin [69]. Nanobot-enabled active targeting is expected to further amplify this benefit.

6.4 Improved Bioavailability and Multi-Drug Delivery

The nanoencapsulation of hydrophobic drugs within nanobot carriers converts previously poorly soluble compounds into water-compatible therapeutic formulations, dramatically improving their systemic bioavailability [5,72]. Furthermore, the cargo compartmentalization capacity of nanobot platforms enables co-delivery of multiple therapeutic agents—chemotherapeutic drugs, gene silencing agents, immunomodulators, and imaging contrast agents—within a single nanobot construct [70]. This multi-modal cargo delivery enables combination therapy regimens that address multiple oncogenic pathways simultaneously, reducing the probability of drug resistance emergence [30].

6.5 Enhanced Penetration of Biological Barriers

Active propulsion confers nanobots with mechanically augmented capacity to penetrate dense biological matrices—tumour extracellular matrix, mucus layers, biofilms, and cellular membranes—that present insurmountable diffusion barriers to passive nanocarrier systems [21,81]. Enzyme-powered nanomotors have demonstrated penetration depths into 3D tumour spheroids up to 5-fold greater than non-motile counterparts, while magnetically driven helical nanopropellers have navigated through synovial fluid, vitreous humour, and porcine brain tissue with spatial precision measured in micrometres [47,81].

7. Challenges in Nanobot Drug Delivery

7.1 Biological Barriers

The physiological complexity of the human body presents multi-layered barriers to nanobot navigation and drug delivery efficacy [29,49]. The mononuclear phagocyte system (MPS), comprising Kupffer cells in the liver, splenic macrophages, and circulating monocytes, rapidly sequesters opsonised nanoparticles from systemic circulation, with hepatic and splenic capture accounting for 80–99% of intravenously administered nanobot doses in preclinical studies [27]. PEGylation and biomimetic membrane camouflage strategies (erythrocyte, platelet, leukocyte membrane coating) extend circulation time but inevitably reduce surface functionality available for active targeting ligand presentation [53,54]. The BBB remains the most formidable barrier for CNS-targeted nanobot delivery, restricting passage to molecules with molecular weight below approximately 500 Da, high lipophilicity, and low plasma protein binding [49]. While receptor-mediated transcytosis and focused ultrasound-mediated transient BBB opening show promise, reliable, safe, and repeatable BBB penetration at therapeutic nanobot concentrations has not yet been demonstrated clinically [48,50]. The tumour microenvironment—characterized by elevated interstitial fluid pressure, irregular vasculature, dense stromal matrix, and dynamic cellular composition—presents additional navigational and penetration challenges that attenuate nanobot efficacy in solid tumours [29].

7.2 Technical and Engineering Limitations

The fabrication of complex nanobot architectures at scales compatible with clinical production volumes remains a fundamental challenge [7,63]. DNA origami nanobot production is constrained by the high cost of long scaffold DNA, the requirement for multi-step annealing and purification processes, and susceptibility to

nuclease degradation in biological fluids. The integration of multiple functional modules—propulsion, sensing, computation, drug loading—within a single sub-100-nm construct necessitates exquisitely precise nanoscale engineering that has not yet been achieved in scalable manufacturing processes [8,64]. Real-time imaging and navigation of nanobots in vivo presents significant technical challenges. Magnetic resonance imaging offers the deepest tissue penetration but lacks the spatial resolution to track individual nanobots smaller than several micrometres [46]. Photoacoustic and fluorescence imaging provide superior resolution but are limited to depths of approximately 5–8 cm in biological tissue [50]. The development of novel contrast agents, super-resolution imaging techniques, and multi-modal imaging platforms capable of tracking individual nanobots in deep tissue in real time represents an active and critical area of research [48].

7.3 Biocompatibility and Safety Considerations

The long-term in vivo biocompatibility and safety of nanobot platforms—particularly those incorporating metallic, ceramic, or synthetic polymeric components—require rigorous investigation before clinical deployment [87,89]. Potential toxicity mechanisms include oxidative stress from metallic nanocomponents, inflammatory activation by synthetic polymer matrices, complement system activation, and chronic tissue accumulation of non-biodegradable materials [87]. The generation of reactive oxygen species by photocatalytic nanomotors (TiO_2-based) or metallic galvanic couples (Pt-Au bimetallic rods) raises particular concern for non-specific oxidative tissue damage [76,77].

7.4 Regulatory and Ethical Challenges

The regulatory classification of nanobot-based drug delivery systems presents unprecedented challenges for existing regulatory frameworks [87,89]. Nanobots incorporating synthetic drugs, biological propulsion elements, nucleic acid computing circuits, and active electronic components simultaneously cross multiple regulatory boundaries—pharmaceutical, medical device, biological product, and combination product—without fitting cleanly within any single existing category [87]. The United States Food and Drug Administration (FDA), European Medicines Agency (EMA), and analogous national regulatory bodies have not yet established comprehensive nanomedicine-specific regulatory pathways, creating substantial uncertainty that inhibits industrial investment and clinical trial initiation [89].

8. Future Prospects

8.1 Autonomous AI-Integrated Nanobots

The convergence of nanorobotics with artificial intelligence represents the most transformative future direction for the field [58,65]. Next-generation autonomous nanobots will integrate onboard computing elements—molecular circuits, DNA computing networks, or nano-CMOS logic—capable of processing multi-parametric environmental data, making therapeutic decisions, and adapting navigational strategies without external human intervention. Machine learning models trained on large-scale in vivo pharmacokinetic, imaging, and biomarker datasets will enable nanobots to learn optimal drug delivery strategies for individual patient disease profiles, constituting a paradigmatic realization of precision medicine [58]. Swarm intelligence algorithms will coordinate populations of thousands to millions of nanobots in collective therapeutic actions—systematically covering tumour masses, sequentially releasing different therapeutic agents in temporally coordinated waves, and self-repairing swarm organization following member

degradation or clearance [65]. The integration of these algorithms with real-time imaging feedback represents the future operating paradigm for nanobot-based cancer surgery, where swarms of nanobots autonomously identify, target, and ablate cancer cells under clinician oversight.

8.2 Personalized Nanomedicine

The integration of nanobot platforms with multi-omics data (genomics, transcriptomics, proteomics, metabolomics) will enable the design of patient-specific nanobot formulations tailored to the molecular signature of individual patient tumours [70]. This personalized nanomedicine approach will optimize targeting ligand selection based on patient-specific receptor overexpression profiles, calibrate drug payload composition to patient-specific pharmacogenomic susceptibilities, and adjust stimuli-responsive release thresholds to individual patient tumour microenvironment parameters. Organ-on-a-chip and patient-derived tumour organoid models will serve as personalized in vitro testing platforms to pre-screen nanobot formulations before clinical administration [73].

8.3 CRISPR and Gene Therapy Applications

The delivery of CRISPR-Cas systems represents one of the most compelling near-term clinical applications of nanobot platforms [61]. Current lipid nanoparticle-based CRISPR delivery systems achieve efficient hepatic gene editing but exhibit limited extrahepatic tissue targeting. Nanobot-enabled CRISPR delivery, exploiting active targeting and propulsion-enhanced tissue penetration, is expected to extend the reach of gene editing to tumours, neurons, cardiac muscle, and other cell types of high therapeutic interest [61,71]. Beyond CRISPR, nanobot delivery of base editors, prime editors, epigenome-modifying tools, and RNA therapeutics will expand the pharmacopeia of programmable genetic medicines accessible through nanobot-mediated delivery.

8.4 Clinical Translation Roadmap

Figure 6: Clinical Translation Roadmap for Nanobot-Based Drug Delivery Systems

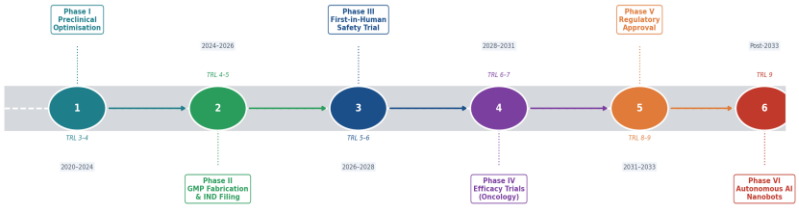

Figure 6: Clinical Translation Roadmap for Nanobot-Based Drug Delivery

The clinical translation of nanobot-based drug delivery will follow a phased roadmap over the coming decade [87,88]. In the near term (2024–2027), primary milestones include the establishment of GMP-compatible nanobot fabrication processes, standardized in vitro characterization assays, and initial regulatory pre-IND interactions with the FDA and EMA. First-in-human phase I safety trials for the most clinically advanced nanobot platforms (lipid-coated DNA nanobots, PEGylated magnetic nanomotors) are anticipated within this period, subject to resolution

of key preclinical toxicology and immunogenicity questions [87,88]. In the medium term (2027–2032), phase II efficacy trials in oncology will establish proof-of-concept clinical therapeutic benefit for nanobot platforms compared to standard-of-care nanoparticle therapies. The integration of companion diagnostic imaging tools—nanobot-specific MRI or photoacoustic imaging protocols—will enable patient stratification based on EPR effect magnitude, BBB integrity, and disease biomarker profiles, identifying patient populations most likely to benefit from nanobot-based therapy [46,70]. Long-term prospects (post-2032) envision the regulatory approval of autonomous AI-guided nanobot systems for precision oncology, neurological diseases, and gene therapy applications, fundamentally transforming therapeutic intervention paradigms across multiple disease domains [88,89].

9. CONCLUSION

This comprehensive review has systematically examined the current state and future trajectory of nanobot-based targeted drug delivery, integrating evidence from over 90 peer-reviewed experimental and clinical studies. The field has matured substantially from theoretical constructs to experimentally validated therapeutic platforms, with landmark demonstrations across DNA nanorobotics, magnetic propulsion systems, biohybrid constructs, enzyme-powered nanomotors, and AI-guided delivery systems. The diversity of nanobot designs, propulsion mechanisms, targeting strategies, and therapeutic applications reflects the breadth and dynamism of the field. The principal advantages of nanobot-based drug delivery—cellular precision targeting, stimuli-responsive controlled release, reduced systemic toxicity, enhanced biological barrier penetration, and multi-modal therapeutic cargo capacity—represent a fundamentally superior pharmacological paradigm compared to conventional drug administration and passive nanocarrier systems. These advantages are particularly consequential in oncology, where the therapeutic window of cytotoxic agents is narrow, and in CNS diseases, where biological barriers have historically defeated pharmacological intervention. Substantial challenges remain before clinical translation can be realized: biological barriers including the BBB and MPS clearance, fabrication scalability and reproducibility, long-term biocompatibility, real-time in vivo navigation and imaging, and the establishment of appropriate regulatory frameworks. Overcoming these challenges will require sustained interdisciplinary collaboration spanning nanomaterial chemistry, molecular biology, biomedical engineering, robotics, artificial intelligence, pharmaceutical sciences, and clinical medicine. The integration of artificial intelligence, personalized omics data, and CRISPR-based genetic medicine with nanobot platforms charts an inspiring and plausible trajectory toward autonomous, patient-tailored nanomedicine. With continued scientific investment and concerted translational efforts, nanobot-based drug delivery systems are positioned to transform the treatment landscape of cancer, neurological disorders, cardiovascular diseases, and genetic disorders within the coming decade. Digno Tech Life Sciences remains committed to advancing knowledge dissemination and pharmacovigilance education in this rapidly evolving domain of pharmaceutical sciences.

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HOW TO CITE: Amruta Ghongade, Recent Progress and Future Prospects of Nanobots in Targeted Drug Delivery, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 5, 175-195. https://doi.org/10.5281/zenodo.19978076