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REVIEW ARTICLE

Recent Advances in Metal-Based Nanomaterials for the Diagnosis and Treatment of Hematological Malignancies

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ABSTRACT

Background: **Hematological malignancies, including leukemias, lymphomas and multiple myeloma, remain a major clinical challenge due to the limitations of conventional therapies, such as multidrug resistance, off-target toxicity, and the limited specificity of targeted agents to distinct molecular subtypes. Metal-based nanomaterials (M-NMs) have recently garnered considerable interest as multifunctional platforms capable of overcoming these obstacles, owing to their unique physicochemical properties, including surface plasmon resonance, superparamagnetism, facile surface functionalization and responsiveness to exogenous stimuli.**
Methods: **This narrative review comprehensively examines recent advances in M-NMs for the diagnosis and treatment of hematological malignancies, with a focus on their transition from inert drug carriers to active theranostic agents. The review first examines the design principles of M-NMs as intelligent delivery systems, highlighting active targeting strategies via antibody–antigen or aptamer recognition, stimuli-responsive controlled release triggered by tumor microenvironmental signals or external physical fields, and synergistic delivery with chemotherapeutics to overcome drug resistance. We then elucidate the direct therapeutic mechanisms based on metal activity, encompassing Fenton chemistry-driven oxidative stress, ferroptosis, magnetic hyperthermia and photothermal conversion, as well as their integration with immunomodulation and multimodal imaging for theranostic applications.**
Results: **Current evidence highlights several biological barriers specific to hematological malignancies, including blood compatibility, circulation kinetics and the protective bone marrow microenvironment, while nanotechnology-based strategies may help address these challenges. Long-term biosafety remains an important consideration for non-biodegradable M-NMs, with emerging approaches focusing on biodegradable or renally clearable architectures. Despite substantial progress, clinical translation remains constrained by target heterogeneity, manufacturing complexity and incomplete understanding of therapeutic sensitivity determinants.**
Conclusions: **We conclude that future development should prioritize the engineering of biocompatible, degradable nanoplatforms with integrated imaging and immunostimulatory functions, and emphasize that deeper mechanistic insights into metal-cell interactions and microenvironmental modulation will be important for advancing the development and clinical translation of M-NMs in precision hematology.**
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KEYWORDS

metal-based nanomaterials, hematological malignancies, theranostics, ferroptosis, immunomodulation, active targeting, biosafety

LIST OF ABBREVIATIONS

ALL - acute lymphoblastic leukemia
AML - acute myeloid leukemia
Ara-C - cytarabine
CAR-T - chimeric antigen receptor T-cell
CD - cluster of differentiation
CLL - chronic lymphocytic leukemia
DLBCL - diffuse large B-cell lymphoma
GPX4 - glutathione peroxidase 4
HMGB1 - high mobility group box 1
ICD - immunogenic cell death
IONPs - iron oxide nanoparticles
LSCs - leukemia stem cells
MNPs - magnetic nanoparticles
MM - multiple myeloma
M-NMs - metal-based nanomaterials
MOFs - metal-organic frameworks
MRI - magnetic resonance imaging
NIR - near-infrared
PBMCs - peripheral blood mononuclear cells
PD-L1 - programmed death-ligand 1
PLGA - poly (lactic-co-glycolic acid)
RBCs - red blood cells
ROS - reactive oxygen species
SERS - surface-enhanced Raman spectroscopy
SPIONs - superparamagnetic iron oxide nanoparticles
TfR - transferrin receptor

INTRODUCTION

The drug-based nanomedicine paradigm, which employs various nanomaterials to encapsulate or load therapeutic agents, has become a mainstream strategy largely owing to its capacity to improve drug bioavailability and reduce systemic toxicity [1-3]. Nevertheless, hematological malignancies remain a major clinical challenge, with leukemias, lymphomas, and multiple myeloma representing the three major categories [1,2]. The current treatment landscape is constrained by several interrelated limitations: conventional chemotherapy frequently encounters multidrug resistance, driven in part by the overexpression of efflux transporters [4]; targeted agents are effective only in specific molecular subtypes and are often compromised by acquired resistance [1]; and immunotherapies, including CAR-T cells, are associated with substantial toxicity profiles [5,6]. Furthermore, the unique pathophysiological features of hematological tumors - including their disseminated nature within the circulatory system and the protective bone marrow microenvironment - pose additional obstacles that complicate the direct translation of nanomedicine strategies originally developed for solid tumors [1,2]. These distinctive characteristics collectively underscore the need for nanotherapeutic approaches specifically adapted to the biological realities of hematological malignancies.

In parallel with the development of drug loaded nanocarriers, the intrinsic physicochemical properties of metal-based nanomaterials have attracted growing interest for their direct diagnostic and therapeutic applications [7]. The landscape of such materials encompasses diverse compositions, including noble metals such as gold, silver, and platinum; magnetic materials like iron oxide nanoparticles; and metal-organic frameworks (MOFs) - all of which exhibit advantageous features including surface plasmon resonance, superparamagnetism, favorable surface functionalization capabilities, and responsiveness to external stimuli [7 - 10]. These properties have enabled "drug free" nanomedicine strategies, wherein the materials themselves can confer diagnostic or therapeutic functions without relying on loaded chemotherapeutics [7]. However, the non-biodegradability of certain conventional metal nanomaterials has raised biosafety concerns, motivating the exploration of degradable alternatives such as acid labile MOFs and iron-based nanoparticles that can release metal ions under specific physiological conditions [8,9,11]. For hematological malignancies, these materials may offer distinctive opportunities: their circulation half-life can be extended through surface engineering; their multimodal imaging capabilities align with the frequent monitoring requirements in hematological oncology; and their potential interactions with hematopoietic microenvironments warrant further investigation [7,8,10,12].

The role of metal ions in oncology has garnered increasing attention, evolving from their traditional perception as enzymatic cofactors toward recognition as potential therapeutic effectors - a shift highlighted by the discovery of non-apoptotic regulated cell death pathways such as ferroptosis, an iron-dependent oxidative mechanism that has been investigated in the context of leukemia therapy [11]. This conceptual evolution has motivated therapeutic strategies wherein nanomaterials serve as delivery vehicles to achieve tumor targeted enrichment and controlled release of metal ions [1,9]. Within this framework, metal-based nanomaterials in hematological malignancies can be considered along two interconnected application axes. The first encompasses intelligent delivery carriers, where the stimuli-responsive properties of these materials facilitate the controlled co-delivery of conventional therapeutics [1,9]. The second involves direct therapeutic and theranostic platforms, where the intrinsic catalytic activities of metal ions may be harnessed for cytotoxic effects, integrated with multimodal imaging capabilities [10,11,13]. Importantly, these two paradigms are not mutually exclusive and may be combined within a single platform to achieve synergistic effects [9]. This review accordingly provides a comprehensive overview of metal-based nanomaterial

design principles for hematological applications, progressing from targeted delivery and controlled release to metal active therapeutic mechanisms and imaging integration, followed by hematology-specific considerations, and concluding with clinical translation challenges and future directions, aiming to offer hematology researchers a framework for rational nanoplatform development [1,8,10].

A schematic framework outlining the structure and key themes of this review is provided in Figure 1.

Metal-based nanomaterials as intelligent drug delivery carriers

For context, non-metallic nanocarriers, including liposomes, polymeric nanoparticles, and protein-based nanocarriers, represent established nanomedicine platforms that have provided important precedents for drug delivery and clinical translation. These systems are not the primary focus of this review but provide a useful benchmark for evaluating the translational potential of emerging metal-based nanomaterials. With this context in mind, the following sections focus on metal-based platforms, which offer unique physicochemical properties - such as surface plasmon resonance and superparamagnetism - that are less readily achievable with conventional non-metallic carriers. In this review, metal-based nanomaterials are defined as platforms containing an explicitly identified metal or metal-containing functional component (e.g., Fe-, Au-, Ag-, Pt-, Cu-, or Mn-containing components, including corresponding metal oxides) that contributes to the structural, physicochemical, diagnostic, therapeutic, or delivery-related functions of the nanoplatform. Platforms lacking a functional metal constituent, such as black phosphorus or silica-only nanoparticles, are discussed only as contextual comparators when their design principles or mechanisms are instructive for understanding metal-based systems.

Targeting strategies: active recognition and microenvironmental response

Antibody recognition of classical Cluster of Differentiation (CD) antigens represents a well-established active targeting strategy in hematologic malignancies. For instance, an electrochemical cytosensor densely loaded with anti CD123 antibodies on a graphene quantum dot/gold nanoparticle electrode enabled specific detection of KG1a cells at concentrations as low as 1 cell/mL, showcasing the ultrasensitive diagnostic potential of antibody-CD antigen interactions [14]. Beyond CD antigens, active targeting has been extended to a diverse array of functional receptors and tumor-associated antigens often linked to the malignant phenotype, including nutrient transporters (folate receptor), adhesion molecules (integrin αvβ3), chemokine receptors (CXCR4), and carbohydrate antigens such as the Thomsen-Friedenreich antigen (TF Ag). Cyclic RGD conjugated iron oxide nanoparticles targeting integrin αvβ3 facilitated receptor-mediated internalization of the water insoluble drug CAPE into multiple myeloma cells, inducing caspase-9-mediated apoptosis with IC_{50} values as low as 7.97 μM while sparing normal cells - an effect retained in bone marrow mimicking co-cultures [15]. Lectin conjugated gold nanoparticles targeting TF Ag, a carbohydrate antigen overexpressed on leukemic but minimally on normal cells, induced dose-dependent apoptosis (up to 51.03%) and G0/G1 arrest in HL 60 cells [16]. Nevertheless, the clinical translation of these strategies may require careful attention to target-related factors, such as receptor recycling, expression stability, and tumor microenvironment heterogeneity. In parallel, aptamers - synthetic nucleic acid or peptide ligands generated through *in vitro* selection - have been explored as alternative targeting moieties capable of high precision recognition of cancer cell markers [17]. Their synthetic origin enables straightforward chemical modifications, facilitating integration into nanoplatforms for biosensing applications, as exemplified by an Au nanoparticle-decorated PTK7 aptamer-based photoelectrochemical cytosensor for ultrasensitive detection of Molt 4 cells [18]. For therapeutic delivery, sgc8c aptamer functionalized mesoporous silica-gold nanovehicles have been developed for targeted delivery of the Akt inhibitor AZD-5363 to T-cell acute lymphoblastic leukemia, achieving specific recognition of CCRF-CEM cells and effective proliferation inhibition *in vitro* and *in vivo* [19].

The integration of stimuli-responsive design with biomimetic camouflage represents a promising strategy to address the systemic toxicity and off-target effects commonly associated with conventional nanomedicines. Non-metallic nanomaterials, such as black phosphorus nanosheets, have also been explored as stimuli-responsive drug delivery platforms, although these systems are discussed here primarily as contextual examples rather than as core metal-based nanomaterials [20]. In parallel, cell membrane-camouflaged platforms have been developed to overcome biological delivery barriers by conferring immune evasion and active homing capabilities. For instance, as a contextual non-metallic comparator, cancer cell membrane-cloaked mesoporous silica nanoparticles have also been explored for pH-responsive drug release, although such systems are not the focus of the metal-based framework discussed here [21]. In contrast, in a non-hematological hepatocellular carcinoma model, membrane-coated Fe_3O_4 nanoparticles loaded with arsenic trioxide demonstrated enhanced ferroptosis through glutathione peroxidase 4 inhibition and lipid peroxide accumulation, leading to sustained tumor elimination *in vivo* [22]. This example is included for mechanistic context rather than as direct evidence in hematological malignancies. Extending this camouflage principle to extracellular vesicles, ZnO nanocrystal-loaded TrojanNanoHorses functionalized with anti-CD20 antibodies enabled selective targeting and ultrasound-activated cytotoxicity toward $CD20^+$ lymphoma cells [23]. Collectively, these findings suggest that the convergence of these strategies holds considerable promise, while also highlighting that challenges related to external stimulation, manufacturing complexity, and clinical

Table 1. Representative metal-based nanoplatforms for hematological malignancies, with selected non-metallic examples included for mechanistic context.

Strategy	Representative nanoplatform	Key mechanism	Representative outcome
Antibody targeting	Graphene quantum dot-gold electrode	Anti-CD123 recognition	Ultrasensitive AML cell detection (KG1a cells, *in vitro*)
Peptide targeting	Iron oxide nanoparticles	Integrin αvβ3 recognition	Enhanced cellular uptake and apoptosis (multiple myeloma, *in vitro*)
Lectin targeting	Gold nanoparticles	TF-Ag recognition	Leukemia-selective apoptosis (HL-60 cells, *in vitro*)
Aptamer targeting	Mesoporous silica-gold nanovehicles	PTK7 recognition	Specific leukemia cell inhibition (T-ALL, *in vitro* and *in vivo*)
Microenvironment-responsive delivery	BP-based DOX nanocarriers (contextual non-metallic comparator)	pH-responsive drug release	pH-responsive DOX release, BP-PEG-DOX: 12.13% at pH 5.0 and 29.46% at pH 7.5 after 25 h, no uniform pH-release direction assigned
Biomimetic camouflage	Membrane-coated Fe_3O_4 nanoparticles	Immune evasion and tumor targeting	Improved accumulation and controlled drug release (HCC, *in vivo*, non-hematological context)
Physical field-responsive delivery	Magnetite-containing magnetic nanocapsules	Magnetic field stimulation	Controlled release and enhanced cytotoxicity (HL-60 cells, *in vitro*)
Synergistic nanotherapy	Iron oxide-based nanoplatforms	ROS amplification	Enhanced chemotherapy efficacy (AML, *in vitro* and *in vivo*)
Drug resistance modulation	Iron oxide nanozymes	Elimination of ROS-high resistant cells	Reversal of venetoclax resistance (monocytic AML, cell-line/primary models)
Ferroptosis-based therapy	Iron oxide nanoparticles with gene silencing	Ferroptosis sensitization	Durable leukemia eradication (leukemia, mouse model)

translation remain key areas for future research.

Stimuli-responsive controlled release and synergistic drug delivery

A central strategy in nanocarrier-based leukemia therapy involves exploiting stimuli-responsive release mechanisms - triggered either by intrinsic tumor microenvironmental signals or by externally applied physical fields - to achieve spatiotemporally controlled drug deployment. Among endogenous cues, pH variation across intracellular and tumor-associated environments has been investigated as a trigger for controlled drug release. Hussein-Al-Ali et al. reported that chlorambucil-loaded chitosan-coated iron oxide nanoparticles (Chloramb-CS-IONPs) exhibited a controlled release profile, with approximately 89.9% of the payload released over 5,000 minutes, following pseudo-second-order kinetics [24]. Kozalak and Kosar similarly observed that bortezomib-loaded SPIONs achieved controlled release specifically within the acidic vacuolar environment, and that this approach resulted in greater growth inhibition of RPMI 8226 cells than free drug at an equivalent 2.5 nM dose [25]. As a contextual non-metallic comparator, Yao et al. investigated pH-responsive doxorubicin release from black phosphorus-based nanosystems. In the description of Figure 7 in the original study by Yao et al. [20], BP-PEG-DOX was reported to reach release efficiencies of 12.13% at pH 5.0 and 29.46% at pH 7.5 after 25 h. However, the same source contains internally inconsistent reporting regarding the pH-dependent release direction and the formulation-specific pH assignment for unmodified BP-DOX. Therefore, this study is cited here only as evidence of pH-responsive release behavior, without assigning a single preferential pH direction to the black phosphorus systems [20]. These observations have prompted parallel investigations into external physical triggers, particularly magnetic fields and near-infrared (NIR) irradiation, which offer the potential for temporal and spatial control over drug release. Kozalak and Kosar demonstrated that integrating bortezomib-SPIONs with a rotary device generating variable magnetic fields (2 - 60 mT) enhanced growth inhibition in MM cells and induced a Bim/Mcl-1 shift consistent with apoptosis [25]. Sousa et al. similarly reported that hydroxyethyl starch magnetic nanocapsules encapsulating oncocalyxone A and magnetite exhibited cytotoxicity against HL-60 cells (IC_{50} = 2.166 μg/mL) and responded to an applied magnetic field, with a hydrodynamic diameter of 143 nm [26].

Beyond controlled release, nanoparticles have been explored in combination with chemotherapeutic agents to achieve synergistic anti-leukemia effects through distinct molecular mechanisms. Dou et al. demonstrated

Table 2. Representative therapeutic, diagnostic, and theranostic metal-based nanoplatforms for hematological malignancies and selected non-hematological models.

Representative nanoplatform	Primary function/ therapeutic mechanism	Imaging modality	Disease model/ study context
Green-synthesized Fe_3O_4 nanoparticles	Oxidative stress-induced apoptosis	-	Multiple myeloma and monocytic leukemia
Iron oxide nanoparticles	Ferroptosis induction	-	Diffuse large B-cell lymphoma
Carboxymethyl stevioside-coated magnetic nanodots	Magnetic hyperthermia	-	C6 glioma cells (*in vitro*, proof-of-concept)
Gold-cobalt ferrite nanocomposites	Photothermal therapy	-	T-lymphoblastic leukemia cells (*in vitro*)
Fe_3O_4@DMSA@Pt thermosensitive hydrogel	Immunogenic cell death (ICD)	-	Lymphoma
Ferumoxytol	Ferroptosis-mediated immunomodulation	-	Prostate cancer models (*in vitro* and *in vivo*, proof-of-concept)
Ferritin-encapsulated Fe_3O_4 nanoparticles	Diagnostic imaging	Dual-modal T_1/T_2 magnetic resonance	No disease model specified (imaging study)
Au nanoparticle-based electrochemiluminescence biosensor	Cellular detection	Electrochemiluminescence	Ramos Burkitt lymphoma cells (*in vitro*)
CD20-targeted SPION-containing PLGA theranostic nanoparticles	Photothermal chemotherapy	Magnetic resonance imaging and ultrasound imaging	B-cell lymphoma

that iron oxide nanoparticles (IONPs) combined with cytarabine (Ara-C) significantly increased apoptosis and reactive oxygen species (ROS) levels in leukemia stem cells (LSCs) from AML cell line KG1a, and *in vivo* this combination reduced abnormal leukocyte counts in peripheral blood and bone marrow while extending the survival of AML-bearing mice [27]. Follow-up work by the same group revealed that IONPs plus Ara-C downregulated IFITM3 expression in KG-1a cells, further suppressing proliferation and inducing apoptosis, with *in vivo* evidence of reduced immature granulocytes and downregulated AML-associated markers (CD33 and CD11b) [28]. The therapeutic potential of iron-based nanomaterials also extends to overcoming drug resistance: Zhang et al. reported that iron oxide nanozymes (IONE) selectively eradicated venetoclax-resistant monocytic AML subpopulations with high intracellular ROS levels, both in cell lines and primary AML models [29]. In a broader therapeutic strategy, Luo et al. developed a ferroptosis-based approach (FAST) combining iron oxide nanoparticles with knockdown of seven ferroptosis-resistant genes, which eradicated leukemia in over 50% of treated mice, with survivors remaining tumor-free for up to 250 days [30]. External magnetic fields have also been used to augment nanoparticle efficacy: Pshenichnikov et al. found that iron oxide magnetic nanoparticles, combined with moderate-intensity magnetic fields (0.26 - 0.36 T, spatial gradient up to 100 T/m), induced elevated ROS levels and enhanced cytotoxicity in Jurkat cells while sparing normal peripheral blood mononuclear cells [31]. Collectively, these findings also reflect a gradual conceptual shift from viewing nanomaterials merely as delivery vehicles toward recognizing them as bioactive partners that actively contribute to therapeutic efficacy. This transition may provide new opportunities for overcoming treatment resistance in hematological malignancies. (Table 1)

Direct therapeutic and theranostic platforms based on metal-based nanomaterials

Direct therapeutic mechanisms based on metal activity

The intrinsic catalytic and physicochemical properties of metal-based nanoparticles enable direct therapeutic mechanisms that operate independently of drug payload delivery, positioning these materials as active therapeutic agents rather than passive carriers. Iron-based nanoparticles, the most extensively investigated within this class, exhibit therapeutic efficacy primarily through two interconnected mechanisms: oxidative stress-driven apoptosis and ferroptosis. The former is largely mediated by Fenton chemistry, in which ferrous iron catalyzes the conversion of hydrogen peroxide to hydroxyl radicals, initiating a cascade of oxidative damage that culminates in apoptotic cell death. The involvement of this mechanism in hematological malignancies has been corroborated by studies demonstrating that green-synthesized Fe_3O_4 nanoparticles, prepared using sea buckthorn extract, reduced the viability of U266 multiple myeloma and THP-1 monocytic leukemia cells to 15.3% and 14.2%, respectively, at 150 μg/mL. Flow cytometry further confirmed late apoptosis as the primary death modality (86.6% for U266, 66.5% for THP-1),

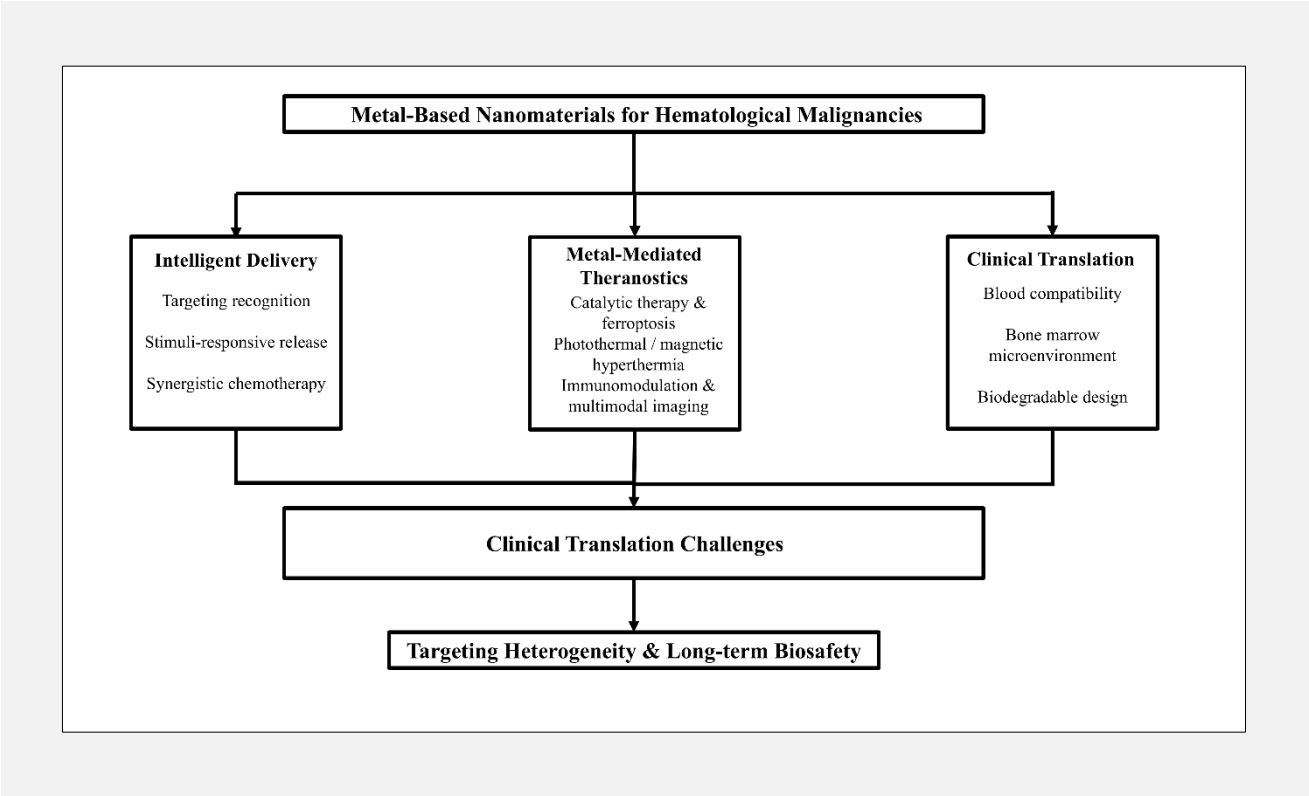


Figure 1. Schematic framework of metal-based nanomaterials for hematological malignancies.

This diagram delineates the three parallel axes reviewed in this article. The top panel represents the overarching category of metal-based nanomaterials. The middle panel illustrates their major functional applications: intelligent delivery (targeting recognition, stimuli-responsive release, and synergistic chemotherapy), metal-mediated theranostics (catalytic therapy/ferroptosis, photothermal/magnetic hyperthermia, and immunomodulation/multimodal imaging), and clinical translation considerations (blood compatibility, bone marrow microenvironment, and biodegradable design). The bottom panel highlights the key clinical translation challenges, emphasizing targeting heterogeneity and long-term biosafety.

driven by caspase-3 activation and oxidative stress [32]. In addition to apoptosis, ferroptosis has emerged as a distinct, iron-dependent cell death pathway, characterized by the accumulation of lipid peroxides and suppression of glutathione peroxidase 4 (GPX4) [33]. In diffuse large B-cell lymphoma, IONPs were found to trigger ferrous iron accumulation, lipid peroxidation, and GPX4 suppression - effects that were mechanistically linked to an elevated labile iron pool through regulation of ferroportin and transferrin receptor [33]. Notably, this dual capacity to induce both apoptosis and ferroptosis suggests a potential advantage of iron-based nanomaterials, although the predominant pathway appears to depend on cell type and tumor redox status - parameters that warrant further investigation.

Beyond catalytic mechanisms, metal nanoparticles can also serve as energy transducers, converting externally applied physical stimuli into localized cytotoxic effects - a modality that fundamentally differs from chemotherapy or ROS generation. Magnetic hyperthermia, typically realized through iron oxide nanoparticles exposed to alternating magnetic fields, has attracted considerable research interest as a potential therapeutic modality. For instance, carboxymethyl-stevioside-coated magnetic dots achieved a specific absorption rate of 209.25 W/g at 359 kHz and 188 Oe, and demonstrated anti-migratory and anti-invasive effects on glioma C6 cells through inhibition of matrix metalloproteinases-2 and -9 [34]. Although this study was conducted in an *in vitro* glioma cell model, it provides proof-of-concept evidence for the therapeutic potential of magnetic hyperthermia, which may inform the design of analogous nanoplatforms for hematological malignancies. Photothermal therapy represents a complementary strategy in which plasmonic nanostructures convert near-infrared light into heat. Gold/cobalt ferrite nanocomposites, for example, demonstrated *in vitro* selective cytotoxicity toward T-lymphoblastic leukemia cells while sparing healthy PBMCs, suggesting their potential for future development in combined photothermal and magnetic applications [35]. Nevertheless, these physical modalities are subject to inherent constraints: magnetic hyperthermia requires careful optimization of field parameters to prevent off-target heating, whereas photothermal therapy is constrained by limited light penetration depth and the need for selective tumor targeting. The integration of

multiple mechanisms within a single nanostructure - for instance, combining magnetic hyperthermia with photothermal therapy - offers potential synergistic benefits, yet also introduces considerable complexity in predicting biological outcomes. Thus, metal-based nanoparticles exhibit diverse direct therapeutic mechanisms, although their optimal deployment in hematological malignancies necessitates careful consideration of the specific malignancy, the tumor microenvironment, and the practical constraints of energy delivery in clinical settings.

Immunomodulation- and imaging-based nanoparticle platforms in hematologic and selected non-hematologic models

The convergence of immune modulation and diagnostic imaging within nanoparticle platforms has attracted growing interest, yet the integration of these distinct functions remains an ongoing challenge. In the realm of immune activation, Fe_3O_4@DMSA@Pt nanoparticles embedded in a thermosensitive hydrogel-induced immunogenic cell death (ICD) in lymphoma cells, with a 4.1 fold increase in calreticulin externalization, 68% nuclear depletion of HMGB1, and ATP secretion of 40.74 nM, which subsequently elicited robust dendritic cell maturation (92% $CD86^+/CD80^+$ DCs) and T cell activation [36]. Similarly, ferumoxytol-mediated ferroptosis was found to augment natural killer cell cytotoxicity, accompanied by upregulation of ULBP ligands and elevated HMGB1 and PD-L1 expression. Although this strategy was evaluated in both *in vitro* and *in vivo* prostate cancer models, it provides proof-of-concept evidence for overcoming the corresponding therapeutic barrier. Its applicability to hematological malignancies requires further disease-specific validation [37]. Concurrently, nanoparticle-based MRI contrast agents have advanced the field of diagnostic imaging. Ferritin encapsulated iron oxide nanoparticles (Fe_3O_4@HFn) afforded dual mode T_1/T_2 contrast, with relaxivities (r_1 = 5.20 s^{-1} mM^{-1}, r_2 = 147.6 s^{-1} mM^{-1} at 3.0 T) substantially exceeding those of clinical Gd-based agents [38]. Nevertheless, the relaxometric performance of iron oxide agents is strongly influenced by physicochemical parameters, as evidenced in Gd-DTPA-coated magnetite/maghemite systems, where magnetic domain orientation and relaxation properties were modulated by variations in particle size and coating thickness [39]. For cellular detection, an Au nanoparticle-based electrochemiluminescence ratiometric cytosensor was developed for lymphoma cells, with a detection limit of 20 cells mL^{-1} via a ratiometric strategy, although its utility is currently confined to ex vivo settings [40]. Collectively, these findings suggest that although nanoparticles hold considerable promise for immune modulation and diagnostic imaging individually, the convergence of both functionalities within a single theranostic platform remains relatively limited in the hematological context, highlighting the need for future designs that co optimize immunostimulatory and diagnostic capabilities.

Integrated nanoplatforms for diagnosis and therapy

The multifunctional properties of nanoplatforms provide opportunities for integrating therapeutic and diagnostic functions within a single system for hematological malignancies. By combining treatment delivery with imaging modalities, these platforms allow the integration of therapeutic intervention with diagnostic assessment. For example, Wang et al. designed a CD20-targeted PLGA-based theranostic nanoplatform (Tsc-NPs) for B-cell lymphoma, in which superparamagnetic iron oxide nanoparticles and perfluoropentane were incorporated to enable magnetic resonance/ultrasound bimodal imaging-guided photothermal-chemo synergistic therapy, resulting in a tumor inhibition rate of approximately 96.57% under near-infrared irradiation [41]. In addition, ferritin-encapsulated iron oxide nanoparticles (Fe_3O_4@HFn) exhibited enhanced dual-mode T_1/T_2 magnetic resonance contrast together with potential applications in targeted imaging and therapeutic monitoring [38]. These findings indicate that multifunctional nanoplatforms may serve as a potential strategy for integrating diagnosis and therapy in hematologic cancer treatment (Table 2).

Special considerations and challenges of metal nanomaterials in the hematological system

Blood compatibility and long-circulation design

The utility of magnetic nanoparticles (MNPs) in biomedical contexts is crucially dependent on their blood interactions, wherein surface properties play a key role in determining biological identity and circulation behavior. Citrate-coated SPIONs, though promising as tracers in magnetic particle imaging, undergo rapid cellular uptake [42]. Natural polyphenol coatings, by contrast, can be attached to magnetite surfaces via -OH groups to confer colloidal stability [43]. SPION-loading was shown to preserve T cell functions - proliferation, cytokine secretion, and antigen-specific cytotoxicity - while leaving macrophage viability intact [44,45]. The safety profile extends further to other blood cells: therapeutic concentrations of $NiFe_2O_4$ nanoparticles demonstrated no toxicity towards healthy PBMCs or RBCs [46]. Nevertheless, systematic evaluation of broader blood compatibility parameters remains limited. Thus, although current investigations have established discrete facets of MNP biocompatibility, an integrated understanding of how surface properties collectively orchestrate blood interactions and circulation kinetics warrants further exploration.

Nanotechnology for overcoming therapeutic barriers: evidence from hematologic and selected non-hematologic models

The treatment of hematologic malignancies continues to face formidable biological barriers, yet nanotechnological strategies - encompassing physical targeting, magnetic actuation, and cellular engineering - offer distinct routes to overcome these obstacles, albeit with inherent performance trade-offs. Nanotechnology has also been

explored for the repair and regeneration of lymphoid organs, including strategies involving targeted delivery, imaging, and modulation of the tissue microenvironment; this review-level evidence provides contextual rather than disease-specific evidence for hematological malignancies [47]. An alternative strategy bypasses *in vivo* delivery entirely: ex vivo perfusion with anti CD52 conjugated magnetic nanoparticles reduced malignant B lymphocyte counts by 44 - 53% in chronic lymphocytic leukemia patient blood [48], whereas gold-deposited magnetic nanoprobes permitted SERS-based detection of circulating plasma cells with single cell resolution [49]. In adoptive cell therapy, magnetic nanoparticles serve dual functions: they enable CAR T cell labeling during manufacturing for subsequent MRI tracking and magnetic accumulation [50], and they deliver IL-12 mRNA-loaded magnetic cores to synergize checkpoint inhibition with magnetic tumor targeting. Although this platform was evaluated in an *in vivo* solid-tumor model, it provides proof-of-concept evidence for magnetically guided immunotherapy rather than direct evidence in hematological malignancies. Its potential application in hematological malignancies requires further validation [51]. Taken together, these diverse strategies highlight that the choice between *in vivo* delivery, ex vivo manipulation, and cellular engineering carries implications not just for treatment outcome, but also for safety profiles – notably immunogenicity and off target effects.

Long-term biosafety and nanocarrier design considerations

In vitro studies have demonstrated that certain metal oxide nanoparticles exhibit cytotoxic activity against leukemic cells while exerting limited effects on healthy PBMCs [31,52]. However, long-term biosafety concerns strongly restrict their clinical translation and need to be addressed. Such concerns are also illustrated by non-hematologic safety evidence, including oxidative damage caused by unmodified iron oxide nanoparticles in the brain [53], and toxicity of mixed metal oxide nanomaterials in aquatic bacterial models [54]. Collectively, these observations underscore the need for systematic evaluation of long-term biodistribution, organ accumulation, clearance, and toxicity, as well as the development of biodegradable or renally clearable nanoarchitectures where appropriate.

CONCLUSION AND PERSPECTIVE

This review has comprehensively examined the progress of metal-based nanocomposites in hematologic malignancies, highlighting their evolution from drug carriers to multifunctional platforms. As delivery vehicles, these nanomaterials have been investigated for targeted payload release through active recognition and microenvironmental responsiveness. Their role as direct therapeutic agents has also garnered attention, wherein catalytic activities - including oxidative stress, ferroptosis, and physical energy conversion such as photothermal and magnetothermal effects - have positioned these materials as active participants in tumor eradication. Meanwhile, the integration of imaging capabilities has opened avenues for theranostic applications.

Despite these advances, clinical translation remains constrained by several challenges. Long-term biosafety concerns, particularly regarding chronic accumulation of non-biodegradable components, pose substantial hurdles. The intrinsic complexity of achieving precise targeting in hematologic malignancies - including target heterogeneity and microenvironmental barriers - continues to limit therapeutic efficacy. Moreover, the heterogeneity and resistance of malignant cells underscore the need for deeper mechanistic insights into the determinants of therapeutic sensitivity. These limitations collectively indicate that further efforts are required to reconcile therapeutic potency with biocompatibility and targeting precision with biological complexity.

Looking forward, future development of metal-based nanoplatforms could benefit from a deeper understanding of target-related factors and microenvironmental heterogeneity to enhance therapeutic specificity. The immunomodulatory capacities of these platforms, particularly their ability to induce immunogenic cell death, could be harnessed to initiate systemic anti-tumor immunity, representing a promising complement to direct cytotoxic approaches. Meanwhile, the path toward clinical translation would be advanced by prioritizing the engineering of biodegradable or renally clearable nanoarchitectures to mitigate long-term biosafety concerns. Addressing manufacturing complexity and ensuring reproducible biological performance will also be critical for clinical adoption. Ultimately, the integration of materials science with systems biology and pharmaceutical engineering may realize the potential of these platforms as intelligent, adaptable tools for the management of hematologic malignancies.

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References:

1. Wu X, Wang F, Yang X, et al. Advances in drug delivery systems for the treatment of acute myeloid leukemia. Small 2024;20(42): e2403409. (PMID: 38934349)

2. Mahmoud AM, Deambrogi C. Advancements in nanotechnology for targeted and controlled drug delivery in hematologic malignancies: shaping the future of targeted therapeutics. Appl Biosci 2025;4(1):16. https://doi.org/10.3390/applbiosci4010016

3. Qian S, Zheng C, Wu Y, Huang H, Wu G, Zhang J. Targeted therapy for leukemia based on nanomaterials. Heliyon 2024; 10(15):e34951. (PMID: 39144922)

4. Su Z, Dong S, Zhao S, et al. Novel nanomedicines to overcome cancer multidrug resistance. Drug Resist Updat 2021;58:100777. (PMID: 34481195)

5. Allegra A, Di Gioacchino M, Tonacci A, Petrarca C, Gangemi S. Nanomedicine for immunotherapy targeting hematological malignancies: current approaches and perspective. Nanomaterials (Basel) 2021;11(11):2792. (PMID: 34835555)

6. Chen K, Wang W, Wang Z. Designing next-generation immune cell therapies with nanomaterials. BMEMat 2025;3(2):e70003. https://onlinelibrary.wiley.com/doi/10.1002/bmm2.70003

7. Huang X, Mahmudul H, Li Z, et al. Noble metal nanomaterials for the diagnosis and treatment of hematological malignancies. Front Biosci (Landmark Ed) 2022;27(2):40. (PMID: 35226983)

8. Li Y, Barmin RA, Zhang R, Kiessling F, Lammers T, Pallares RM. Clinical translation and landscape of superparamagnetic iron oxide nanoparticles. Adv Drug Deliv Rev 2026;229:115756. (PMID: 41360153)

9. Sun L, Liu H, Ye Y, et al. Smart nanoparticles for cancer therapy. Signal Transduct Target Ther 2023;8(1):418. (PMID: 37919282)

10. Kiwumulo HF, Muwonge H, Lubwama M, et al. Iron oxide nanoparticles in leukemia: design, diagnostic applications, and therapeutic strategies. J Egypt Natl Cancer Inst 2025;37(1):44. (PMID: 40459680)

11. Ashoub MH, Razavi R, Heydaryan K, Salavati-Niasari M, Amiri M. Targeting ferroptosis for leukemia therapy: exploring novel strategies from its mechanisms and role in leukemia based on nanotechnology. Eur J Med Res 2024;29(1):224. (PMID: 38594732)

12. Wang B, Hu S, Teng Y, et al. Current advance of nanotechnology in diagnosis and treatment for malignant tumors. Signal Transduct Target Ther 2024;9(1):200. (PMID: 39128942)

13. Wang Y, Yang Y, Zheng X, et al. Application of iron oxide nanoparticles in the diagnosis and treatment of leukemia. Front Pharmacol 2023;14:1177068. (PMID: 37063276)

14. Soleimanian A, Khalilzadeh B, Mahdipour M, et al. An efficient graphene quantum dots-based electrochemical cytosensor for the sensitive recognition of CD123 in acute myeloid leukemia cells. IEEE Sens J 2021;21(15):16451-63. https://ieeexplore.ieee.org/document/9427510

15. Smith B, Li Y, Fields T, et al. Tumor integrin targeted theranostic iron oxide nanoparticles for delivery of caffeic acid phenethyl ester: preparation, characterization, and anti-myeloma activities. Front Pharmacol 2024;15:1325196. (PMID: 38510655)

16. Akram SM, Al-Saffar AZ, Hadi NA, Akram SM. Utilization of novel lectin-conjugated Au nanoparticles as Thomsen-Friedenreich onco-antigen target for in vitro cytotoxicity and apoptosis induction in leukemic cell line. Life Sci 2022;311(Pt A):121163. (PMID: 36368415)

17. Lamberger Z, Bargel H, Humenik M. Aptamer-modified nanohydrogel microarrays for bioselective cancer cell immobilization. Adv Funct Mater 2022;32(45):2207270. https://onlinelibrary.wiley.com/doi/10.1002/adfm.202207270

18. Hu X, Wang Y, Zuping X, et al. Novel aggregation-enhanced PEC photosensitizer based on electrostatic linkage of ionic liquid with protoporphyrin IX for ultrasensitive detection of Molt-4 cells. Anal Chem 2022;94(8):3708-17. (PMID: 35172575)

19. Yang A, Luo D, Jia Y, et al. Targeted delivery of AZD5363 to T-cell acute lymphocytic leukemia by mSiO2-Au nanovehicles. Colloids Surf B Biointerfaces 2023;230:113505. (PMID: 37574619)

20. Yao Y, Gao X, Zhou Z. The application of drug loading and drug release characteristics of two-dimensional nanocarriers for targeted treatment of leukemia. Front Mater 2023;10:1209186. https://www.frontiersin.org/articles/10.3389/fmats.2023.1209186/full

21. Zhao Q, Sun X, Wu B, et al. Construction of homologous cancer cell membrane camouflage in a nano-drug delivery system for the treatment of lymphoma. J Nanobiotechnology 2021;19(1):8. (PMID: 33407527)

22. Liu J, Li X, Chen J, et al. Arsenic-loaded biomimetic iron oxide nanoparticles for enhanced ferroptosis-inducing therapy of hepatocellular carcinoma. ACS Appl Mater Interfaces 2023;15(5): 6260-73. (PMID: 36695492)

23. Dumontel B, Susa F, Limongi T, et al. Nanotechnological engineering of extracellular vesicles for the development of actively targeted hybrid nanodevices. Cell Biosci 2022;12(1):61. (PMID: 35568919)

24. Hussein-Al-Ali SH, Hussein MZ, Bullo S, Arulselvan P. Chlorambucil-iron oxide nanoparticles as a drug delivery system for leukemia cancer cells. Int J Nanomedicine 2021;16:6205-16. (PMID: 34526768)

25. Kozalak G, Kosar A. *In vitro* evaluation of bortezomib-loaded superparamagnetic iron oxide nanoparticles for multiple myeloma cells under guide-targeted variable magnetic fields. ChemNanoMat 2025;11(12):e202500225. https://onlinelibrary.wiley.com/doi/10.1002/cnma.202500225

26. Sousa ACC, Romo AIB, Almeida RR, et al. Starch-based magnetic nanocomposite for targeted delivery of hydrophilic bioactives as anticancer strategy. Carbohydr Polym 2021;264:118017. (PMID: 33910740)

27. Dou J, Li L, Guo M, et al. Iron oxide nanoparticles combined with cytosine arabinoside show anti-leukemia stem cell effects on acute myeloid leukemia by regulating reactive oxygen species. Int J Nanomedicine 2021;16:1231-44. (PMID: 33633448)

28. Dou J, Mei F, Xu H, et al. IONPs combined with cytarabine downregulated IFITM3 expression to inhibit acute myeloid leukemia. Front Oncol 2025;15:1515956. (PMID: 40969269)

29. Zhang S, Lou S, Bian W, et al. Selective eradication of Venetoclax-resistant monocytic acute myeloid leukemia with iron oxide nanozymes. Biochem Biophys Res Commun 2024;719:150117. (PMID: 38761635)

30. Luo T, Wang Y, Wang J. Ferroptosis assassinates tumor. J Nanobiotechnology 2022;20(1):467. (PMID: 36329436)

31. Pshenichnikov S, Omelyanchik A, Efremova M, et al. Control of oxidative stress in Jurkat cells as a model of leukemia treatment. J Magn Magn Mater 2021;523:167623. https://www.sciencedirect.com/science/article/abs/pii/S0304885320325907

32. Alzaidy AH, Ganduh SH, Abed MJ, Dawi EA, Jasim LS, Ashoub MH. Microwave assisted solvothermal green synthesis of Fe3O4 nanoparticles using sea buckthorn for multiple myeloma and monocytic leukemia treatment. Sci Rep 2025;15(1):25743. (PMID: 40670555)

33. Huang QT, Hu QQ, Wen ZF, Li YL. Iron oxide nanoparticles inhibit tumor growth by ferroptosis in diffuse large B-cell lymphoma. Am J Cancer Res 2023;13(2):498-508. (PMID: 36895978)

34. Gupta R, Sharma D. (Carboxymethyl-stevioside)-coated magnetic dots for enhanced magnetic hyperthermia and improved glioblastoma treatment. Colloids Surf B Biointerfaces 2021;205:111870. (PMID: 34034224)

35. Motorzhina A, Jovanovic S, Belyaev V, et al. Innovative gold/cobalt ferrite nanocomposite: physicochemical and cytotoxicity properties. Processes 2021;9(12):2264. https://www.mdpi.com/2227-9717/9/12/2264

36. Yan M, Peng J, Wu H, Ma M, Zhang Y. Injectable magnetic-nanozyme based thermosensitive hydrogel for multimodal DLBCL therapy. Gels 2025;11(3):218. (PMID: 40136923)

37. Kim KS, Choi B, Choi H, Ko MJ, Kim DH, Kim DH. Enhanced natural killer cell anti-tumor activity with nanoparticles mediated ferroptosis and potential therapeutic application in prostate cancer. J Nanobiotechnology 2022;20(1):428. (PMID: 36175895)

38. Zhang J, Peng X, Liu J, Yang S, Xu H, Liang M. Ferritin-encapsulated iron oxide nanoparticles for dual-mode MRI contrast enhancement and targeted cancer imaging. Anal Chim Acta 2026;1382:344863. (PMID: 41330689)

39. Eguía-Eguía SI, Gildo-Ortiz L, Pérez-González M, Tomas SA, Arenas-Alatorre JA, Santoyo-Salazar J. Magnetic domains orientation in (Fe3O4/γ-Fe2O3) nanoparticles coated by gadolinium-diethylenetriaminepentaacetic acid (Gd3+-DTPA). Nano Express 2021;2(2):020010. https://iopscience.iop.org/article/10.1088/2632-959X/ac0107

40. Zhou H, Ding K, Yu Q, Wang H, Liu J, Wang Z. Enhanced electrochemiluminescence ratiometric cytosensing based on surface plasmon resonance of Au nanoparticles and nanosucculent films. Biosens Bioelectron 2021;189:113367. (PMID: 34091285)

41. Wang Z, Huang J, Lv W, et al. Ultrasound/magnetic resonance bimodal imaging-guided CD20-targeted multifunctional nanoplatform for photothermal/chemo synergistic therapy of B-cell lymphoma. J Pharm Sci 2025;114(2):967-982. (PMID: 39551237)

42. Kampen L, Remmo A, Twamley SG, et al. Rapid cellular uptake of citrate-coated iron oxide nanoparticles unaffected by cell-surface glycosaminoglycans. Nanoscale Adv 2024;6(15):3825-37. (PMID: 39050941)

43. Matías-Reyes AE, Alvarado-Noguez ML, Pérez-González M, et al. Direct polyphenol attachment on the surfaces of magnetite nanoparticles, using Vitis vinifera, Vaccinium corymbosum, or Punica granatum. Nanomaterials (Basel) 2023;13(17):2450. (PMID: 37686958)

44. Pfister F, Dörrie J, Schaft N, et al. Human T cells loaded with superparamagnetic iron oxide nanoparticles retain antigen-specific TCR functionality. Front Immunol 2023;14:1223695. (PMID: 37662937)

45. Lim J, Petaroudi M, Pearce G, Yasakçi V, Unak P. Effects of fluorodeoxyglucose conjugated and unconjugated iron oxide magnetic nanoparticles on macrophages: a pilot study. Braz Arch Biol Technol 2021;64:e21200736. https://www.researchgate.net/publication/355625319_Effects_of_Fluorodeoxyglucose_Conjugated_and_Unconjugated_Iron_Oxide_Magnetic_Nanoparticles_on_Macrophages_a_Pilot_Study

46. Samanta S, Ahmed R, Greneche JM, et al. Unleashing the multifunctionality of biocompatible superparamagnetic spinel $NiFe_2O_4$ nanoparticles: exploration of its efficacy towards leukemic cells and MDR pathogenic bacteria. New J Chem 2025;49(40):17662-85. https://pubs.rsc.org/en/content/articlelanding/2025/nj/d5nj02037a

47. Liu B, Wang DA. Application of nanomaterials in the repair and regeneration of lymphatic organs and corresponding biophysical simulation strategies. Adv NanoBiomed Res 2025;5(2):2400081. https://onlinelibrary.wiley.com/doi/10.1002/anbr.202400081

48. Janker S, Doswald S, Schimmer RR, et al. Targeted large-volume lymphocyte removal using magnetic nanoparticles in blood samples of patients with chronic lymphocytic leukemia: a proof-of-concept study. Int J Mol Sci 2023;24(8):7523. (PMID: 37108680)

49. Zhang D, Chen X, Lin J, et al. Ultrasensitive detection of circulating plasma cells using surface-enhanced Raman spectroscopy and machine learning for multiple myeloma monitoring. Anal Chem 2025;97(7):4101-10. (PMID: 39854732)

50. Zhang W, Gaikwad H, Groman EV, Purev E, Simberg D, Wang G. Highly aminated iron oxide nanoworms for simultaneous manufacturing and labeling of chimeric antigen receptor T cells. J Magn Magn Mater 2022;541:168480. (PMID: 34720339)

51. Zheng C, Yi K, Du Y, et al. Immuno-packed T-cell-fusogenic liposome empowers adoptive T cell therapy for solid tumor treatment. Adv Mater 2026;38(8):e10842. (PMID: 41055330)

52. Taeby M, Ashoub MH, Asghari M, Farsinejad A, Amiri M. Sol-gel synthesis of strontium ferrate (SrFeO3) nanoparticles and evaluation of anti-leukemic effects against leukemic cell lines. J Sol-Gel Sci Technol 2024;109(1):56-65. https://link.springer.com/article/10.1007/s10971-023-06251-2

53. Dora MF, Taha NM, Lebda MA, et al. Quercetin attenuates brain oxidative alterations induced by iron oxide nanoparticles in rats. Int J Mol Sci 2021;22(8):3829. (PMID: 33917107)

54. Na M, Nam SH, Moon K, Kim J. Development of a nano-QSAR model for predicting the toxicity of nano-metal oxide mixtures to Aliivibrio fischeri. Environ Sci Nano 2023;10:325-37. https://pubs.rsc.org/en/content/articlelanding/2023/en/d2en00672c