RESEARCH PAPER

Nanorobots in Leukemia: Advances, Challenges and Clinical Potential

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ABSTRACT
Leukemia is a major global health challenge, characterized by uncontrolled proliferation of abnormal hematopoietic cells, with subtypes such as acute myeloid leukemia (AML) associated with high relapse rates and poor survival. Conventional chemotherapy is limited by nonspecific drug distribution, poor pharmacokinetics and severe systemic toxicity, necessitating more targeted and selective approaches. Survival of leukemic stem cells within protective bone marrow niches and multidrug resistance (MDR) further contribute to treatment failure. Nanorobotics offers an active, targeted drug delivery paradigm for leukemia that overcomes the limits of passive diffusion. Recent advances include DNA origami nanorobots that release drugs in response to specific stimuli, magnetically guided nanodevices capable of deep-tissue navigation, and enzyme-powered nanosystems enabling autonomous movement in biological fluids. Spherical nucleic acids have shown improved intracellular uptake and cytotoxic efficacy in preclinical models. Despite these developments, barriers to clinical translation persist, including immune clearance, toxicity of non-biodegradable components, manufacturing complexity and the absence of standardized regulatory frameworks. Future directions include the exploratory integration of artificial intelligence (AI) to potentially support navigation optimization and system coordination, alongside personalized nanomedicine platforms; these applications remain conceptual or early preclinical. Collectively, nanorobotics holds significant potential to transform future leukemia treatment through targeted, minimally invasive and precision-driven strategies.

Keywords: Nanorobotics, Leukemia, Targeted drug delivery, DNA origami, Precision oncology, Multidrug resistance.

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1. INTRODUCTION

Leukemia represents one of the most significant hematological malignancies worldwide, associated with substantial morbidity, mortality and risk of relapse[1,2]. It comprises a heterogeneous group of malignancies classified into acute and chronic forms based on disease progression and cellular lineage. The most common subtypes are acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), which progress rapidly, and chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL), which progress at a slower pace. These diseases arise from accumulated genetic and epigenetic changes in hematopoietic stem cells, resulting in excessive proliferation of immature leukocytes (blasts) that interfere with normal hematopoiesis and the immune response[1,2].

Treatment relies mainly on systemic chemotherapy, which targets rapidly dividing cells and induces remission[3]. Radiotherapy is a frequent complementary therapy, especially for localized disease or the central nervous system, by inducing DNA damage in cancer cells[1]. Hematopoietic stem cell transplantation has curative potential in selected patients. In recent decades, monoclonal antibodies, tyrosine kinase inhibitors (e.g., imatinib in CML) and immunotherapies such as CAR-T cell therapy have further improved outcomes in certain leukemias[4,5].

Despite these advances, conventional treatment retains notable limitations. Systemic toxicity remains a major concern, as non-specific drug distribution damages healthy dividing cells[3]. Multidrug resistance (MDR), survival of leukemic stem cells in protective bone marrow niches and high relapse rates continue to hinder long-term effectiveness[6,7], and only a limited fraction of administered drug reaches leukemic sites because of biological barriers such as the bone marrow microenvironment and drug efflux mechanisms.

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Nanorobotics has therefore emerged as a promising approach in targeted oncological therapy[8]. Nanorobots are engineered nanoscale devices that perform specific biomedical tasks, such as targeted drug delivery, molecular sensing and controlled drug release. They can navigate actively, achieve target specificity and release drugs in a site-directed manner, overcoming drawbacks of conventional therapy. This review provides an overview of recent advances, challenges and clinical potential of nanorobotics in leukemia management[8,9].

2. MATERIALS AND METHODS

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological transparency and reproducibility, and was not registered in PROSPERO or any other prospective registry. PubMed/MEDLINE, Scopus and Google Scholar were searched for publications from January 2006 to April 2026 using Medical Subject Headings (MeSH) terms and free-text keywords, including "nanorobotics," "nanorobots," "leukemia," "hematological malignancy," "targeted drug delivery," "DNA nanotechnology," "DNA origami," "nanomedicine," "magnetic nanorobots," "biohybrid nanorobots," "spherical nucleic acids," "clinical translation" and "precision oncology," combined with Boolean operators (AND, OR, NOT). A representative PubMed string was: ("nanorobot*"[tiab] OR "DNA origami"[tiab] OR "nanomedicine"[MeSH]) AND ("leukemia"[MeSH] OR "acute myeloid leukemia"[tiab] OR "hematological malignancy"[tiab]) AND ("targeted drug delivery"[tiab] OR "clinical translation"[tiab]) NOT ("solid tumor"[tiab] OR "review protocol"[tiab]). Reference lists of eligible articles were screened manually to capture additional studies.

2.1 Eligibility criteria. Included were peer-reviewed original research articles, systematic reviews or meta-analyses in English (2006 to 2026) addressing nanotechnology or nanorobotics-based approaches to leukemia diagnosis, treatment or drug delivery, whether in vitro, in vivo or clinical. Excluded were conference abstracts, editorials, letters, book chapters and other non-peer-reviewed sources (preprints, news articles); studies focused exclusively on non-hematological malignancies without transferable relevance; articles without full-text access; duplicate publications; and studies with unverifiable methodological data.

2.2 Study selection and PRISMA flow. Two reviewers independently screened titles and abstracts, then full texts; disagreements were resolved by consensus. Database searching identified 412 records (PubMed: 187; Scopus: 143; Google Scholar: 82) and manual reference screening 58 more, giving 470 records. After removal of 89 duplicates, 381 records were screened and 274 excluded as irrelevant (non-leukemia focus, non-nanotechnology or off-topic). Of 107 full texts assessed, 70 were excluded (not peer-reviewed/web-only, n=9; non-English, n=3; insufficient nanorobotics content, n=14; full text not accessible, n=11; duplicate reporting, n=33), leaving 37 peer-reviewed studies for synthesis (Figure 1).

2.3 Data extraction and quality assessment. Data were extracted on study design, nanorobotic platform, target leukemia subtype (AML, ALL, CML, CLL), therapeutic payload, key in vitro/in vivo findings, safety data and translational limitations. Quality was appraised independently by two reviewers (a third resolved discrepancies) using ARRIVE 2.0 for in vivo studies, Cochrane Risk of Bias 2.0 (RoB 2) for clinical studies and the Scale for the Assessment of Narrative Review Articles (SANRA) for reviews, and studies were stratified as high, moderate or low quality. Moderate- and high-quality studies contributed to the primary evidence synthesis. Of the 37 studies, 20 (54%) were high quality, 14 (38%) moderate and 3 (8%) borderline; the borderline studies served only as supporting context and did not inform the primary conclusions. High-quality studies were predominantly original research in indexed journals (Nature Biotechnology, Blood Advances, Journal of Hematology and Oncology), while moderate-quality studies were narrative reviews with transparent methodology. No studies were rated low quality.

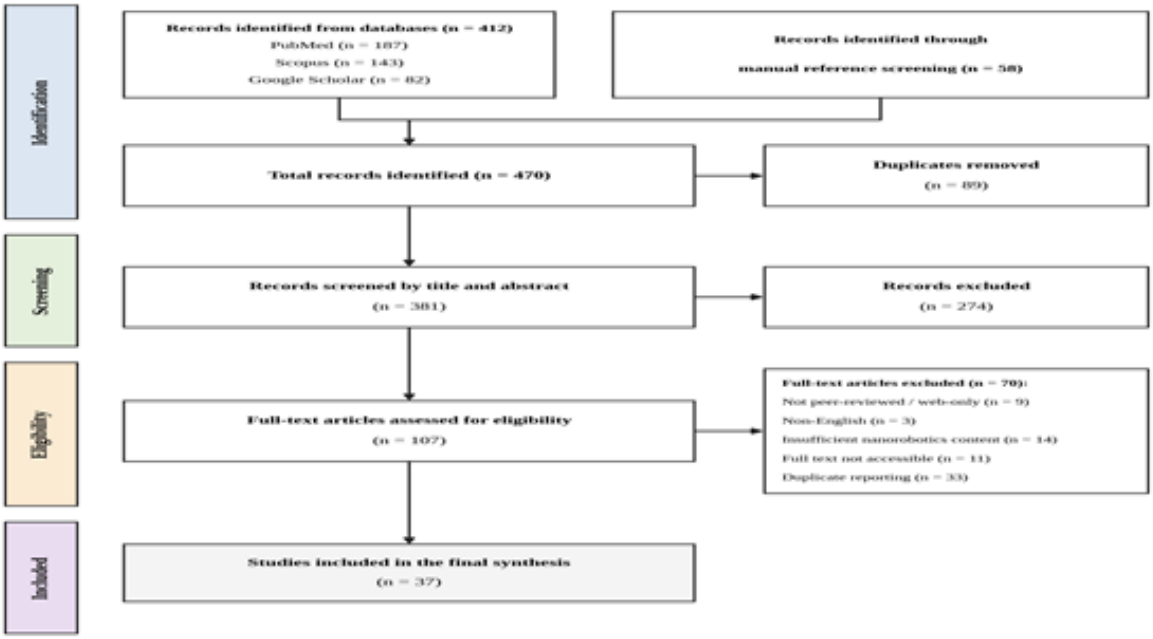


Figure 1. PRISMA 2020 flow diagram of the study selection process for the systematic review

3. RESULTS AND DISCUSSION: ADVANCES IN NANOROBOTICS FOR LEUKEMIA

Nanorobotics in leukemia has advanced considerably in targeted drug delivery, molecular recognition and controlled therapeutic release. These approaches achieve greater specificity toward leukemic cells while reducing the systemic toxicity of traditional treatments. This section examines the principal mechanisms, categories and applications of nanorobotic systems, with a critical assessment of their benefits, limitations and translational prospects. Nanorobots navigate the bloodstream, target leukemic cells and deliver therapeutic agents in a controlled fashion (Figure 2).

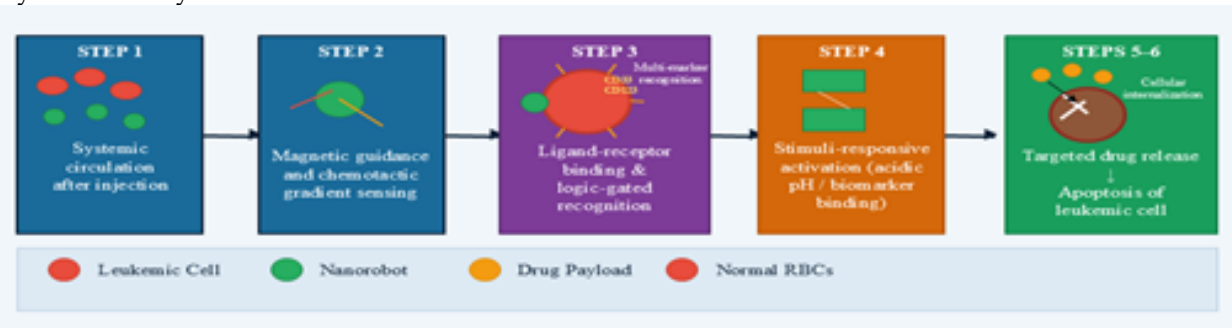


Figure 2. Nanorobot-mediated targeted drug delivery in leukemia, depicting circulation, target recognition, stimuli-responsive activation and therapeutic action. Schematic created by the authors based on mechanistic principles described in[3,7,10,11].

3.1 Mechanisms of Nanorobots in Leukemia

3.1.1 Active navigation and propulsion. Nanorobots shift drug delivery from passive diffusion to active, targeted navigation within the hematological microenvironment. Traditional chemotherapy relies on random dispersion of drug molecules, giving poor targeting and high systemic toxicity. Nanorobots instead use active propulsion, such as enzyme-driven systems fuelled by endogenous substrates (glucose, urea), for directed motion through biological fluids. This improves delivery efficiency, as nanorobots can respond to biochemical gradients, including the hydrogen peroxide (H_2O_2) released by leukemic cells under oxidative stress[6,7].

3.1.2 Target recognition and binding. Nanorobots achieve high specificity by detecting and attaching to surface biomarkers on leukemic cells. CD33 and CD123 are highly expressed on blasts and leukemic stem cells (LSCs) in AML and are therapeutic targets[10,12], and CD19 is the dominant marker in B-cell ALL[13]. CLL-1 is particularly important for eradicating minimal residual disease (MRD) because it is expressed on malignant cells but not on normal hematopoietic stem cells. Adhesion molecules (CD44, CXCR4) can be targeted to disrupt interactions between leukemic cells and the bone marrow niche, making cells more vulnerable to therapy[3,10].

3.1.3 Logic-gated activation. To address tumor heterogeneity and improve targeting precision, advanced DNA nanorobots are engineered with molecular logic gates that perform Boolean operations[7]. These programmable systems improve selectivity and safety

through conditional activation. AND-gated nanorobots activate only when several biomarkers are present together, reducing off-target delivery to healthy tissue, whereas OR-gated systems respond to any of several antigens, offering a way to overcome antigen escape and lower the chance of relapse[4].

3.1.4 Stimuli-responsive drug release. Controlled release at the target site is the final stage of nanorobot function[7,14]. DNA origami nanorobots use locked or caged architectures that are stable under physiological conditions but change structure in response to a particular stimulus[14,15]. The mildly acidic tumor microenvironment (pH 6.5) is among the most common triggers of structural activation and payload release[14,15]. This local release delivers a high dose of cytotoxic agent to leukemic cells with minimal systemic exposure.

3.2 Types of Nanorobotic Systems

Nanorobotic systems can be classified by structural design and propulsion strategy. The ability to maneuver within the complex hematological environment and reach protected sites such as the bone marrow niche is the main factor in choosing a system[6,16].

3.2.1 DNA nanorobots. DNA nanorobots are made by DNA origami, in which single DNA strands are folded into programmable three-dimensional structures. They are typically container-like systems closed by molecular locks and opened by specific biological cues[11,15,17]. *Advantages:* They are highly biocompatible and biodegradable owing to their nucleic acid composition, and highly programmable, allowing molecular logic gates (AND, OR) for conditional activation based on leukemia-associated markers such as CD33 and CD123[7]. This greatly enhances targeting specificity and reduces off-target effects on healthy cells[11]. *Limitations:* They are vulnerable to enzymatic degradation and clearance in blood, which may limit efficacy, and some high-efficacy designs can cause rapid tumor cell death leading to tumor lysis syndrome, so dosage must be carefully regulated[7].

3.2.2 Magnetic nanorobots. Magnetic nanorobots are controlled by external magnetic fields, moving in a translational or rotational manner, and often replicate biological propulsion to move through viscous biological media[6]. *Advantages:* They can be controlled externally without invasive procedures and targeted precisely, allowing navigation even in deep tissue, which is especially useful for penetrating the bone marrow niche. They can also be combined with magnetic resonance imaging (MRI) for real-time monitoring and targeted intervention[6]. *Limitations:* Non-biodegradable metallic components such as iron, cobalt and nickel may accumulate in critical organs and cause long-term harm, and maintaining precise control in dynamic, high-flow vasculature is a major technical concern[6,16].

3.2.3 Biohybrid nanorobots. Biohybrid nanorobots combine synthetic materials with living biological components, such as genetically engineered bacteria or motile human cells, to enhance functionality[6]. *Advantages:* They exploit the inherent motility and chemotactic responses of biological systems, moving autonomously in response to pathological cues such as hypoxia or biochemical gradients from leukemic cells. They also consume little energy and can use endogenous fuels such as glucose or urea[6,18]. *Limitations:* Biological variability, immunogenicity and the possibility of infection or unwanted inflammation are major concerns[6]. Stability, storage and reproducibility are further problems, because the viability of the biological components must be preserved during preparation and administration[18]. Table 1 compares the three platforms.

Table 1. Comparison of nanorobotic systems in leukemia therapy

System type	Primary propulsion	Key advantage in leukemia	Major clinical limitation
DNA nanorobots[11]	Molecular triggers	High targeting specificity via programmable logic	Limited stability; rapid degradation[14,18]
Magnetic nanorobots[6]	External magnetic fields	Effective navigation and deep tissue penetration[6]	Metal toxicity; bioaccumulation[6,19]
Biohybrid nanorobots[6]	Biological motility (flagella/cellular movement)	Autonomous targeting through chemotaxis[6,18]	Immunogenicity; limited stability[18]

3.3 Applications of Nanorobotics in Leukemia Therapy

Nanorobotic systems offer targeted, controlled and multifunctional strategies for leukemia, combining propulsion with stimuli-responsive release. The principal applications are targeted drug delivery, gene therapy and immunotherapy augmentation.

3.3.1 Targeted drug delivery. *Spherical nucleic acids (SNAs):* SNA-based nanostructures improve intracellular delivery through receptor-mediated uptake, especially via scavenger receptors overexpressed on myeloid cells. After internalization, the nucleic acid framework is degraded by enzymes, giving controlled release of the payload. Preclinical studies show improved uptake and enhanced cytotoxicity compared with free drug[8,20]. *DNA origami systems:* Stimuli-responsive locked configurations release payloads on cues such as the acidic pH of the leukemic microenvironment, giving spatially controlled activation, lower off-target toxicity and better selectivity[7,14]. *Vascular targeting:* Nanorobots carrying pro-coagulant enzymes such as thrombin have been studied for selective targeting of tumor-associated vasculature. After binding endothelial markers they can induce localized thrombosis, restricting blood flow and killing tumor cells, but the risk of rapid

tumor breakdown and tumor lysis syndrome demands tight control[7].

3.3.2 Gene therapy. Nanorobots can serve as delivery vehicles for gene-modulating agents, overcoming major hurdles in intracellular delivery of genetic material[3,7]. *siRNA delivery:* Nanomotor platforms deliver small interfering RNA (siRNA) into leukemic cells, where propulsion enhances cellular penetration, gene silencing and inhibition of oncogenic pathways[7]. *Non-viral vectors:* Nanorobotic vectors are under development as substitutes for viral vectors, with better safety and lower immunogenicity, allowing controlled and targeted delivery of therapeutic genes. *CRISPR/Cas9:* Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9 (CRISPR/Cas9) components in nanostructured carriers show potential for targeted genome editing that modulates leukemia-related signaling pathways. Off-target effects and delivery efficiency remain unresolved[3].

3.3.3 Immunotherapy enhancement. Nanorobotic systems are increasingly applied to improve the effectiveness and precision of immunotherapy in leukemia[5]. *Bispecific targeting:* Nanotechnology-enabled bispecific constructs can bind several leukemia antigens at once, improving specificity, reducing the chance of antigen resistance and increasing immune cell-mediated cytotoxicity[4]. *CAR-T optimization:* Nanotechnology-based modifications have been considered to improve the selectivity and safety of chimeric antigen receptor (CAR)-T cell therapy, particularly targeting leukemia-specific antigens rather than those on normal hematopoietic stem cells. *NK cell-mimicking systems:* Nanoparticles designed to replicate natural killer (NK) cell behavior selectively target leukemic cells and induce apoptosis, using ligand-receptor interactions that boost immune recognition and cytotoxicity[3].

3.3.4 Critical comparison with conventional nanomedicine and immunotherapy. Evaluating nanorobotics requires placing it against established paradigms in leukemia, namely passive nanomedicine and immunotherapy. Conventional passive nanomedicine, exemplified by liposomal daunorubicin-cytarabine (CPX-351; Vyxeos), exploits the enhanced permeability and retention (EPR) effect for preferential accumulation in tumor tissue[21,22]. CPX-351 improved pharmacokinetics and survival over conventional 7+3 chemotherapy in selected older patients, but EPR targeting is limited in hematological malignancies, which lack the solid-tumor vasculature the effect depends on. Nanorobots use active propulsion and receptor-mediated targeting to navigate the marrow microenvironment independently of EPR, a critical distinction when malignant cells sit in protective niches inaccessible to passive carriers[3,6]. However, no nanorobotic system has yet shown clinical superiority over approved liposomal formulations, and comparative data remain largely in vitro.

Approved immunotherapies, including gemtuzumab ozogamicin (CD33+ AML), blinatumomab (B-ALL) and tisagenlecleucel (relapsed/refractory B-ALL), define the current precision frontier in leukemia[4,5]. Nanorobots are better placed to complement than replace them, for example through co-delivery of checkpoint inhibitors with cytotoxic agents, or CD33/CD123 bispecific constructs that counter single-antigen escape, a driver of CAR-T resistance. Zeng et al.[4] showed that a dual-targeting CD33/CD123 nanobody T-cell engager produced potent anti-AML activity with a favorable safety profile. Nevertheless, manufacturing complexity, cost and patient-specific customization impose translational barriers that conventional immunotherapy faces to a lesser degree. Table 2 compares the approaches.

Table 2. Nanorobotics vs. conventional nanomedicine vs. immunotherapy in leukemia

Parameter	Nanorobotics	Conventional nanomedicine	Immunotherapy
Targeting	Active; biomarker recognition (CD33, CD123, CD19); logic-gated activation	Passive; EPR (limited in hematological malignancy); surface ligands	Active; antigen-specific immune engagement (mAbs, CAR-T, BiTE)
Clinical evidence	Largely preclinical; no Phase II/III leukemia trials	FDA-approved (e.g., CPX-351); Phase II/III trials	Multiple FDA/EMA approvals; robust Phase III data
Toxicity	Unknown long-term safety; bioaccumulation; tumor lysis; immune clearance	Less than free drug; residual myelosuppression; infusion reactions	CRS, neurotoxicity (CAR-T); on-target/off-tumor effects; VOD (GO)
MDR coverage	High potential; intracellular delivery bypasses P-gp efflux; MDR inhibitor co-delivery	Moderate; encapsulation can reduce efflux but passive entry is limited	Independent of drug efflux; antigen loss remains a resistance route

Parameter	Nanorobotics	Conventional nanomedicine	Immunotherapy
Translational readiness	TRL 2-4; no regulatory framework or GMP standard	TRL 8-9; established pathways and GMP	TRL 7-9; approved products; CAR-T manufacturing evolving
Cost and scalability	Very high; limited scalability; no commercial pipeline	Moderate; scalable; competition lowers prices	CAR-T very high (~$400,000/patient); mAbs moderate; biosimilars emerging

Abbreviations: BiTE, bispecific T-cell engager; CRS, cytokine release syndrome; EPR, enhanced permeability and retention; GMP, good manufacturing practice; GO, gemtuzumab ozogamicin; mAb, monoclonal antibody; MDR, multidrug resistance; P-gp, P-glycoprotein; TRL, technology readiness level; VOD, veno-occlusive disease.

From a health-economic perspective, the very high production cost of nanorobots, driven by DNA origami synthesis, functionalization and quality control, is a major barrier to adoption. Manufacturing scalability, GMP compliance and cost reduction through platform standardization will be needed before they can compete economically with established therapies, and formal cost-effectiveness analysis is not yet possible because no clinical efficacy data exist. Overall, nanorobotics offers theoretically superior targeting and multifunctionality but lags behind conventional nanomedicine and immunotherapy in clinical evidence, regulatory maturity and cost. Its most plausible path to utility is synergistic integration, such as nanorobot-assisted CAR-T delivery or co-loading of epigenetic modulators with cytotoxic agents, supported by leukemia-specific clinical trials rather than extrapolation from solid-tumor models.

3.4 Advantages Over Conventional Therapy

This section consolidates the mechanistic basis of nanorobotic advantage over conventional chemotherapy. The advantages are demonstrated mainly in preclinical models, and direct head-to-head comparisons with approved leukemia therapies remain limited.

3.4.1 Precision targeting and active navigation. Active propulsion and surface functionalization give site-specific targeting, in contrast to the passive diffusion and vascular transport of traditional modalities[7,18]. *Logic-gated recognition:* Molecular logic gates (AND, OR) in DNA-based nanorobots trigger conditional activation on several leukemia-associated biomarkers, including CD33 and CD123, increasing specificity and reducing interactions with healthy cells[7]. *Active homing:* Nanorobots can be programmed to replicate biological homing, localizing within protective niches such as the bone marrow microenvironment, where malignant cells are poorly accessible to standard therapeutics[3].

3.4.2 Reduced systemic toxicity. Traditional chemotherapy cannot distinguish malignant from healthy rapidly dividing cells, causing extensive toxicity. *Targeted payload delivery:* Localized release increases therapeutic concentration in leukemic cells while reducing exposure of normal tissue[3,20]. *Barrier penetration:* Some platforms, including receptor-targeted lipid nanostructures, cross the blood-brain barrier by transcytosis, broadening options for CNS-involved leukemia[6].

3.4.3 Controlled and stimuli-responsive release. Conventional drugs act systemically immediately after administration, causing wide distribution and side effects, whereas nanorobots release drug in response to specific biological cues. DNA origami nanorobots remain inactive under physiological conditions and undergo conformational change in response to signals such as acidic pH, giving spatial and temporal control of activation[11]. Advanced systems can also deliver therapeutics directly inside cells, increasing efficacy while minimizing extracellular exposure and toxicity[20].

3.4.4 Mechanistic basis of enhanced efficiency. The advantages over passive carriers derive from three integrated capabilities that address the core limitations of leukemia chemotherapy: (i) active propulsion that overcomes diffusion limits in complex biological environments[6,16]; (ii) responsiveness to biochemical cues in the tumor microenvironment, enabling adaptive, targeted therapy[23]; and (iii) receptor-mediated uptake that raises intracellular drug levels[8,20]. Nanorobotic delivery is thus more specific and less toxic than traditional chemotherapy (Figure 3).

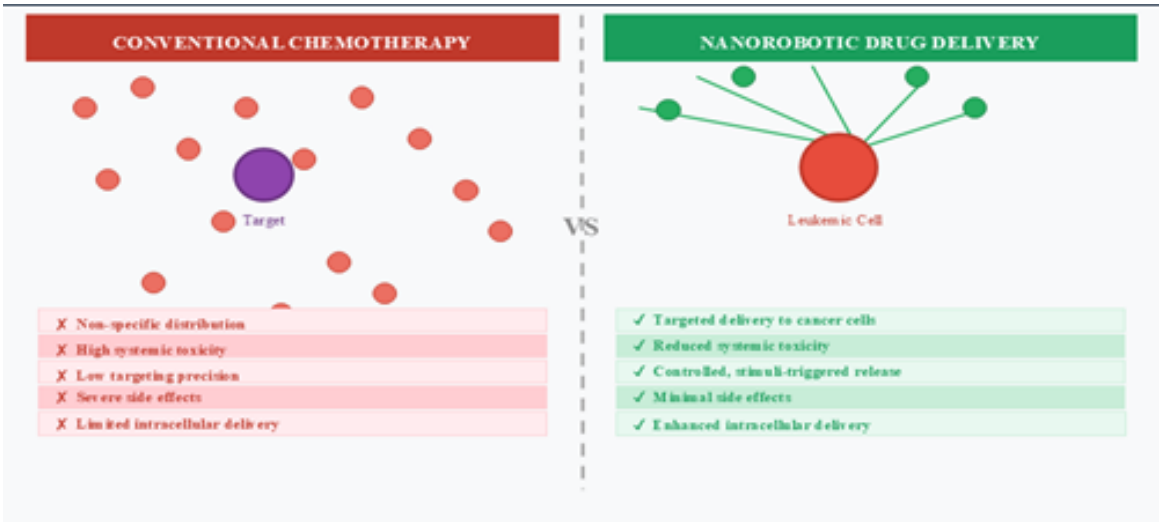


Figure 3. Traditional chemotherapy versus nanorobotic drug delivery, illustrating differences in targeting specificity, systemic toxicity and treatment effectiveness. Schematic created by the authors.

3.5 Challenges and Limitations

Despite strong therapeutic potential, application in leukemia is limited by biological, technical and regulatory barriers between preclinical research and the clinic. Most research is confined to in vitro testing or small animal models, and the disconnect between experimental success and clinical application remains a significant obstacle[5].

3.5.1 Biocompatibility and long-term toxicity. A major design issue is the lack of safe, predictable interaction with complex biological systems[24]. Size, surface charge and composition strongly determine biological responses. *Protein corona:* Nanorobots adsorb plasma proteins in the bloodstream, forming a protein corona that alters their biological identity, may conceal targeting ligands and reduces leukemic cell specificity[25]. *Bioaccumulation:* Non-biodegradable materials, such as metallic components used for imaging or propulsion, can build up in the liver, spleen and kidneys, and prolonged retention may cause chronic toxicity, inflammation and tissue damage[19]. *Cytotoxic effects:* Some nanomaterials generate reactive oxygen species (ROS), causing oxidative stress, mitochondrial dysfunction and damage to normal cells[26].

3.5.2 Immune clearance and opsonization. The immune system is a major obstacle to circulation and function of nanorobots. The mononuclear phagocyte system (MPS) and liver and spleen macrophages rapidly identify and destroy circulating nanorobots, restricting bioavailability and the chance of reaching leukemic sites[24,27]. Stealth modifications such as PEGylation (polyethylene glycol coating) or biomimetic coatings reduce immune recognition[27], but repeated exposure can still induce anti-nanoparticle antibodies that accelerate clearance and reduce efficacy.

3.5.3 Scalability and manufacturing. Large-scale manufacture is a significant challenge for clinical translation. Complex fabrication methods such as DNA origami demand high precision but typically lack scalability[22,28], and uniform size, structure and functionalization are technically difficult to maintain across large batches. Multifunctional nanorobots also carry high material, synthesis and quality-control costs[22], which may restrict clinical adoption and accessibility[28].

3.5.4 Regulatory and ethical considerations. Nanorobotics is at an early regulatory stage. Nanorobotic systems combine properties of drugs, biologics and medical devices, which confuses categorization and regulatory pathways[28], and no standardized criteria exist for assessing pharmacokinetics, biodistribution and long-term safety. As autonomous navigation and responsive behavior are added, predictability and control in complex biological settings become concerns[7]. Aggressive strategies such as vascular targeting or tumor destruction can cause tumor lysis syndrome, so treatment parameters must be carefully optimized for efficacy and safety[7]. Overall, serious biological and technical drawbacks restrict clinical translation (Figure 4).



Figure 4. Key biological and technical barriers to the clinical translation of nanorobotic systems. Schematic created by the authors.

3.5.5 Conflicting evidence and unresolved debates. Several areas of genuine scientific disagreement warrant acknowledgment. First, the structural stability of DNA nanorobots in physiological fluids is contested: unmodified DNA origami degrades rapidly in serum, though chemical modifications such as phosphorothioate substitution can prolong circulatory half-life[14,29], and whether this suffices in leukemia patients with dysregulated immune function is unresolved. Second, the relevance of EPR in hematological malignancies is debated; many argue it is inapplicable without solid-tumor vasculature[3,6], while others suggest that bone marrow sinusoidal fenestrations may create EPR-like patterns[30]. Third, immune clearance variability across platforms is poorly predicted by in vitro models, and PEGylation, the standard stealth strategy, may paradoxically enhance immunogenicity on repeat dosing through accelerated blood clearance[27]. These conflicts underscore the need for standardized hematological-model preclinical testing before clinical translation.

3.6 Clinical Potential and Future Perspectives

Nanorobotics represents a shift from random to targeted drug delivery. Although the field remains preclinical, current developments indicate high potential for clinical translation, especially for inaccessible niches such as the bone marrow microenvironment.

3.6.1 Clinical translation. Nanorobots have not entered clinical practice as autonomous therapeutic agents. A critical distinction must be made between conventional nanotechnology-based delivery systems (liposomal and polymeric carriers), which have progressed through clinical trials and approval with improved pharmacokinetics and reduced toxicity, and true nanorobotic systems with programmable actuation, active navigation and stimuli-responsive release, which remain exclusively preclinical. Differences in tumor biology, immune response and microenvironment between animal models and humans sustain a meaningful gap between preclinical success and clinical applicability. Table 3 compares representative preclinical and clinical-stage platforms.

Table 3. Preclinical vs. clinical-stage nanotechnology platforms in leukemia

Platform / leukemia type	Stage	Key outcome / status	Translational barrier
CPX-351 (Vyxeos), liposomal daunorubicin-cytarabine; therapy-related AML or AML with myelodysplasia-related changes	FDA approved (2017)	Improved overall survival vs. 7+3 in older adults	Passive; no active navigation; EPR limited
Gemtuzumab ozogamicin (Mylotarg); CD33+ AML	FDA approved (re-approved 2017)	Improved OS in favorable cytogenetic risk; in clinical use	Hepatotoxicity (VOD); needs CD33 selection; earlier withdrawal for toxicity
CD33/CD123 bispecific nanobody T-cell engager[4]; AML (CD33+/CD123+)	Preclinical / early Phase I	Potent anti-AML activity; favorable safety in vitro and in mice	Unclear regulatory category; IND pending; human immunogenicity unknown
CLL-1 CAR-T nanobody constructs[12]; AML (CLL-1+)	Preclinical	Less off-tumor toxicity; spares HSCs	No human data; complex GMP manufacturing; undefined pathway

Platform / leukemia type	Stage	Key outcome / status	Translational barrier
Logic-gated DNA origami nanorobots (Douglas et al.)[11]; leukemia (various), proof of concept	Preclinical (in vitro, murine)	Selective tumor cell death; conditional activation in vitro	Nuclease degradation in serum; no IND or regulatory class; GMP not feasible at current TRL
Magnetically guided nanorobots[6]; general cancer / leukemia	Preclinical (in vitro, phantom)	Effective in vitro navigation; deep penetration in phantoms	Metal bioaccumulation; no human data or regulatory precedent

Abbreviations: AML, acute myeloid leukemia; CAR-T, chimeric antigen receptor T-cell; GMP, good manufacturing practice; HSC, hematopoietic stem cell; IND, Investigational New Drug application; OS, overall survival; TRL, technology readiness level; VOD, veno-occlusive disease.

Current FDA and EMA guidelines classify therapeutic agents as drugs, biologics or devices, whereas nanorobots with programmable logic, propulsion and biological components may combine features of all three[28]. A dedicated regulatory framework for autonomous nanomedical devices is therefore needed, with guidance on long-term biodistribution testing, nanorobot-immune interaction studies and standardized in vitro-in vivo correlation (IVIVC) models for hematological applications. Until such frameworks exist, translation of true nanorobotic systems will remain impeded regardless of bench advances.

3.6.2 Personalized medicine. Nanorobots can be engineered to identify specific biomarkers on leukemic cells. Surface functionalization with ligands, antibodies or aptamers against CD19, CD33 or CD123 enables selective binding[21], and logic-gated systems release payloads only in response to specific biological triggers[5], improving specificity and sparing normal tissue. Patient-specific cell membrane coatings are an emerging biomimetic strategy that may improve targeting efficiency and biocompatibility and support personalized platforms.

3.6.3 Integration of artificial intelligence. The intersection of AI and nanorobotics is conceptually promising but largely unexplored. Computational models may in principle support navigation optimization, system coordination and data-driven decisions in complex biological environments, but none of these applications has been validated in nanorobotic contexts relevant to leukemia. Swarm intelligence has been proposed to coordinate multiple nanorobotic units, but experimental demonstrations in hematological settings are absent, and AI-assisted control of drug release remains an aspirational direction. Safety validation, algorithmic transparency and regulatory compliance are essential prerequisites for any clinical use.

3.6.4 Future research directions. Several challenges must be addressed for clinical translation: (i) few leukemia-specific studies, since most research uses generalized cancer models[3]; (ii) insufficient long-term data on biodistribution, bioaccumulation and clearance[31]; (iii) protein corona effects that alter targeting efficiency and require improved surface engineering[25]; and (iv) the lack of global evaluation frameworks, which makes comparison and validation of platforms difficult. Future studies should focus on standardized testing procedures, improved biocompatible materials and multifunctional systems that integrate diagnosis, therapy and monitoring in one platform.

4. CONCLUSION

Nanorobotics represents a significant shift from conventional systemic chemotherapy toward a more responsive and targeted therapeutic approach in leukemia management. Advances in nanoscale engineering, DNA-based nanostructures and functionalized nanoparticle systems demonstrate the potential to improve drug delivery, enhance targeting specificity and overcome microenvironmental barriers such as those within the bone marrow niche. Stimuli-responsive nanocarriers and biohybrid systems highlight the capability of nanotechnology to enable controlled drug release and improved therapeutic precision, addressing key limitations of traditional treatments, particularly nonspecific toxicity and resistance.

Despite these developments, substantial challenges remain for clinical translation. Biocompatibility, immune clearance, protein corona formation and long-term safety continue to limit in vivo applicability. Technical constraints involving large-scale manufacturing and cost, and the absence of standardized regulatory frameworks, must be resolved to ensure safe and effective clinical use.

Future progress will depend on interdisciplinary integration of nanotechnology with molecular biology and computational approaches. Artificial intelligence may in future support targeting accuracy and adaptive control, although such applications remain conceptual. Continued research on safety, standardization and leukemia-specific validation will be essential.

Nanorobotics holds significant potential to transform leukemia therapy through precision targeting, controlled drug delivery and reduced systemic toxicity. However, its clinical application remains constrained by limited human data, regulatory ambiguity and scalability challenges. Until leukemia-specific clinical evidence is established, nanorobotics should be regarded as a promising but still experimental strategy rather than an immediate clinical alternative.

5. RECOMMENDATIONS

To aid clinical translation of nanorobotic systems in leukemia, future studies should focus on well-designed in

vivo and clinical research to verify safety and efficacy. To reduce immune clearance and chronic toxicity, more attention should be paid to biocompatible and biodegradable materials.

Reproducibility and clinical approval are possible only through standardization of manufacturing processes and regulatory frameworks. Cross-disciplinary collaboration among nanotechnology, molecular biology and artificial intelligence should be promoted to enhance targeting precision and system adaptability. Improving cost-effectiveness and scalability will be crucial for wide, equitable access in clinical settings.

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7. ETHICS STATEMENT
This study is a narrative and systematic review of the published literature. No human participants or animal experiments were directly involved in the conduct of this review. Accordingly, ethical approval and informed consent were not required.

8. CONFLICT OF INTEREST
The authors declare no conflict of interest.

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