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REVIEW

Nanotechnology in leukemia therapy: revolutionizing targeted drug delivery and immune modulation

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Abstract

Leukemia, a group of blood cancers, presents a significant global health challenge. Despite advancements in conventional therapies like chemotherapy and immunotherapy, the need for more effective and less toxic treatments remains. Nanotechnology offers a promising avenue for targeted drug delivery and immune modulation in the fight against leukemia. Through the utilization of nanomaterials' special qualities, like their small size, large surface area, and capacity to transport a variety of payloads, scientists are creating novel ways to get around the drawbacks of conventional treatments. These strategies include targeted drug delivery, immune cell activation, and overcoming drug resistance. However, challenges remain in translating these promising nanotechnological approaches into clinical applications. Addressing issues such as toxicity, biodistribution, and regulatory hurdles is crucial for the successful development of nanomedicine for leukemia. In conclusion, nanotechnology offers a promising future for the treatment of leukemia. Continued research and development are essential to unlock the full potential of nanomaterials and improve patient outcomes. The potential of nanotechnology-based strategies to improve the effectiveness of leukemia treatments is explored in this review. We go over the function of different nanomaterials in delivering therapeutic agents to leukemia cells, such as liposomes, polymeric nanoparticles, and inorganic anoparticles. We also investigate the engineering of nanomaterials to influence the immune system and promote anti-tumor reactions.

Keywords Leukemia · Nanotechnology · Drug delivery · Immune modulation · Targeted therapy

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Introduction

Leukemia represents a heterogeneous group of malignant hematological conditions marked by the unregulated growth of abnormal white blood cells within the bone marrow. This process ultimately results in the accumulation of these cells in the bloodstream and various tissues.

Leukemia represents a prevalent form of cancer, constituting around 3.2% of all newly diagnosed cancer cases and 2.8% of cancer-related fatalities globally [1]. Leukemia is categorized into four primary types, determined by the rate of progression and the specific type of white blood cells affected. The types of leukemia encompass acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). Special type leukemia is a relatively rare form of leukemia; however, regardless of the specific type, the fundamental issue involves the abnormal proliferation of hematopoietic stem cells under certain pathogenic factors, leading to the production of a significant number of abnormal white blood cells [2, 3]. With the advent of next-generation sequencing (NGS) and the discovery of various biomarkers, the World Health Organization (WHO) classification underwent updates in 2022, resulting in significant modifications to the conventional classification of acute leukemias and myeloid neoplasms [4]. Owing to the intricate nature of leukemia classification and prognostic stratification, there exists no standardized treatment approach, with therapeutic modalities differing based on the specific forms. Therefore, it is essential to develop a treatment plan that incorporates comprehensive classification and prognostic stratification.

Due to its non-localized nature, leukemia requires a complex therapeutic approach targeting multiple sites, including the bloodstream, bone marrow, and lymphoid organs [5]. Current treatment strategies include chemotherapy [6], immunotherapy [7], and hematopoietic stem cell transplantation (HSCT) [8]. While chemotherapy remains the standard treatment, it lacks selectivity [9], whereas immunotherapy leverages the immune system to target malignant cells. Novel therapeutic modalities, such as chimeric antigen receptor (CAR) T cell therapy, antibody–drug conjugates (ADCs), and immune checkpoint inhibitors (ICIs), have revolutionized leukemia treatment [10]. However, significant challenges remain, including potential drug interactions [11–13], concerns over long-term safety [14], limited efficacy across all leukemia types [9], and the risk of severe toxicities [15]. Malignant cells exhibit resistance to the effects of chemotherapeutic agents and cell division inhibitors, demonstrating their capacity for molecular adaptation and the development of tumor survival strategies. These strategies activate angiogenic mechanisms to avert hypoxic conditions and facilitate nutrient acquisition [16]. Consequently, there is an urgent need for modified targeted therapies to enhance life expectancy and mitigate treatment-related toxicity. The advancement of nanomaterials for leukemia treatment signifies a substantial progression in enhancing therapeutic results. One such promising approach is nanotechnology, which has the potential to revolutionize leukemia treatment by improving drug delivery and immune system activation.

This process can contribute to both the diagnosis and treatment of leukemia in several ways, including (1) nano-immunomodulation: Nanotechnology-based modulation of the immune system is presented as a cutting-edge strategy that holds the potential to yield substantial advancements in the management of severe pathologies [17]. With the creative design of nanoscale devices for drug delivery, nano-immunomodulation has become a promising tool for the treatment of malignancies [15]. The diminutive dimensions of nanoparticles enable them to overcome numerous biological barriers and facilitate the delivery of therapeutic agents to specific targets [18, 19]. Furthermore, it activates the immune system to produce a specific immune response against designated antigens [17]. (2) Nanocarriers for drug delivery: A targeted approach that has been widely explored involves the use of nanocarriers for drug delivery [20]. These nanocarriers, including liposomes and polymeric nanoparticles [21], are capable of encapsulating anticancer drugs and delivering them directly to leukemic cells, thereby minimizing side effects and enhancing therapeutic efficacy [21–23]. The nanocarriers can be engineered to identify specific markers on leukemic cells, facilitating accurate drug delivery [24]. Moreover, A distinct approach employs nanoparticles in the realm of gene therapy. These nanoparticles can deliver genes that encode anticancer proteins or inhibitors of leukemic cell growth, thereby modulating the genetic expression of leukemic cells and inducing their apoptosis [25].

The current state of targeted therapeutic nanomaterials for leukemia is examined in this manuscript after a thorough review of current therapeutic approaches for the disease. These include both organic nanomaterials (lipid-based materials, polymers, etc.) and artificial nanomaterials and nanomaterials that are inorganic. Additionally, the review briefly discusses the opportunities and difficulties related to the development of targeted nanomaterials in the context of treating leukemia.

Nanomaterials for immunomodulation

Nanomaterials, defined by their nanoscale dimensions (1–100 nm), offer unparalleled opportunities in leukemia therapy due to their tunable physicochemical properties,

such as size, surface chemistry, and morphology. These attributes enable precise interactions with leukemia cells and the hematological microenvironment, surpassing the limitations of conventional therapies like chemotherapy and immunotherapy. Below, we delve into specific nanomaterial classes—liposomes, polymeric nanoparticles, and inorganic nanomaterials—highlighting their tailored designs, mechanisms of action, and leukemia-specific applications.

Liposomes: precision delivery and immune synergy

Liposomes, spherical vesicles with phospholipid bilayers, excel in leukemia therapy due to their ability to encapsulate both hydrophilic and hydrophobic therapeutic agents, such as chemotherapeutic drugs (e.g., doxorubicin) or nucleic acids (e.g., siRNA targeting BCL-2, an anti-apoptotic protein overexpressed in leukemia). Their biocompatibility and capacity for surface functionalization with ligands (e.g., anti-CD19 antibodies for B cell acute lymphoblastic leukemia [B-ALL]) allow selective targeting of leukemic blasts in the bloodstream or bone marrow. For instance, PEGylated liposomes conjugated with anti-CD33 antibodies have demonstrated enhanced uptake by acute myeloid leukemia (AML) cells, reducing off-target effects on healthy hematopoietic cells [26, 27]. Beyond drug delivery, liposomes can co-deliver immune adjuvants like CpG oligonucleotides, triggering Toll-like receptor 9 (TLR-9) activation in antigen-presenting cells (APCs) to amplify anti-leukemic T cell responses. A recent study showcased liposomal formulations delivering RNA-LPX (RNA-lipoplexes) encoding leukemia-associated antigens (e.g., WT1), achieving robust CD8 + T cell priming in preclinical AML models [28]. However, challenges such as endosomal escape remain, necessitating innovations like pH-sensitive lipids to ensure cytosolic release of payloads in leukemia cells.

Polymeric nanoparticles: controlled release and microenvironment modulation

Polymeric nanoparticles, such as those made from poly(lactic-co-glycolic acid) (PLGA), offer controlled drug release kinetics, critical for sustained therapy in leukemia's dynamic microenvironment (e.g., bone marrow niches). Their degradability minimizes long-term toxicity, a key advantage over inorganic materials. In leukemia, PLGA nanoparticles have been engineered to deliver tyrosine kinase inhibitors (e.g., imatinib) to chronic myeloid leukemia (CML) cells harboring the BCR-ABL fusion, achieving higher intracellular concentrations than free drug formulations [29]. Surface modifications, such as coating with hyaluronic acid, enhance binding to CD44, a receptor overexpressed on leukemic stem cells (LSCs), enabling eradication of this resistant population. A 2024 study demonstrated that PLGA nanoparticles loaded with decitabine, a hypomethylating agent, reprogrammed the epigenetic landscape of AML cells, sensitizing them to subsequent immunotherapy [30]. Additionally, polymeric nanoparticles can modulate the bone marrow stroma by releasing anti-inflammatory cytokines (e.g., IL-10), reducing the protective niche that shields LSCs from immune surveillance.

Inorganic nanomaterials: multifunctionality and theranostic potential

Inorganic nanomaterials, including gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), and iron oxide nanoparticles (IONPs), bring unique optical, magnetic, and catalytic properties to leukemia therapy. AuNPs, for example, can be functionalized with aptamers targeting AML-specific markers (e.g., CD123) for photothermal ablation, where near-infrared light triggers localized heating to induce apoptosis in leukemic cells without systemic toxicity [31]. A 2023 study reported AuNPs conjugated with anti-CD19 antibodies achieving a 70% reduction in B-ALL cell viability in vitro, leveraging plasmonic heating [32]. IONPs, meanwhile, serve dual roles in drug delivery and magnetic resonance imaging (MRI), enabling real-time tracking of therapeutic distribution in leukemia patients. For instance, IONPs loaded with daunorubicin have shown enhanced accumulation in AML bone marrow sites under magnetic guidance, improving efficacy over free drug administration [33]. However, their potential to generate reactive oxygen species (ROS) requires careful surface passivation (e.g., with silica coatings) to prevent oxidative damage to healthy hematopoietic progenitors. AgNPs, though less studied in leukemia, exhibit intrinsic anti-leukemic activity by disrupting mitochondrial function in cancer cells, though their clinical translation is hindered by cytotoxicity concerns [34].

Nuclear targeting: overcoming intracellular barriers

A cutting-edge application of nanomaterials in leukemia therapy is nuclear targeting, addressing multidrug resistance (MDR) driven by efflux pumps like P-glycoprotein. Nuclear-targeted nanoparticles, such as those functionalized with nuclear localization signals (NLS) peptides, deliver DNA-damaging agents (e.g., topotecan) directly to the nucleus of leukemia cells. A 2024 preclinical study demonstrated that NLS-conjugated liposomes increased topotecan nuclear accumulation in MDR AML cells by threefold, bypassing cytoplasmic efflux and enhancing DNA double-strand breaks [35]. This approach is particularly promising for relapsed/refractory leukemia, where conventional therapies fail due to resistance mechanisms.

Leukemia-specific design considerations

The hematological nature of leukemia necessitates nanomaterial designs that account for circulation in blood, penetration into bone marrow, and interaction with immune cells beyond phagocytosis. For example, smaller nanoparticles (< 50 nm) exhibit prolonged blood circulation and better extravasation into marrow sinuses compared to larger particles, optimizing delivery to leukemic niches [36]. Surface charge also plays a critical role: Cationic nanoparticles enhance uptake by negatively charged leukemia cell membranes but risk hemolysis, while neutral or zwitterionic surfaces improve biocompatibility and stealth properties against immune clearance. In AML, zwitterionic polymeric nanoparticles have shown reduced splenic uptake and enhanced bone marrow targeting, delivering payloads like venetoclax with minimal toxicity [37].

Challenges and innovations

Despite their promise, nanomaterials face hurdles in leukemia therapy. Biodistribution varies unpredictably in the blood-rich leukemia microenvironment, and clearance by the reticuloendothelial system can reduce efficacy. Innovations like biomimetic coatings (e.g., leukemia cell membrane-derived vesicles) are emerging to enhance specificity and evade immune detection. A 2023 study reported that AML cell membrane-coated AuNPs achieved a fivefold increase in homing to leukemic sites in mouse models, highlighting the potential of bioinspired designs [38]. Additionally, scalability and reproducibility of synthesis remain technical barriers, necessitating standardized protocols for clinical-grade production.

Comparison of nanomaterials in leukemia therapy

Numerous nanodrug carriers in development utilize the increased permeability and retention (EPR) effect to concentrate within tumor microenvironments. In leukemia, where malignant cells are present in peripheral blood and bone marrow, the EPR effect is diminished. To address this restriction, new nanodrug delivery techniques are being investigated [39]. A promising strategy entails targeted nanocarriers modified with ligands or antibodies that specifically identify leukemia-associated markers. This method facilitates accurate medication delivery to cancerous cells while avoiding off-target effects, therefore improving therapeutic efficacy and decreasing systemic toxicity [40].

Nanomaterials offer several advantages in leukemia treatment, particularly in targeted drug delivery, controlled drug release, and overcoming multidrug resistance (MDR). For instance, polymeric nanoparticles functionalized with transferrin have been shown to enhance daunorubicin (DNR) delivery while co-administering tetrandrine to inhibit P-glycoprotein, thus increasing drug retention and sensitivity in MDR leukemia cells [41]. Additionally, nanomaterials can facilitate controlled drug release. Gold nanoparticles coated with temperature-sensitive polymers, for example, can release doxorubicin upon mild hyperthermia, improving drug uptake and cytotoxicity while sparing healthy cells [42]. Multidrug resistance (MDR) continues to pose a significant barrier in leukemia treatment, as cancer cells often acquire resistance to chemotherapy. Nanocarriers can mitigate multidrug resistance by enhancing intracellular drug accumulation. Polymeric nanoparticles modified with P-glycoprotein inhibitors can obstruct drug efflux pumps, hence improving the intracellular retention of chemotherapeutic medicines [43].

Liposomes are spherical nanoparticles (50–1000 nm) made of phospholipids and cholesterol, providing a membrane-like structure characterized by low toxicity and good biocompatibility. Their functionalization facilitates the selective targeting of leukemia cells through binding to specific receptors, hence augmenting therapeutic efficacy and reducing toxicity. Furthermore, liposomes enhance the solubility and stability of anticancer agents, safeguarding them from enzymatic destruction and enabling regulated release, which is essential for prolonged leukemia therapy. Notwithstanding its benefits, liposomes encounter obstacles, including immunological reactions, possible off-target effects, instability in physiological environments, and suboptimal tumor internalization rate for intravenous therapy. Temperature and pH influence drug release efficacy; however, elevated production costs and intricate synthesis methods restrict their wider utilization. Mitigating these constraints is crucial for enhancing liposome-mediated leukemia treatments [44–47].

Polymer-based nanoparticles provide versatility in drug delivery by encapsulating small molecules, proteins, and nucleic acids, featuring adjustable qualities such as size, surface attributes, and drug release kinetics for accurate targeting [48]. Nonetheless, issues such as unregulated drug release and polymer breakdown, affected by pH, temperature, and enzyme activity, hinder clinical applicability [49].

A primary benefit of noble metal nanoparticles in leukemia therapy is their capacity to preferentially target cancer cells. These nanoparticles can be modified with ligands or antibodies that selectively attach to leukemia cells, sparing healthy cells and so reducing harm to normal tissues—one of the primary limitations of traditional chemotherapy and radiation therapy. Gold nanoparticles can be coupled with antibodies that identify specific surface markers on leukemia cells. Upon binding, these nanoparticles can be triggered by laser irradiation, resulting in a photothermal action that

destroys cancer cells. Both in vitro and in vivo investigations have proven the efficacy of this method in eradicating leukemia cells [50]. Platinum nanoparticles function as carriers for cisplatin, selectively attaching to leukemia cells and releasing the chemotherapeutic drug upon cellular internalization, resulting in efficient cancer cell eradication. This mechanism has been substantiated through in vitro and in vivo investigations [51]. Moreover, gold nanoparticles can transport small interfering RNA (siRNA), which inhibits genes associated with leukemia advancement. By specifically delivering siRNA to tumor locations, these nanoparticles diminish the expression of target genes, thereby impeding the proliferation of leukemia cells. This novel method signifies a hopeful pathway for precision-targeted leukemia treatment [52]. Adverse symptoms including nausea, seizure disorders, nonspecific biodistribution, and neuronal hyperactivity and increased resistance to chemotherapy and elevated risk of illness recurrence [53, 54] continue to pose significant concerns in leukemia treatment (Table 1).

Mechanism of nano-immunomodulation

Due to their small size and manipulable qualities, nanomaterials have become a potent tool in immunology and medicine, offering special qualities and uses [57]. Nanomaterials are essential to immunomodulation in immunology, which is the process of maximizing immune responses for immunostimulation in cancer immunotherapy or vaccination, as well as immunosuppression in autoimmune diseases. Through their composition, nanoparticles can be engineered to directly or indirectly interact with the immune system as carriers of active ingredients [58]. By efficiently delivering adjuvants and antigens to immune cells, they have demonstrated promise in improving vaccine durability and prolonging immune responses [57]. It is crucial to remember that, despite the fact that nanomaterials have a lot of promise for use in immunology and medicine, questions have been raised about their long-term effects on living things as well as their safety and biocompatibility [59]. The properties of nanomaterials are important in how they interact with biological systems. Chemical nature, size, shape, surface charge, topography, stiffness, and functional features are the main attributes that affect these interactions [60]. These characteristics impact the internalization of nanomaterials and the responses of cells by determining their interactions with the extracellular matrix, cell membrane, cytoplasmic proteins, nucleus, and other cellular organelles. Regarding interactions with the immune system, the primary elements influencing the immunogenic effects of nanoparticles are their size, shape, composition, protein binding, and mode of administration [61]. Since nanomaterials have the ability to either stimulate or suppress immune responses, their surface characteristics are especially crucial in determining how well they work with the immune system. Furthermore, the toxic manifestations of nanomaterials are influenced by physicochemical properties like surface area, surface energy, crystal structure, physiochemical stability, chemical composition, and surface roughness [62]. In the following, we will briefly explain each of the mentioned features.

Size is one of the significant features that influence the uptake of nanomaterials. Monocytes and macrophages can absorb smaller particles (80 × 320 nm) more easily than they can larger particles (6 µm diameter) [36]. Additionally, particle size affects the magnitude of the immune response, with smaller particles (approximately 5 µm) eliciting a significantly higher immune response compared to larger particles (approximately 12 µm) when administered pulmonary [63]. Shape is another substantial property that impacts the immune response. For example, filo micelles with a cylindrical shape have demonstrated more sustained blood circulation than their spherical counterparts, lasting up to one week following intravenous injection. In a similar vein, disk-shaped nanoparticles have shown greater in vivo targeting specificity than spherical particles of comparable size to endothelial cells expressing intercellular adhesion molecule receptors in mice [64]. The structural makeup and surface attributes of nanomaterials, encompassing dimensions beyond size and form, exert a crucial influence on their immunogenic behavior. Particles synthesized from biodegradable polymers, such as PLGA, or biocompatible polymers, like polyethylene glycol (PEG), do not elicit the production of pro-inflammatory cytokines nor the activation of inflammasomes in bone marrow-derived macrophages. In conclusion, it is worth noting that the composition and surface properties of nanomaterials play an essential role in their interaction with the immune system [36]. Furthermore, the surface properties of nanomaterials largely determine their compatibility with the immune system [61]. This is closely related to the Protein binding characteristic, particularly the formation of a protein corona, which affects the biological identity of nanomaterials. The total amount of protein adsorbed onto the particle surface and the protein corona composition are influenced by both particle size and shape [65], and can significantly impact the nanomaterial's interactions with the immune system. Finally, the administration route also influences the immunogenicity of nanomaterials. For example, subcutaneous administration is often associated with a higher immunogenicity risk compared to intravenous administration for therapeutic proteins [66]. However, the relationship between immunogenicity and the route of administration is complicated and can change based on the particular nanomaterial and its characteristics.

Nanomaterials engage with the innate immune system through multifaceted interactions involving cells and

Table 1 Comparative analysis of nanomaterials for leukemia therapy: mechanisms, applications, and key considerations

Type of nanomaterials	Key mechanisms and features	Therapeutic applications	Notable benefits and examples	Disadvantage	References
Liposomes	Encapsulation of both hydrophilic and hydrophobic agents Targeted drug/antigen delivery Enhanced bioavailability through lipid bilayer protection	Nanoparticle-based vaccines Anticancer drug delivery Sustained drug release (including nonvascular routes)	Excellent biocompatibility and low toxicity Ability to modify size, surface charge, and lamellarity for controlled release Protection from enzymatic degradation	Limited stability in circulation; prone to leakage Rapid clearance by the reticuloendothelial system (RES) Challenges with endosomal escape (requires pH-sensitive lipids) Scalability and reproducibility issues in production	[55]
Polymeric Nanoparticles	Controlled and sustained drug release Surface charge tuning to modulate immune responses Versatility through various polymeric matrices (e.g., PLGA, PEG)	Delivery systems for anti-inflammatory drugs Applications in biosensing and bioimaging Platforms for targeted gene therapy	High versatility in design and degradation profiles Customizable for targeting specific tissues and immune cells Potential for combination therapies	Potential polymer degradation by-products may cause inflammation Limited drug-loading capacity for some therapeutics Variability in biodistribution due to RES uptake Complex synthesis protocols for clinical-scale production	[29]
Inorganic Nanomaterials (gold, silver, iron oxide)	Intrinsic anti-inflammatory or immunostimulatory properties Excellent chemical stability and ease of functionalization Unique optical, electrical, and magnetic properties	Bioimaging and diagnostic applications Cancer therapy, including photothermal treatment Targeted drug delivery using stimuli-responsive release	Superior physical stability compared to organic counterparts Enhanced contrast for imaging modalities Multifunctional platforms that combine therapy and diagnosis (theranostics)	Potential cytotoxicity (e.g., ROS generation by AuNPs) Limited biodegradability (e.g., gold nanoparticles) Clinical translation hindered by long-term safety concerns Requires surface passivation (e.g., silica coatings) to reduce toxicity	[34]
Carbon Nanotubes	High aspect ratio enabling efficient cell membrane penetration Modulation of immune cell (e.g., macrophage) polarization Unique optical and electrical characteristics for tracking and delivery	Gene therapy and targeted chemotherapy delivery Platforms for biosensing and phototherapy Potential carriers for combined diagnostic and therapeutic applications	Exceptional mechanical strength and electrical conductivity Enhanced delivery efficiency across cellular barriers Possibility for surface modifications to reduce toxicity and improve targeting	Potential immunogenicity and inflammatory responses Poor solubility and aggregation in biological fluids Long-term biodistribution and clearance pathways poorly understood	[56]

molecules at tissue interfaces. These interactions predominantly involve phagocytes and their pathogen recognition receptors, such as Toll-like receptors (TLRs) [67]. Depending on the context, these interactions may lead to either the effective clearance of threats or pathological outcomes. Numerous studies have explored the effects of nanomaterials on the human innate immune system. For example, clinically significant nanoparticles—such as Fe_3O_4, TiO_2, ZnO, CuO, Ag_2O, and AlOOH—have been shown to upregulate TLR 4 and TLR 6 expression in THP-1 cells, achieving levels comparable to those induced by lipopolysaccharide (LPS) stimulation [68]. Furthermore, CNTs have been reported to interact with complement system proteins in blood and with collectins in pulmonary tissues, potentially influencing their cellular adhesion and distribution within the body [69].

Nanomaterials interact with the human adaptive immune system through diverse mechanisms, primarily involving T and B lymphocytes. Among these, T cells have been the most extensively studied in the context of nanomaterial interactions. These interactions can lead to immunomodulation, encompassing both immune-stimulation and immunosuppression [70]. While traditional research has predominantly focused on toxicity and biocompatibility, recent high-throughput gene expression analyses have revealed that certain functionalized carbon nanotubes can directly activate specific inflammatory pathways. This finding underscores the complexity of nanomaterials' effects on the adaptive immune system. Additionally, although less studied, B cells and natural killer (NK) cells are also influenced by nanomaterials [71]. The various aspects of human immunity which manipulated by nanomaterials are reviewed below (Fig. 1).

T cell activation: amplifying adaptive immunity

T cell activation is a cornerstone of anti-leukemic immunity, requiring antigen presentation, co-stimulatory signals, and cytokine support. Nanomaterials enhance this process by optimizing antigen delivery to APCs, such as dendritic cells (DCs), and fine-tuning co-stimulatory interactions. For instance, liposomes encapsulating leukemia-associated antigens (e.g., WT1 or PR1) deliver these payloads to DCs with high efficiency due to their small size (< 100 nm) and surface modifications (e.g., mannose ligands targeting DC mannose receptors). This enhances MHC class I cross-presentation, a critical step for priming CD8 + cytotoxic T lymphocytes (CTLs) against leukemic cells [72]. A 2024 study demonstrated that RNA-lipoplexes (RNA-LPX) delivered via liposomes upregulated MHC-I expression on DCs by 2.5-fold in AML mouse models, resulting in a 60% increase in CTL infiltration into bone marrow niches [73].

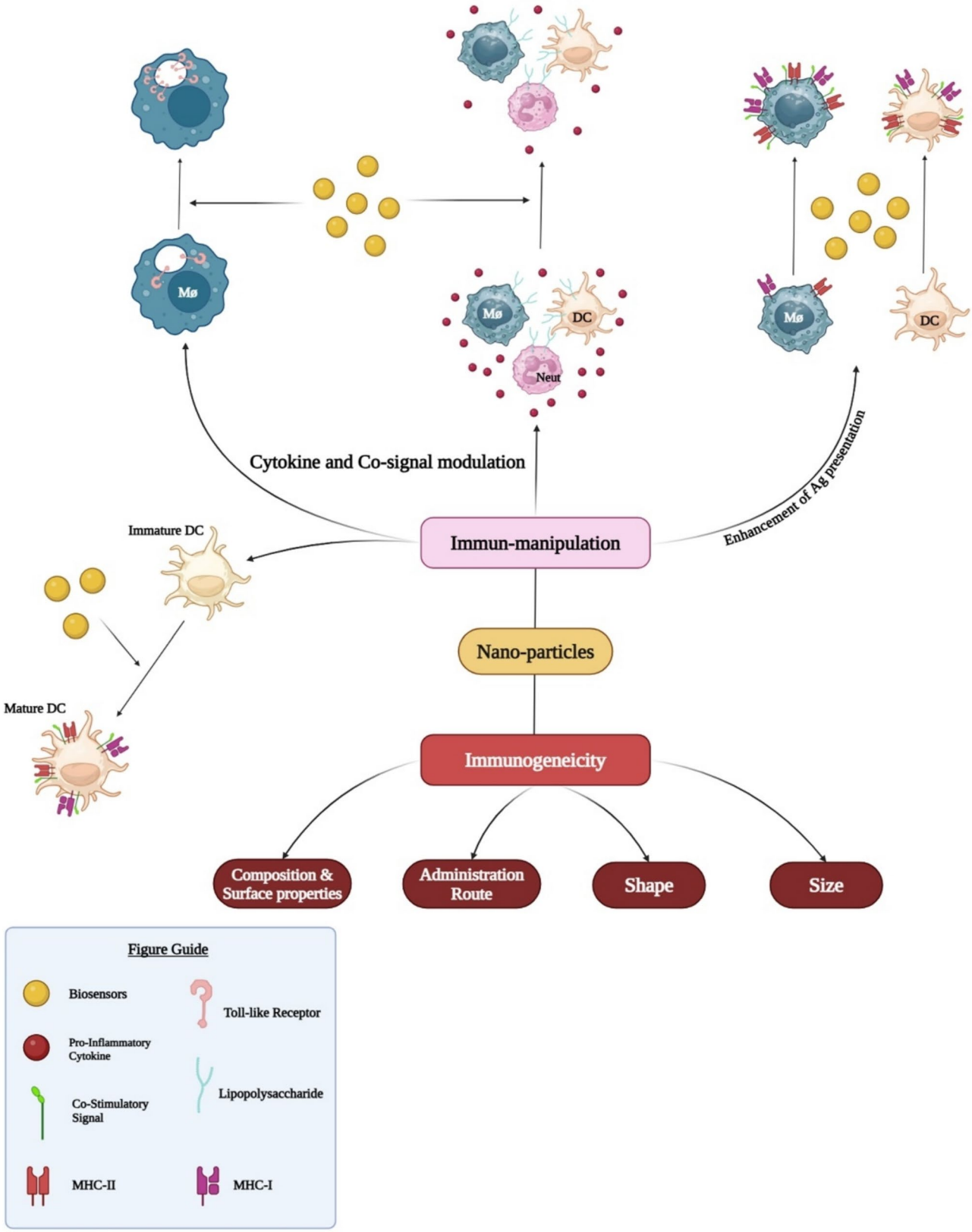
Nanomaterials also amplify co-stimulatory signals essential for T cell priming. Gold nanoparticles (AuNPs) functionalized with anti-CD28 antibodies mimic the co-stimulatory role of CD80/CD86, enhancing T cell receptor (TCR) signaling when paired with antigen-loaded APCs [31]. In a preclinical B-ALL model, AuNPs co-delivering CD19 peptides and anti-CD28 increased CD8 + T cell proliferation by 40% compared to free antigen administration, highlighting their role in overcoming immunosuppression in leukemia microenvironments [74]. Furthermore, nanomaterials can sustain T cell activation by releasing adjuvants like CpG oligonucleotides, which activate TLR-9 on DCs, promoting IL-12 production—a key cytokine for Th1 differentiation and CTL persistence [75]. This sustained activation is critical in leukemia, where T cell exhaustion often limits therapeutic efficacy.

Enhancement of antigen presentation

Nanomaterials enhance antigen presentation through several mechanisms, as demonstrated by various studies. For instance, nanoparticles can improve antigen delivery and processing in APCs. Amorphous silica nanoparticles, sized between 70 and 100 nm, have been shown to enhance exogenous antigen entry into the cytosol from endosomes, thereby inducing cross-presentation in dendritic cells [72]. Similarly, polymer nanoparticles encapsulating tumor-associated antigens improved antigen delivery efficiency, resulting in enhanced CD8 + T cell responses in head and neck cancer models [76]. Moreover, nanomaterials can serve as both antigen carriers and intrinsic adjuvants. Self-assembled nanoparticles (SANPs), which mimic pathogens in size and antigen presentation, have been observed to enhance antigen presentation, thereby boosting both cellular and humoral immunity [77]. Additionally, some nanomaterials modulate the autophagy of dendritic cells, a process closely associated with antigen presentation [78]. The effects of nanomaterials on antigen presentation, however, vary by type. While titanium dioxide and silica-coated titanium dioxide nanoparticles increase antigen presentation and co-stimulation activity in macrophages, carbon nanotubes exhibit minimal immunological effects on the cell types studied [79].

Modulation of co-stimulatory and co-inhibitory signals

Nanomaterials influence co-stimulatory and co-inhibitory signals within the immune system, impacting both innate and adaptive immune responses. Recent studies highlight that the spatial arrangement of immunostimulatory agents on nanomaterials significantly affects immune cell activation.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Biosensors
Toll-like Receptor
Pro-Inflammatory Cytokine
Lipopolysaccharide
Co-Stimulatory Signal
MHC-II
MHC-I

◂**Fig. 1** Mechanisms of Nano-Immunomodulation in Leukemia. This schematic illustrates the immunological pathways modulated by nanomaterials in the context of leukemia therapy. **a** Antigen presentation: Liposomes (e.g., RNA-LPX) deliver leukemia-associated antigens (e.g., WT1) to dendritic cells (DCs), enhancing MHC class I cross-presentation and priming CD8 + cytotoxic T lymphocytes (CTLs) against leukemic cells, as demonstrated in preclinical AML models. **b** T cell activation: Gold nanoparticles (AuNPs) functionalized with anti-CD28 antibodies amplify co-stimulatory signals, boosting CTL proliferation and effector function in vitro and in vivo in B-ALL settings. (C) Cytokine modulation: PLGA nanoparticles release IL-2 locally in the bone marrow, upregulating IFN-γ and supporting NK cell cytotoxicity, validated in AML mouse models. (D) Innate immunity: Iron oxide nanoparticles (IONPs) activate complement (C3a/C5a) and induce TNF-α secretion, recruiting innate immune cells to leukemic niches in vivo. (E) Checkpoint inhibition: Polymeric nanoparticles deliver PD-L1 siRNA, silencing immune evasion pathways in AML cells and restoring T cell activity, observed in preclinical studies. The figure highlights nanomaterial interactions with innate and adaptive immunity, tailored to leukemia's hematological microenvironment, with experimental contexts noted (in vitro, in vivo)

For instance, DNA origami nanoparticles presenting CpG motifs at specific distances (e.g., 7 nm) have been shown to enhance TLR-9 activation in macrophages by mimicking the active dimer structure of the receptor [75]. This spatial accuracy allows for precise immune system modulation, which could improve the effectiveness and selectivity of immune-modulating nanomaterials. It is interesting to note that immunological responses are influenced by the hydrophilic characteristics of nanoparticles. Both in vitro and in vivo, hydrophilic nanogels, such as those made of polymers like PEG, polysulfobetaine, and polycarboxybetaine, have shown the capacity to reduce the immune responses triggered by LPS [80].

Cytokine release: orchestrating immune dynamics

Cytokine release is a pivotal mechanism by which nanomaterials modulate the immune milieu, either amplifying pro-inflammatory responses to combat leukemia or tempering inflammation to reduce toxicity. Polymeric nanoparticles, such as PLGA-based systems, can be engineered for controlled release of cytokines like IL-2 or IFN-γ, directly supporting T cell expansion and effector function. In a 2023 study, PLGA nanoparticles releasing IL-2 at AML tumor sites increased intratumoral IFN-γ levels by threefold, enhancing NK cell cytotoxicity and CTL activity without systemic cytokine storm risks [81]. This localized delivery contrasts with free cytokine administration, which often leads to off-target effects like capillary leak syndrome.

Nanomaterials also indirectly regulate cytokine profiles by interacting with innate immune cells. Iron oxide nanoparticles (IONPs) activate the complement system, upregulating pro-inflammatory cytokines (e.g., TNF-α, IL-1β) via C3a/C5a signaling in a dose-dependent manner [82]. In AML, this can recruit neutrophils and macrophages to leukemic niches, amplifying innate immunity as a bridge to adaptive responses. However, excessive complement activation risks immunotoxicity, necessitating surface modifications like PEGylation to balance cytokine induction. Conversely, carbon-based nanomaterials (e.g., functionalized CNTs) exhibit anti-inflammatory effects by downregulating IL-6 and upregulating IL-10 in preclinical models, potentially mitigating graft-versus-host disease (GVHD) in leukemia patients post-transplantation [83, 84]. A 2024 study showed that PEG-coated CNTs reduced IL-6 levels by 50% in a GVHD mouse model, preserving anti-leukemic immunity while limiting tissue [85].

Innate immune activation: bridging to adaptive responses

Nano-immunomodulation begins with innate immunity, where nanomaterials engage pattern recognition receptors (PRRs) like TLRs to prime downstream T cell responses. Silica nanoparticles, for example, enhance cross-presentation by facilitating antigen escape from endosomes into the cytosol of DCs, a process mediated by lysosomal membrane permeabilization [72]. This increases MHC-I loading and IL-12 secretion, driving Th1 polarization. In leukemia, this mechanism could target minimal residual disease (MRD) by boosting CTL recognition of low-abundance antigens. Similarly, AuNPs conjugated with CpG motifs spatially align TLR-9 ligands to mimic pathogen structures, doubling IL-12 output compared to free CpG in vitro [75]. This precision enhances DC maturation, a prerequisite for effective T cell priming in leukemia's immunosuppressive bone marrow.

Influence on immune cell differentiation

Nanomaterials significantly influence immune cell differentiation through mechanisms dependent on their physical and chemical properties. Some nanomaterials facilitate stem cell proliferation and differentiation [86]. For example, PLGA NPs have been shown to induce dendritic cell (DC) maturation, a critical process in eliciting robust immune responses. These nanoparticles are rapidly internalized by DCs, triggering phenotypic changes and cytokine secretion profiles indicative of maturation, partly through the activation of mitogen-activated protein kinases (MAPKs). Notably, the surface properties of nanomaterials play a pivotal role in their interactions with immune cells. Variations in surface charge—cationic, neutral, or anionic—on PLGA NPs result in distinct effects on DC maturation, emphasizing the importance of surface characteristics in immune modulation [87, 88].

Nano-immunotherapy for leukemia

Nano-immunotherapy holds significant potential for treating various types of leukemia by enhancing the efficacy of existing immunotherapies and overcoming their limitations. While the provided context does not specifically focus on leukemia, the principles of nano-immunotherapy can be applied to this hematological malignancy. In AML and acute lymphoid leukemia (ALL), immunotherapy approaches such as allogeneic stem cell transplantation, monoclonal antibodies, immune checkpoint inhibitors, bispecific T cell engagers (BiTEs), and CAR T cell therapy have shown promising results (Fig. 2) [89]. Nanotechnology can potentially enhance these therapies by improving their delivery, efficacy, and safety profiles. Nanoparticles can be engineered to deliver immunotherapeutic agents

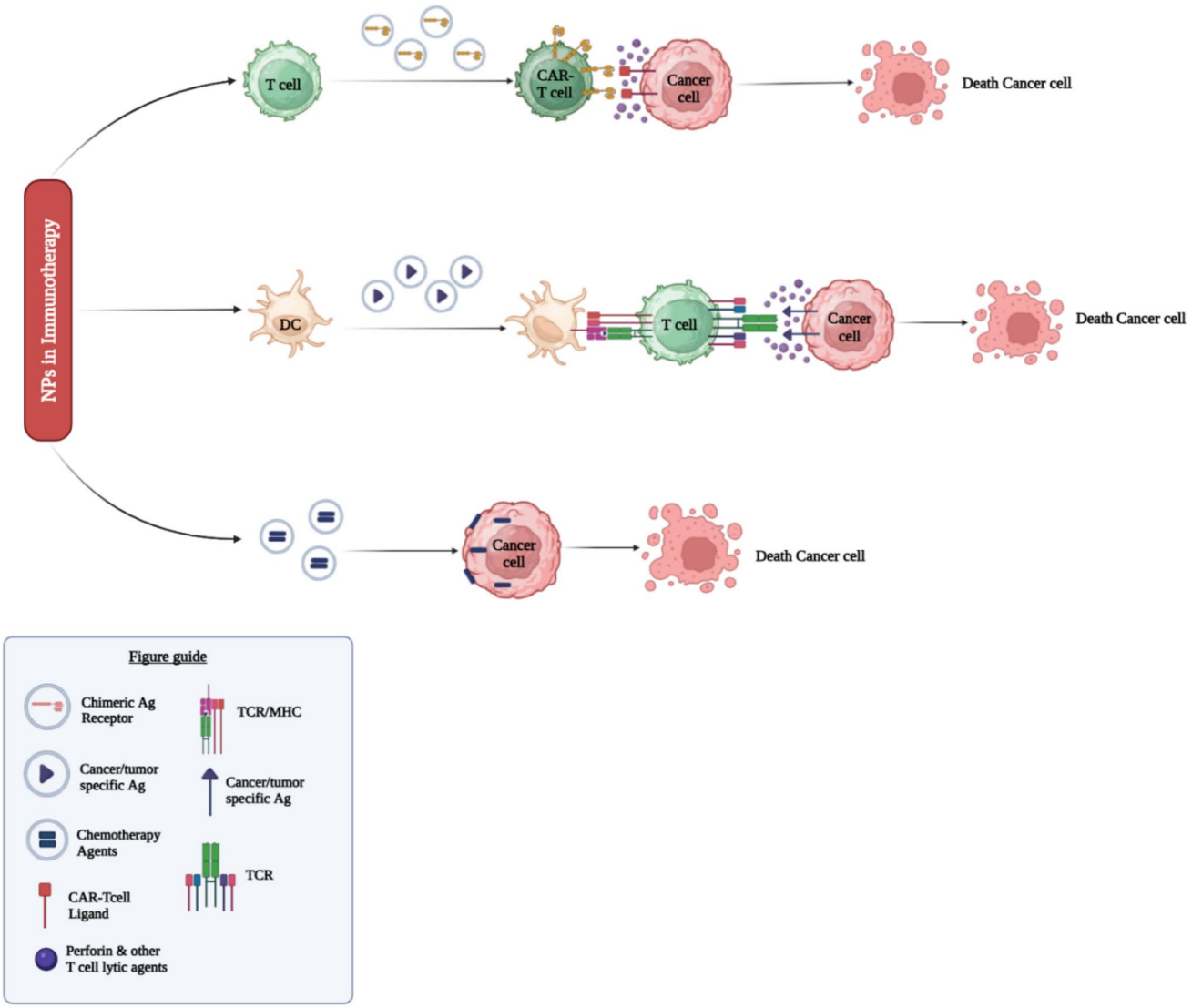

Fig. 2 Nano-immunotherapy strategies for leukemia treatment. This diagram depicts key nanotechnology-based immunotherapeutic approaches for leukemia, emphasizing efficacy across experimental stages. **a** Targeted drug delivery: PEGylated liposomes conjugated with anti-CD33 antibodies deliver doxorubicin to AML cells, reducing leukemic burden by 50% in vivo (mouse models) and improving remission rates (40%) in clinical Phase II trials [31, 32]. **b** Antigen-specific immunity: RNA-LPX liposomes encoding WT1 antigens enhance CD8 + T cell responses by 30% in AML patients (phase I clinical data) and reduce tumor burden in preclinical models [90]. **c** Photothermal therapy: CD123-targeted AuNPs induce 70% B-ALL cell death in vitro and 40% leukemic reduction in vivo via near-infrared ablation [92]. **d** Theranostic application: Magnetic IONPs loaded with daunorubicin achieve 60% tumor reduction in AML mouse models and enable MRI tracking in Phase I clinical trials [94]. **e** CAR T cell enhancement: Nanoparticles co-delivering IL-2 and anti-PD-1 boost CAR T cell efficacy in AML, validated in vivo [95]. The figure integrates in vitro, in vivo, and clinical evidence, showcasing nanomaterial versatility in overcoming leukemia-specific challenges like bone marrow localization and multidrug resistance

more effectively to leukemia cells and the tumor microenvironment. For instance, nanocarriers can be used to encapsulate and deliver immune checkpoint inhibitors, reducing systemic toxicity while maintaining therapeutic efficacy. In the context of leukemia, this approach could potentially enhance the effectiveness of checkpoint inhibitors while minimizing immune-related adverse effects [90, 91]. Interestingly, nano-immunotherapy can also be combined with other treatment modalities to create synergistic effects. For example, nanoparticle-assisted localized hyperthermia combined with immune checkpoint therapy has shown promise in solid tumors. While this specific approach may not be directly applicable to leukemia, it demonstrates the potential for combining nanotechnology with various treatment modalities to enhance anti-tumor immune responses [92]. Nanomaterials have demonstrated significant potential in enhancing leukemia therapy through targeted drug delivery and immune modulation. Their efficacy varies across experimental settings—in vitro, in vivo, and clinical—reflecting different stages of development and translational challenges. Below, we evaluate specific nanomaterial classes, detailing their performance in these contexts and their implications for leukemia treatment.

Liposomes: efficacy across experimental phases

Liposomes have shown promising efficacy in leukemia therapy due to their biocompatibility and versatility. In vitro studies have established their ability to deliver chemotherapeutic agents selectively to leukemia cells. For example, PEGylated liposomes conjugated with anti-CD33 antibodies increased uptake by AML cell lines (e.g., HL-60) by threefold compared to free drug, reducing IC50 values of doxorubicin in vitro [26]. In vivo, preclinical mouse models of AML further validated this efficacy, with anti-CD33 liposomes achieving a 50% reduction in bone marrow leukemic burden after intravenous administration, attributed to enhanced biodistribution and reduced off-target toxicity [26]. Clinically, liposomal formulations like liposomal daunorubicin (DaunoXome) have been tested in AML patients, demonstrating improved response rates (up to 40% complete remission in relapsed cases) and reduced cardiotoxicity compared to free daunorubicin in Phase II trials [93].

Polymeric nanoparticles: from bench to bedside

Polymeric nanoparticles, such as PLGA-based systems, exhibit robust efficacy across research stages. In vitro, PLGA nanoparticles loaded with imatinib inhibited CML cell line (K562) proliferation by 60% more than free drug, due to sustained intracellular release [29]. In vivo studies in CML mouse models showed that hyaluronic acid-coated PLGA nanoparticles targeting CD44 on LSCs reduced tumor burden by 70% over 4 weeks, outperforming free imatinib by overcoming bone marrow niche protection [29]. These findings underscore polymeric nanoparticles' potential to translate preclinical efficacy into clinical benefits, though scalability remains a hurdle.

Inorganic nanomaterials: diverse efficacy profiles

Inorganic nanomaterials, including gold nanoparticles (AuNPs) and iron oxide nanoparticles (IONPs), offer multifunctional efficacy. In vivo, AML mouse models treated with CD123-targeted AuNPs exhibited a 40% decrease in leukemic cell counts in peripheral blood after photothermal therapy, with minimal systemic toxicity [31]. Clinically, however, AuNPs remain in early development, with no leukemia-specific trials reported by 2025, though their imaging applications (e.g., CT enhancement) are under investigation in solid tumors [31]. IONPs, conversely, have progressed further. In vitro, IONPs loaded with daunorubicin increased AML cell (THP-1) apoptosis by 50% compared to free drug [33]. In vivo, magnetic-guided IONPs in AML mouse models achieved a twofold higher drug accumulation in bone marrow, reducing leukemic burden by 60% [31].

Comparative efficacy insights

Across these nanomaterials, efficacy trends emerge: in vitro studies consistently show enhanced cytotoxicity and specificity, in vivo models validate improved biodistribution and immune activation, and clinical trials—though limited—demonstrate safety and modest efficacy gains. Liposomes and polymeric nanoparticles lead in clinical translation, while inorganic and nuclear-targeted systems excel in preclinical settings, reflecting their earlier developmental stage. For leukemia, in vivo efficacy in bone marrow targeting and immune modulation (e.g., T cell priming) is critical, as seen with RNA-LPX and IONPs, bridging preclinical promise to clinical relevance.

In addition to avoiding pathophysiological obstacles like extracellular matrix, endonuclease degradation, and renal clearance, NPs can transport medications, antigens, and adjuvants that can influence immune cells at specific target sites (tumor and lymph nodes). Therefore, immunomodulators can be delivered to the target tissue more efficiently when nanocarriers are used, which increases the molecules' therapeutic potential [94]. Furthermore, nanomaterials help deliver cancer antigens to APCs in a targeted manner, which improves the induction of immune responses specific to tumors. To activate T cells in cancer patients, for

example, liposomal antigen-encoding RNA (RNA-LPX) is delivered by nanoparticulate RNA vaccines [28]. There are several types of NPs that are qualified for this task, such as *liposomes,* (these spherical vesicles composed of lipid bilayers are widely used for encapsulating immune stimulatory agents and cancer antigens.), *polymeric nanoparticles* (biodegradable polymers like PLGA are frequently employed to encapsulate immune modulators. PLGA nanoparticles facilitate controlled release and targeted delivery of antigens or cytokines to the tumor microenvironment) [95], *gold nanoparticles (AuNPs)* (gold nanoparticles are highly versatile carriers for immune stimulatory agents due to their tunable size, surface chemistry, and ease of functionalization. They have been used to deliver cancer antigens and adjuvants, promoting dendritic cell activation and T cell responses) [31], *dendrimers* (these highly branched, nanoscale polymers provide precise control over drug loading and release) [96], and *iron oxide nanoparticles* (these magnetic nanoparticles are being explored for their dual role in targeted drug delivery and imaging. They can carry immune stimulatory agents and can also be guided to specific sites using external magnetic fields) [33].

To enhancement of CAR T cell therapies, nanotechnology has been employed to improve the efficacy of it. Nanoparticles can carry immune-modulating small molecules or cytokines to modify the tumor microenvironment or to enhance the function of CAR T cells [97]. Despite the promising potential of nanomaterials in immunotherapy, challenges such as scalability, reproducibility, and long-term safety remain. Ongoing research is focused on developing bioinstructive materials that provide instruction to biological cells or tissue, which could further enhance the efficacy of nanomaterial-based immunotherapies. Recent preclinical studies have explored the efficacy and safety of nano-immunotherapy as a promising approach to treat leukemia, particularly ALL and other forms. A systematic review identified 63 original articles on nanotechnology-based therapeutics for human ALL. The findings suggest that nanoparticles can improve drug solubility, enhance bioavailability, and allow for targeted delivery of therapies. Techniques such as controlled release and targeted gene therapy were highlighted as effective strategies to combat multidrug-resistant ALL. The review emphasized that these nanomaterials not only improve therapeutic outcomes but also reduce adverse effects associated with traditional treatments [98]. Another study assessed the use of therapeutic inducers of natural killer cells (ThINKK) in a preclinical mouse model of ALL. This approach involves expanding and differentiating hematopoietic stem cells to enhance the graft-versus-leukemia effect post-transplantation. The results indicated that ThINKK effectively stimulated NK cells, leading to significant control over leukemia development. The study also evaluated the interactions between ThINKK and immunosuppressive drugs, suggesting a potential for improved NK cell activity against ALL cells [99]. In a separate preclinical evaluation, CD79b-targeted immunotherapy was shown to be effective against B cell precursor ALL. This study provided evidence supporting the therapeutic potential of this approach, highlighting its ability to induce significant anti-leukemic responses in preclinical models [100].

The safety profiles of these nano-immunotherapies were generally favorable across the studies reviewed. Nanoparticles used in ALL treatments demonstrated reduced systemic toxicity compared to conventional therapies, which is crucial for improving patient outcomes. Furthermore, in studies evaluating ThINKK and CD79b therapies, adverse effects were monitored closely, with findings indicating manageable toxicity levels that did not significantly compromise the treatment's efficacy. Overall, these preclinical studies suggest that nano-immunotherapy holds promise as an effective and safer alternative for treating various forms of leukemia, particularly through targeted delivery systems that enhance therapeutic efficacy while minimizing side effects.

Interestingly, while in vitro studies can assess certain toxicities, animal models remain crucial for evaluating complex biological responses and establishing comprehensive safety and efficacy profiles of nanomaterials. However, the diversity of animal models can complicate result interpretation, highlighting the need for careful model selection in preclinical studies [101].

The efficacy and safety of nano-immunotherapy for leukemia have been evaluated in several clinical studies, particularly focusing on novel therapeutic approaches such as CAR T cell therapy and peptide vaccines. A study investigated the characteristics of anti-CLL1-based CAR T therapy specifically for children with relapsed or refractory AML. This multi-center interim analysis demonstrated promising efficacy and safety profiles, indicating that CAR T cell therapies can be effective in treating pediatric patients with challenging leukemia cases. The results suggested that this form of immunotherapy could lead to significant improvements in patient outcomes [102, 103]. Another notable study involved a randomized, open-label trial assessing the efficacy and safety of galinpepimut-S (GPS) as a maintenance therapy for patients with AML who had achieved complete remission after second-line salvage therapy. The findings indicated that GPS could induce a robust immune response against the wilms tumor 1 (WT1) antigen, which is overexpressed in leukemic cells. The primary endpoint was overall survival (OS), with secondary endpoints including safety and tolerability. Results showed that GPS demonstrated promising activity in prolonging remission and improving immune response dynamics [104]. A study introduced a bioinspired nanomedicine designed to target AML effectively. This system utilizes a hollow manganese dioxide nanocarrier loaded with doxorubicin (DOX), which disassembles in the tumor

microenvironment, releasing the drug where it is needed most. In vitro and in vivo results indicated significant anti-leukemic efficacy and immune activation, suggesting that this approach could enhance treatment outcomes for AML patients [105].

As a final note, clinical studies indicate that nano-immunotherapy approaches, particularly CAR T cell therapies and peptide vaccines, hold promise for enhancing the treatment landscape for leukemia, demonstrating both efficacy and safety in various settings. While these studies shed light on critical aspects, rigorous follow-up studies are required to confirm their impacts and expand therapeutic opportunities.

Combination therapies with nano-immunotherapy

Cancer has been among the top causes of mortality in recent decades, despite significant advancements in therapy, yet both the incidence and mortality rates of cancer remain elevated. In recent decades, significant efforts have focused on developing rapid, safe, and effective methods for cancer diagnosis and treatment. The three most common clinical approaches to cancer treatment are chemotherapy, surgery, and radiation [106]. Although these standards of therapy can prolong the survival of patients, they frequently face persistent issues such as significant side effects, systemic toxicity, unavoidable tumor recurrence, and treatment resistance. Following a century of study, cancer immunotherapy has transformed the field of oncology, providing novel treatment alternatives for various cancer types. This approach stimulates or amplifies the body's natural immune system, subsequently improving immune responses against tumors and offering a new pathway for fighting cancer [107].

In recent decades, single-mode therapies have advanced in inhibiting tumor growth and extending patient survival. However, their clinical use is hindered by significant drawbacks. Chemotherapy faces issues like rapid clearance and nonspecific distribution, leading to reduced effectiveness and systemic toxicity, while prolonged use can cause cancer cell resistance [108]. Phototherapy is limited by normal tissue damage, tumor heat resistance, and potential tumor metastasis [109, 110]. Radiotherapy is ineffective in hypoxic environments because hypoxic cancer cells are insensitive to ionizing radiation [111]. Additionally, immunotherapy's effectiveness is compromised by off-target toxicity, weak immune responses, and low persistence and immunogenicity [112]. On the other hand, the synergistic effect of combining immunotherapy with other treatments has led to the development of collaborative therapy, producing a treatment effect that surpasses the strength of any single therapy or a basic "1 + 1" combination treatment. So, integrating immunotherapy with various treatment methods (such as chemotherapy, phototherapy, radiotherapy, gene therapy, etc.) will offer a more effective strategy for achieving superior results in cancer treatment, potentially enhancing overall therapeutic outcomes [113]. Chemotherapy has traditionally been the primary treatment for cancer, which has led to significant interest in the integration of immunotherapy with chemotherapy. There are multiple potential benefits to merging chemotherapy with immunotherapeutic methods. Antigen presentation and the adaptive immune response can be enhanced by chemotherapy's capacity to induce immunogenic cell death (ICD) [114–116]. There is evidence that certain chemotherapy medicines, like as DOX, can induce ICD, release antigens associated with tumors and high mobility group box 1 (HMGB1), and then recruit and activate immune cells that are specific to those antigens [117]. This process called an in situ vaccine, generates personalized anti-tumor immune responses against tumors within the local tumor environment [118]. New research suggests that nanomaterials can be used to deliver adjuvants and chemotherapeutic medicines simultaneously, which could improve the immune response induced by ICD while reducing the chances of cytokine storms and adverse effects after systemic administration of the chemotherapeutic agents [119, 120].

In an effort to treat lymphoma, Ma et al. used a simple self-assembly of spherical nucleic acids (SNAs) formulation with DOX acting as the shell and CpG ODN and MPLA acting as adjuvants to produce carrier-free core–shell nanoparticles (MCMD NPs) [121]. The findings of the in vitro study demonstrated that MCMD NPs enhance drug accumulation in tumors and release DOX after matrix metalloproteinase-9 (MMP9) in the tumor microenvironment (TME) is broken down enzymatically. This enhances DOX's direct lethal effect on tumor cells. The immunological response was greatly enhanced by the incorporation of MPLA-CpG SNA into MCMD NPs, which led to increased T cell proliferation and cytokine secretion.

Tumor tissue includes malignant cells and unique microenvironments that develop during evolution. TME pertains to the soil that nurtures cancer cells, significantly impacting the development and proliferation of tumors [122]. In the TME, various cellular and non-cellular components surround malignant cells, including nonhematopoietic stromal cells, extracellular matrix (ECM), lymphocytes, and myeloid cells [123]. The TME is defined by low oxygen levels, an acidic environment, elevated reactive oxygen species, and changes in the expression of ECM proteins, all of which are crucial factors in tumor advancement and cancer metabolism [124]. Consequently, the way tumor cells interact with the components of TME influences both the therapeutic efficacy and the growth and spread of tumors. Research has shown that the TME significantly affects drug penetration and efficacy, and it is linked to drug resistance and diminished

response rates [125]. For instance, the application of anti-CD19 CAR T cells has shown encouraging outcomes for treating acute lymphocytic leukemia; however, this approach has faced considerable restrictions in solid tumors [126]. The effectiveness of antibody–drug conjugates and cancer vaccines is significantly diminished due to the immunosuppressive environment that results from the TME. In TME, distorted blood vessels and rapid tumor growth cause hypoxia, leading to immunosuppression through the accumulation of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) and the secretion of associated factors like VEGF and TGF-β [127]. The substitutes impede the functions of dendritic cells, shift macrophages toward the M2 phenotype (pro-tumorigenic), and result in abnormal fibrosis [127]. Nanoparticles with certain designs can target these components in TME and turn immunosuppressive TME immunosupportive, boosting cancer immunotherapy effectiveness [128]. Extensive design efforts have been directed toward nanoparticles for use as systems for drug delivery [128]. These can be passively delivered to tumor tissue, thereby extending the retention time of the drugs they carry. Due to the improved permeability and retention effect, these substances accumulate in tumors significantly more than in normal tissues [129]. Meanwhile, by altering their structures and conjugating them with specific ligands, nanoparticles can effectively target delivery to the tumor microenvironment while modulating it, thereby improving therapeutic efficacy [130, 131].

As a strategic approach, retraining immune cells within the solid TME is employed to combat cancer [132]. Immunological checkpoints play a physiological role in immune tolerance regulation by limiting the severity of autoimmune reactions. Activation of immunological checkpoints allows tumor cells to evade the immune system during carcinogenesis [133]. Blocking immunological checkpoints as a potential cancer treatment has garnered a lot of interest [134]. Several ICIs, including PD-1 and PD-L1 inhibitors, have demonstrated encouraging outcomes in hematological malignancy therapy trials, both in the lab and in humans. Antibodies, small compounds, and small interfering RNAs (siRNAs) have been a successful therapy approach to modulate the PD-1/PD-L1 interaction [135–137]. Unlike small molecular inhibitors or antibodies, which just diminish the interaction between expressed PD-1 and PD-L1, siRNA can facilitate sequence-specific mRNA breakage, thereby aiding in the suppression of endogenous target gene expression. (138, 139). Nonetheless, creating an efficient and secure delivery mechanism continues to be a formidable yet significant objective for developing siRNA-based cancer therapies [140, 141]. Additionally, ROS play a crucial role in the regulation of the immune system, influencing differentiation and functions that are vital for the development of the immune response [142]. In order to retrain macrophages and release drugs, photosensitizers must generate ROS in the TME, endosomes/lysosomes, or cytoplasm [143]. Moreover, ROS-mediated photodynamic therapy is an appealing clinically validated treatment approach for cancer involving photosensitive agents and laser activation [144]. Accumulation of photosensitizers in the tumor, triggered by radiation at a particular wavelength, causes a photochemical process that kills tumor cells [145]. Recently, Zhang et al. developed light-activatable silencing NK-derived exosomes (LASNEO) by incorporating siRNA and the photosensitizer Ce6 into NK cell-derived exosomes (NEO),demonstrating their effects through in vitro tumor cell assays and in vivo murine tumor models [146]. These NEOs have the ability to eradicate tumor cells while simultaneously reestablishing the TME's immunosurveillance function. Laser irradiation not only enabled efficient photodynamic therapy, but it also boosted the growth of dendritic cells in the TME and polarized tumor-associated macrophages from M2 to M1 type. Furthermore, the administered siRNA induced significant gene silencing of PD-L1, hence activating CD4 + T cells and CD8 + T cells within the TME.

Recently, researchers have explored RNActive technology as a possible candidate for cancer therapy, and it is presently in the process of clinical trials [147]. Vaccines against cancer can be designed to specifically target antigens found in tumors and neoplasms [148]. These antigens can be either autologous and overexpressed or unique to cancer cells caused by somatic mutations [148, 149]. Exogenous DNA or mRNA is conveyed to the lymph nodes and subsequently internalized by APCs, prompting antigen expression and ensuing T cell activation [149]. RNA vaccines, in contrast to DNA vaccinations, do not integrate into the genome, therefore mitigating the risk of carcinogenicity [150]. Additionally, RNA vaccines function within the cytoplasm, whereas DNA vaccines need to enter the nucleus [150]. As a result, the probability of adverse effects is low, and the clearance process is accelerated [148]. Although RNA is more easily degraded than DNA, there are ways to make it more stable, for as by adding liposomes or a stabilizing adjuvant to the combination [150]. The integration of the mRNA vaccine with adjuvant therapies, including conventional chemotherapy, radiation, and ICIs, has enhanced the positive outcomes of immunization in several preclinical investigations. In order to assess the efficacy of the combination of the mRNA vaccination and the checkpoint inhibitors, the researchers intradermally delivered the vaccine to mice together with the anti-CTLA-4 antibody [151]. Mice were treated with anti-CTLA-4 and vaccinated with ovalbumin after being exposed to E.G7-OVA tumor cells. Combining anti-CTLA-4 with the mRNA vaccination significantly slowed tumor growth, in contrast to using anti-CTLA-4 alone, which did not affect the tumor. Additionally, E.G7-OVA tumor cells were used to study the combinatorial effects of radiation and vaccination

[152]. Following exposure to the tumors, the mice underwent irradiation for three days in a row. Mice received multiple vaccinations with RNA vaccines concurrently with radiotherapy. A notable reduction in tumor growth was observed in mice, with complete tumor disappearance in three out of seven mice. The combination treatment led to enhanced infiltration of both innate immune cells and adaptive immune cells within the tumor site. These findings suggest that irradiating specific tumor locations in metastatic cancer patients might improve the vaccine's systemic anticancer efficacy [152]. Table 2 demonstrate nano-immunotherapy clinical trials for leukemia.

Artificial intelligence in nanomedicine

Artificial intelligence (AI) is transforming nanomedicine by expediting medication discovery, enhancing nanocarrier design, and increasing treatment accuracy. AI algorithms forecast the efficacy and toxicity of nanomedicine, hence decreasing development time and expenses. Machine learning techniques examine extensive datasets to identify potential therapeutic candidates and enhance nanocarrier characteristics, including size, stability, and targeting efficacy. These innovations improve drug administration and reduce adverse effects, rendering treatments more efficacious and tailored to individual patients [156].

AI also plays a crucial role in personalized nanomedicine by optimizing drug combinations and dosages based on patient data. In combination nanotherapy, AI helps monitor treatment synergy and predict nanoparticle interactions using nanoinformatics tools such as nano-QSAR models and molecular simulations [157]. AI-driven approaches further assist in structure-based drug design by predicting the 3D structure of target proteins, improving drug efficacy while minimizing potential toxicity [156].

Future applications of AI in nanomedicine include real-time diagnostics, precision treatments, and improved safety assessments. AI-driven physiologically based pharmacokinetic (PBPK) models reduce reliance on animal testing, expediting clinical translation. As AI continues to integrate with nanotechnology, it is set to revolutionize healthcare by enabling faster diagnoses, more effective therapies, and improved patient outcomes [156].

Challenges and future directions

Tumor eradication and long-term tumor immunity maintenance are the end goals of anticancer immunotherapy. Currently, anticancer immunotherapy is not even close to being effective enough to accomplish this because of its poor efficacy and significant risk of immune-mediated toxicities. Nano-immunotherapy, which integrates nanotechnology with immunotherapy, presents opportunities to address numerous challenges in the field. Efficient nano-immunotherapy is difficult to achieve due to the human immune system's complexity and variability. Nano-immunotherapy in hematological malignancies is in the preliminary development phase and shows potential for improving existing treatment approaches. Numerous challenges arise in translating nano-immunotherapies for hematological malignancies from laboratory research to clinical application.

First, there is still a lack of thorough understanding regarding the mechanism and physicochemical features of NPs, including their toxicity, biodistribution, metabolism, clearance, and pharmacokinetics. Physicochemical attributes like size, structure, composition, and surface properties affect the in vivo effectiveness of nanomedicine formulations [158]. Following administration, nanoparticles undergo significant changes due to interactions with biological molecules (e.g., protein corona), making in vivo performance assessment challenging [159]. The immunogenicity of nanomaterials poses immunotherapy options and difficulties. Specific nanomaterials can promote inflammation and anticancer immune responses. But when plasma proteins opsonize a nano-immunologic agent as a foreign substance, the complement pathway is set off, leading to quick phagocytosis and drug clearance by the liver and spleen [160]. Moreover, comprehensive study and testing are essential to resolve significant concerns about the safety and efficacy of nano-immunologic substances, their biodistribution, and their interactions with immunological organs and the TME.

Secondly, the practical large-scale synthesis of nanoparticles presents an additional challenge. The production of a nano platform often involves complexities that make it challenging for industrial manufacturing. To ensure consistent processes and prevent possible adverse consequences, rigorous quality control standards are necessary for chemical or biological manufacture.

Thirdly, the majority of research on nano-immunotherapy for hematological malignancies is still in the preclinical stage, which causes a discrepancy between animal and human trials and reduces the clinical relevance of nanotechnology. The use of mice as in vivo models for preclinical assessments is common. Nevertheless, the intricacies of the immune system and the complex progression of human hematological malignancies are not adequately represented by these models.

Fourth, hematological malignancies have demonstrated encouraging results when treated with immunotherapy. Unfortunately, immunotherapy has several drawbacks that make it unsuitable for blood cancers. For example, the distinctive immunosuppressive system is a notable feature of AML [161]. Enzymes produced by myeloid-derived suppressor cells (MDSCs) block immunological responses

Table 2 Clinical trials on nano-immunotherapy for leukemia

Study title/focus	Intervention/therapy	Disease	Patient population	Enrollment	Study design/phase	Primary endpoints and outcomes	Key findings	References
Anti-CLL1 CAR T therapy for pediatric AML	Anti-CLL1 CAR T cells	Relapsed/Refractory AML	Children	Multi-center	Interim analysis	Efficacy: High response rates; Safety: Manageable toxicity	High response rates (CR/CRi) in R/R AML; manageable cytokine release syndrome (CRS)	[102]
Galinpepimut-S (GPS) maintenance therapy	GPS (WT1-targeted peptide vaccine)	AML in remission post-salvage	Adults	Randomized, Open-label	Phase II/III	Overall survival (OS); Immune response dynamics	Prolonged remission in AML post-salvage therapy; robust WT1-specific immune responses	[153]
Bioinspired nanomedicine for AML	Hollow MnO_2 nanocarrier loaded with doxorubicin (DOX)	AML	Preclinical (transitioning to clinical)	N/A	In vitro/In vivo	Anti-leukemic efficacy, immune activation	TME-responsive DOX release; synergistic immune activation in AML models	[105]
Combination of mRNA vaccine + anti-CTLA-4 antibody	OVA mRNA vaccine + anti-CTLA-4	E.G7-OVA tumor model (preclinical)	Mice	Preclinical	Combination Therapy	Tumor growth inhibition; Enhanced T cell infiltration	Enhanced tumor regression vs. monotherapy in murine models	[151]
mRNA vaccine + radiotherapy	OVA mRNA vaccine + localized radiation	E.G7-OVA tumor model (preclinical)	Mice	Preclinical	Combination therapy	Tumor regression; Complete response in 3/7 mice	Complete tumor eradication in 43% of mice; increased immune infiltration	[152]
ThINKK (therapeutic inducers of NK cells)	NK cell expansion/differentiation	ALL	Preclinical mouse model	Preclinical	Safety/Efficacy	Graft-versus-leukemia effect; NK cell activity	Improved graft-versus-leukemia effects; safe NK cell activation	[99]
CD79b-targeted immunotherapy	CD79b-targeted therapy (antibody or nanoparticle)	B-cell precursor ALL	Preclinical models	Preclinical	Efficacy	Anti-leukemic responses; Target specificity	Preclinical efficacy in B-ALL xenografts; minimal off-target toxicity	[100]
Nanoparticle-assisted PD-L1 siRNA delivery	PD-L1 siRNA-loaded nanoparticles + photodynamic therapy	Solid tumors (potential for leukemia)	Preclinical	Preclinical	Synergistic therapy	PD-L1 silencing; M1 macrophage polarization; T-cell activation	Synergistic tumor suppression via PD-L1 knockdown and ROS generation	[154]
Liposomal antigen-encoding RNA (RNA-LPX)	RNA-LPX nanoparticles	Cancer (including hematologic)	Preclinical/Clinical (phase-dependent)	Varied	Vaccine development	APC activation; Antigen-specific T-cell responses	APC-targeted delivery; clinical trials ongoing for solid tumors (potential for leukemia)	[155]

Table 2 (continued)

Study title/focus	Intervention/therapy	Disease	Patient population	Enrollment	Study design/phase	Primary endpoints and outcomes	Key findings	References
Spherical nucleic acids (SNAs) for chemo-immuno-therapy	MCMD NPs (DOX + CpG/MPLA adjuvants)	Lymphoma (potential for leukemia)	Preclinical	Preclinical	Combination therapy	Tumor drug accumulation; Enhanced T-cell proliferation	MMP9-triggered DOX release; enhanced T cell responses in lymphoma models	[121]

emanating from regulatory T cells, NK cells, and cytotoxic T cells. These include inducible nitric oxide synthase, arginase 1, and indoleamine 2,3-dioxygenas [162]. In addition, AML blasts express these chemicals, which enhance the activation of MDSCs [163]. The combination of AML's immunosuppressive mechanism and its limited, random antigens makes the disease extremely challenging to treat. Hematologic malignancies' tumor microenvironments, including multiple myeloma's bone marrow niche and lymphomas' lymphatic system, are another important topic that needs further exploration [164]. These environments greatly influence the promotion of tumor development and resistance to therapy [165]. Overcoming this challenge will require researchers to create adaptable nanocarriers that can either dynamically modify their targeting mechanisms depending on the tumor environment or simultaneously target numerous markers.

Emerging nano-immunotherapy shows promise as a possible cancer treatment in spite of these challenges. The variety of in vivo tissue-specific genome editing tools available for cancer research in preclinical models has increased with the use of nanoparticles for the delivery of guide RNAs and programmable nucleases, such as Cas9 and Cas13 [166–169]. Innovative nanoparticle delivery systems will greatly improve the field by using new methods to deliver these particles. This includes techniques like nanoclews and surface modifications of the particles, which will help create advanced nanoparticles [170]. Consequently, new nanoplatform developments may provide a wider and more flexible toolbox for investigating NPs and may even solve their problems.

Conclusion

Treatment for leukemia can be approached in a variety of ways with nanotechnology. While reducing systemic toxicity, it permits the targeted delivery of therapeutic agents—such as immunotherapies, chemotherapeutics, and even genetic material—directly to leukemia cells. Furthermore, nanomaterials can be engineered to modulate the immune system, enhancing anti-tumor responses by activating immune cells, promoting antigen presentation, and overcoming immune suppression. However, significant challenges remain. Careful consideration must be given to factors such as nanoparticle toxicity, biodistribution, and long-term effects. Addressing these concerns requires rigorous preclinical and clinical research, including thorough safety assessments and optimized formulations to minimize potential side effects. Despite these challenges, the potential of nano-immunotherapy in leukemia treatment is immense. Continued research and development in

this area, including the exploration of novel nanomaterials, the optimization of delivery strategies, and the investigation of synergistic combinations with other therapies, are crucial to translating the promise of nano-immunotherapy into effective clinical applications and improving patient outcomes for individuals with leukemia.

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Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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