Heliyon 10 (2024) e34951

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Targeted therapy for leukemia based on nanomaterials

Suying Qian [a], Cuiping Zheng [b], Yanfang Wu [c], Huiyan Huang [c], Gongqiang Wu [d,*], Junyu Zhang [e,**]

[a] Department of Hematology and Oncology, Ningbo No.2 Hospital, Ningbo, 315000, China
[b] Department of Hematology and Oncology, Wenzhou Central Hospital, Wenzhou, 325099, China
[c] Department of Hematopathology, The First People's Hospital of Fuyang, Hangzhou, 311499, China
[d] Department of Hematology and Oncology, Dongyang People's Hospital, Jinhua, 322103, China
[e] Department of Hematopathology, Lishui Central Hospital, Lishui, 323020, China

ARTICLE INFO

Keywords:
Leukemia
Targeted therapy
Nanomaterials

ABSTRACT

Leukemia is a kind of hematopoietic stem cell malignant clonal disease. Drug therapy is the core treatment strategy for leukemia, but the current therapeutic drugs have defects such as low bioavailability, large adverse reactions and inconvenient intravenous administration. Targeted therapy can combine drugs with specific carcinogenic sites on cells to kill cancer cells and avoid damage to normal cells, which has gradually become the mainstream method of leukemia treatment. In addition, nanomedicine delivery systems can significantly improve drug efficacy through controlled size and targeted optimization of drug delivery by modification strategies. Therefore, the targeted treatment of leukemia based on nanomaterials has great research value and application prospect. This paper gives an overview of the current therapeutic strategies for leukemia, and then reviews the cutting-edge targeted therapeutic nanomaterials for leukemia, including organic nanomaterials (mainly carbon-based nanomaterials, lipid materials, polymers, etc.) and inorganic nanomaterials (mainly noble metal nanoparticles, magnetic nanoparticles, hollow mesoporous materials, etc.). The challenges and prospects for the future development of targeted nanomaterials in the treatment of leukemia are also briefly reviewed.

1. Introduction

Leukemia is a heterogeneous group of malignant hematological disorders characterized by the uncontrolled proliferation of abnormal white blood cells (WBCs) in the bone marrow, which eventually leads to their accumulation in the blood and other tissues. Leukemia is one of the most common types of cancer, which accounts for approximately 3.2 % of all new cancer cases and 2.8 % of all cancer deaths worldwide [1]. Despite advances in the diagnosis and treatment of leukemia, it remains a challenging disease to manage, particularly in older adults and patients with relapsed or refractory disease. Further research is needed to better understand the underlying mechanisms of leukemia and to develop more effective treatments for this disease (see Fig. 7).

Leukemia is a group of cancers that affect the blood and bone marrow. This disease is characterized by the accumulation of abnormal white blood cells that interfere with the normal functioning of the immune system [2]. Leukemia can be classified into four main types based on the speed of progression and the type of white blood cells involved. These include acute lymphoblastic leukemia

* Corresponding author.
** Corresponding author.
E-mail addresses: wugongqiang59@126.com (G. Wu), zjy11162023@163.com (J. Zhang).

https://doi.org/10.1016/j.heliyon.2024.e34951
Received 20 March 2024; Received in revised form 21 June 2024; Accepted 18 July 2024
Available online 21 July 2024

(ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). Special type leukemia is a relatively rare type of leukemia, but no matter which type, the essence of hematopoietic stem cells under some pathogenic factors abnormal proliferation to produce a large number of abnormal white blood cells. Due to the complexity of leukemia classification and prognosis stratification, there is no uniform and fixed treatment method, and the treatment mode varies according to different types. Thus it is necessary to formulate a treatment plan combined with detailed classification and prognosis stratification.

The current therapies mainly include radiotherapy, chemotherapy, targeted therapy, immunotherapy and stem cell transplantation. Radiotherapy uses alpha, beta and gamma rays produced by radioactive isotopes to damage the chromosomes of cancer cells so that they lose the ability to grow and multiply. The sensitivity of the tumor to radiation determines the effect of radiotherapy, so the treatment method of radiotherapy is specific to the cancer, such as lymphoma. However, the radiation of radiotherapy has the same killing effect on normal tissues of the human body, and the larger side effects are often unbearable for patients. Chemotherapy is the primary approach to the induced remission phase of treatment, which uses drugs to kill cancer cells with the goal of achieving a complete remission quickly. After achieving complete remission, the second stage of treatment, that is, post-remission therapy, is mainly chemotherapy and hematopoietic stem cell transplantation. After complete remission, there are still residual leukemia cells in the body, called minimal residual lesions. In order to achieve long-term disease-free survival and recovery, consolidation and maintenance therapy must be performed to remove minimal residual lesions. Treatment options need to be selected considering age, type, minimal residual lesions and drug resistance after treatment, availability of stem cell donors and targeted therapeutic drugs. The commonly used drugs for inducing remission therapy include vincristine, daunorubicin, doxorubicin, mitoxantrone, glucocorticoid, etc. Consolidation and reinforcement therapy are commonly used with drugs such as cytarabine. The drugs are taken orally, injected intravenously, and are carried throughout the body by the circulatory system. However, drug molecules cannot distinguish between normal cells and cancer cells, so they have serious side effects [3,4].

The development of new drugs and nanomaterials for leukemia treatment represents a significant step forward in improving therapeutic outcomes. By precisely targeting leukemia cells and delivering drugs effectively, these new approaches hold the potential to significantly improve the lives of patients with leukemia. Nanodrug delivery system is a new application in the field of nanotechnology in medicine. The size of nano drug delivery system, structure and function of transport depends on the different characteristics and synthesis methods of nanomaterials, to build and design the ideal nanometer carrier. The nanoscale size and controllable modification of delivery systems exhibit great advantages in improving drug pharmacokinetics and pharmacodynamics, which may lead to better therapeutic effects. At present, the research has a lot of progress in nano drug delivery system, the extension of drug circulation time, improve the bioavailability, increase retained in the tumor site, to reduce the resistance and reduce anti-cancer drug adverse reaction shows strong potential. Nanocarriers used in nano-drug delivery systems are mainly divided into two categories: organic nanocarriers and inorganic nanocarriers. Organic nanocarriers mainly include polymers, liposomes and proteins, while inorganic nanocarriers include gold nanoparticles, silicon nanoparticles, iron nanoparticles (such as iron oxide) and other inorganic salt nanoparticles.

Many nanodrug carriers currently under development rely on enhanced penetration and retention effects (EPRs) to passively accumulate in the tumor microenvironment and kill cancer cells. In leukemia, where leukemia stem cells and their progeny circulate in the peripheral blood or bone marrow, the EPR effect may not be effective. To address this challenge, alternative nanodrug delivery strategies are being explored for leukemia treatment [5]. One promising approach involves the use of targeted nanodrug carriers that can actively seek out and bind to leukemia cells. These targeted nanodrug carriers are designed to recognize specific markers or receptors expressed on the surface of leukemia cells, allowing them to deliver the drugs directly to the tumor cells while minimizing off-target effects. This targeted delivery system holds significant potential in enhancing the efficacy of leukemia treatment. By precisely delivering the drugs to the tumor cells, it minimizes the side effects that often result from traditional chemotherapy methods, which often affect healthy cells as well. Additionally, the nanodrug carriers can be designed to release the drugs only when they reach the tumor cells, further ensuring maximum efficacy and minimal toxicity. Hence, the treatment of leukemia necessitates the precise targeting and binding of individual circulating cells [6].

Targeted therapy refers to the specific combination of drugs with specific carcinogenic sites on cells through biological, physical or chemical means to kill cancer cells and avoid damage to normal cells, which has gradually become the mainstream method of leukemia treatment [7]. In the treatment of leukemia, a combination of multiple drugs is usually used in order to achieve synergistic effect and improve the therapeutic effect. For example, the combination of imatinib and cytarabine has shown remarkable efficacy in the treatment of chronic myeloid leukemia. In addition, studies have shown that combining anti-tumor drugs with immunomodulators can effectively improve the treatment effect and prolong the survival of patients. Multiple organs and tissues are involved in the growth and spread of leukemic cells. Therefore, identifying the cancer sites targeted by targeted therapy can help improve the accuracy of treatment and reduce side effects. For example, Philadelphia chromosome positive acute lymphoblastic leukemia (Ph + ALL) is characterized by high recurrence rate, short disease-free survival time, and poor prognosis. With the advent of tyrosine kinase inhibitors (TKI), the efficacy and prognosis of Ph + ALL patients have been significantly improved. Imatinib was the first TKI to target the BCR-ABL fusion gene in Ph + ALL, followed by the development of the second generation TKI, Nilotinib, Dasatinib, Bosutinib, and the third generation TKI, Pratinib. Despite the remarkable efficacy of TKI combined chemotherapy in terms of therapeutic response, frequent recurrence and drug resistance remain a challenge. The main side effects of TKIs include hematological toxicity (such as thrombocytopenia, neutrophilic leukopenia, and anemia), which may lead to dose-limiting and require adjustment of treatment regimen. In addition, there are non-hematological toxicities such as fatigue, rash, and gastrointestinal discomfort. TKIs target the BCR-ABL fusion protein, but there is a risk of resistance, which may lead to recurrence or refractory disease. Long-term use of TKIs may increase the risk of secondary malignancies, and monitoring for toxicity and resistance is required for life, which brings economic and psychological burden. Hematopoietic stem cell transplantation (HSCT) has long been considered the only cure for Ph + ALL. However,

it is crucial to carefully evaluate the risks and benefits of this combination therapy on an individual patient basis. The decision to proceed with HSCT should be based on a comprehensive assessment of patient comorbidities, disease characteristics, and overall prognosis. Additionally, close monitoring and follow-up are essential to ensure timely intervention and management of any adverse events or relapses that may occur. For the use of TKI after transplantation, a new generation of TKI maintenance therapy may reduce the risk of recurrence after transplantation and should be considered as a valuable treatment option. Overactivation of B cell receptor (BCR) signaling pathway is closely related to the occurrence and development of chronic lymphocytic leukemia (CLL). For instance, BTK inhibitors bind to BTK and prevent it from phosphorylating downstream substrates, thus blocking BCR signaling. Similarly, PI3K inhibitors block the activity of PI3K, which is a key enzyme in the phosphoinositide 3-kinase (PI3K) pathway that regulates cell growth, proliferation, and survival. Bruton tyrosine kinase (BTK), phosphatidylinositol-3 kinase (PI3K) and spleen tyrosine kinase (SYK) as the key kinases of this pathway have become the research focus of CLL targeted therapy.

The BTK inhibitors ibrutinib and PI3K inhibitors Idelalisib and Duvelisib have been approved for clinical use with low toxicity and good efficacy in certain high-risk patients (such as 17P deletion). However, there are still limitations such as drug resistance, medication sequence, cost of use and low selectivity. Therefore, new inhibitors are constantly being developed to seek better bioavailability, higher exposure, and more complete targeting inhibition. ACP - 196 (acalabrutinib), for example, is a kind of the second generation BTK inhibitors, higher selectivity, and of better pharmacological characteristics, including the effective plasma concentration and rapid oral absorption and short half-life. In addition, TGR - 1202 is a second generation of oral PI3K delta inhibitors, good clinical activity, compared to other similar low incidence of drug adverse reaction, better tolerability.

These new targeted drugs are becoming more and more prominent in the treatment of CLL and may gradually replace traditional chemical immunotherapy. At present, the overall long-term survival rate of acute myeloid leukemia (AML) is still not high, and the prognosis of high-risk patients and elderly patients is still not ideal. But AML is a complex and heterogeneous disease with multiple mutated genes. Therefore, the emergence of new targeted drugs for certain mutated genes has brought hope for patients with relapsed refractory or high-risk AML, as well as AML patients with certain genetic mutations. Such as FLT3 inhibitors sorafenib, middotoline, quezatinib; IDH inhibitor ivotinib and encidil are equal. The FLT3 gene, which is frequently mutated in AML, encodes for a tyrosine kinase receptor involved in cell proliferation and survival. Mutations in FLT3 lead to constitutive activation of the receptor, promoting leukemic cell growth; Bcl-2 inhibitor Vinetoke et al. Through regulating the MCL - 1, the FLT3 inhibitors can reduce the dimension of Nike pull resistance, thereby enhance the curative effect of combination. About 25 % of the patients with AML with FLT3 - ITD mutation, the gene mutation can activate the AML cells proliferation and survival related signaling pathways, including the MAPK/ERK, PI3K/AKT and JAK/STAT signaling pathway, resulting in patients with poor prognosis. The rational application of targeted drugs will greatly improve the survival rate of AML patients. The Bcl-2 gene encodes for a protein that regulates apoptosis, or programmed cell death. Overexpression of BCL-2 in leukemic cells prevents them from undergoing apoptosis, contributing to their survival and proliferation. Similarly, mutations in the IDH gene family, particularly IDH1 and IDH2, are also common in AML. These mutations result in the production of oncogenic metabolites that promote leukemic cell growth. IDH inhibitors, such as enasidenib and ivosidenib, target these mutant IDH enzymes, restoring normal cellular metabolism and inhibiting leukemic cell proliferation. Results show that in a previous study, IDH mutation generate 2-HG, suggesting IDH1/2 gene mutations can reduce the oxidation of antiapoptotic proteins the BCL-2 activity. Therefore, IDH inhibitors mainly depends on 2-HG lowering the inhibition of the BCL-2 TKI represented by imatinib is the first-line drug in the treatment of chronic myeloid leukemia (CML), which can significantly improve the treatment efficiency of CML and the survival rate of early patients. However, the drug does not cure CML, and resistance may occur, and the efficacy of advanced CML patients is poor, can not prevent the recurrence and progression of the disease. Second-generation TKIs (Nilotinib, dasatinib, Bosutinib) are effective against a range of BCR-ABL mutations except T315I. The third generation of TKIs can be targeted to inhibit BCR-ABL-positive CML cells containing T315I mutations. Selecting appropriate targeted drugs according to the type of leukemia and the individual's own conditions can effectively improve the patient's condition, and some types of leukemia have the

Table 1
List of targeted factors for leukemia cells.

Ligand	Targeting	Internalization mechanism
Sgc8 [8]	Targets PTK7 (protein tyrosine kinase-7) overexpressed in T-ALL cells	endocytosis
Anti-CD19 [9]	Targets CD19 overexpressed in B-ALL cells	endocytosis
Heptapeptide DT7, transferrin [10]	Targets the transferrin receptor overexpressed in T-ALL cell	endocytosis
Peptidomimetic LLP2A [11]	Targets activated a4b1 integrin expressed on childhood ALL cell	endocytosis
NL-1 antibody [12]	Targets overexpressed CALLA (CD10) in B-ALL cells	endocytosis
Nonapeptide CD21 [13]	Targets CD21	endocytosis, pinocytosis
Anisamide [14]	Targets overexpressed sigma receptors	ND
CD22DE12 SiRNA [15]	Targets CD22DE12 in aggressive B-ALL cells	None
WHI–P131 [16]	Targets tyrosine kinase JAK3 that regulates the activation of some important oncogenic proteins	None
Amino acid L-Phe [17]	Targets Pyruvate kinase, PK, to reduce the ROS level	None
Dasatinib [18]	Targets LCK tyrosine kinase	None
Hyaluronic acid [19]	Targets CD44	RHAMM
Lintuzumab [20]	Targets CD33	CDC
CXCL12 [21]	Targets CXCR4	endocytosis

possibility of recovery under the right treatment (Table 1).

At the same time, new drugs with high bioavailability, good specific targeting performance and new nanodrug carriers are also being developed. For example, Sun et al. loaded curcumin with liposomes and modified hyaluronic acid targeting CD44 on the nanostructure, which solved the low water solubility and low in vivo activity of the drug and realized the targeting and treatment of AML leukemia cells [22]. Guo et al. used cyclodextrin as a drug carrier, loaded siRNA and targeted the overexpressed LSC antigen on AML cell surface through antibody targeting, thus downregulating disease-causing genes, causing cell apoptosis and achieving the treatment of leukemia [23]. Targeted drugs face challenges of specificity, potentially causing off-target effects on healthy cells, leading to side effects. There are significant differences in gene mutations and molecular features among different AML patients, leading to drug resistance issues. Researchers are exploring new drug design strategies to improve specificity and resistance. Nanomaterial carriers can enhance the efficacy of targeted therapy for leukemia by constructing precise nanomaterial systems. Furthermore, the integration of nanomaterials with immunotherapy has also emerged as a promising strategy for leukemia treatment [24]. For instance, acute myeloid leukemia (AML) is a kind of malignant myeloid cells cloned disease. In recent years, the emergence of new targeted drugs has revolutionized the treatment of cancer, and is expected to make a breakthrough in the treatment of AML. These include second-generation DNA methyltransferase inhibitors, B-cell lymphoma 2 (BCL-2) inhibitors, fms-like tyrosine kinase 3 (FLT3) inhibitors, isocitrate dehydrogenase inhibitors, anti-CD33 monoclonal antibody, and Smoothened Inhibitor (SMO) inhibitor, tumor protein p53 targeted drugs, anti-CD47 monoclonal antibody, nuclear export protein 1 (XPO1) inhibitor, etc. Immunotherapy aims to activate the patient's immune system to attack cancer cells. By combining nanomaterials with immunotherapy agents, such as chimeric antigen receptors (CARs) or tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), specific leukemia cells can be targeted and destroyed by the immune system. This approach holds great promise for leukemia treatment, as it harnesses the power of the patient's own immune system to eliminate cancer cells [25]. Nanodrug carriers face multiple challenges. Safety and biocompatibility issues are primary concerns, as their in vivo behavior is not fully understood. Additionally, physical barriers and biological factors limit their application. Therefore, further research and resolution of these issues are needed to advance the use of nano-drug carriers in the medical field. Nanomaterials, with their unique physicochemical properties, have emerged as promising agents for targeted therapy in leukemia. In recent years, there have been a number of studies have developed can be used as drug delivery carrier or intervention of new materials, to improve the effectiveness of the leukemia treatment. These materials mainly include liposomes, protein base materials, polymer materials, cell derived materials and inorganic materials, they have the unique performance, can be applied to a variety of therapeutic modalities, such as, gene therapy, immune therapy, radiation therapy, chemotherapy, hemopoietic stem cell transplantation and other emerging treatments.

One of the targeted strategies that have been explored involves the use of nanocarriers for drug delivery. These nanocarriers, such as liposomes and polymeric nanoparticles, can encapsulate anticancer drugs and deliver them directly to the leukemic cells, minimizing side effects and maximizing therapeutic efficacy. The nanocarriers can be designed to target specific markers on the leukemic cells, ensuring precise delivery of the drugs.

Another targeted strategy utilizes nanoparticles for gene therapy. By delivering genes encoding for anticancer proteins or inhibitors of leukemic cell growth, these nanoparticles can modulate the genetic expression of leukemic cells and induce their apoptosis. This approach offers the potential for long-term remission by addressing the root cause of the disease. Furthermore, nanomaterials have also

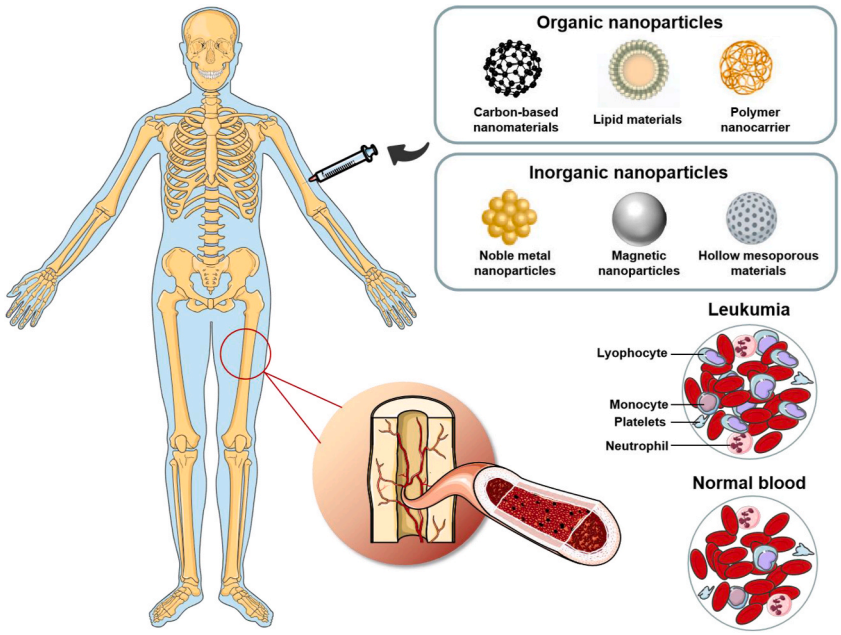


Fig. 1. Nanomaterials for the treatment of leukemia.

been explored for their ability to enhance imaging of leukemic cells. Nanoparticles, such as quantum dots and magnetic nanoparticles, can be used as contrast agents in imaging techniques like magnetic resonance imaging (MRI) and fluorescence imaging. These techniques provide high-resolution images of leukemic cells, aiding in their accurate detection and monitoring during therapy.

In summary, nanomaterials hold great promise in the targeted treatment of leukemia. By delivering drugs and genes directly to leukemic cells, and enhancing their imaging, nanomaterials can improve the effica. This paper reviews the research and application literature of nanomaterials in the treatment of leukemia, which is helpful to understand the opportunities and challenges of the current treatment of leukemia based on nano-drug delivery systems (Fig. 1).

2. Nanomaterials for targeted therapy in leukemia

Nanomaterials are materials with particle sizes of less than 1000 nm, which possess unique physical, chemical, and biological properties that differ from their bulk counterparts, such as high surface area-to-volume ratio, enhanced reactivity, and increased cellular uptake [26]. These properties make nanomaterials attractive candidates for targeted drug delivery and imaging applications in cancer therapy. In particular, nanomaterials can improve the efficacy and safety of leukemia treatment in the following ways. ①Targeted delivery of drugs: Nanomaterials can be functionalized with ligands or antibodies that selectively bind to cancer cells and deliver drugs directly to the tumor site. This approach minimizes the exposure of healthy tissues to chemotherapy drugs, which can cause toxic effects such as nausea, vomiting, hair loss, and organ damage. Moreover, targeted drug delivery can increase the concentration of drugs in the tumor and improve their efficacy, leading to better therapeutic outcomes. For example, PEG-PLL-PLGA NPs (NPs) was synthesized to generate uniform NPs harboring high levels of the anticancer drug daunorubicin (DNR) and Tet. Targeted delivery of PEG-PLL-PLGA drug-loaded vehicles to target cells and tissue is realized by covalently linking Tf to the NPs' surface (Tf-PEG-PLL-PLGA). Tet will be used to block the transport activity of P-gp, and thereby allow DNR to enter and remain in MDR cancer cells, which will increase their sensitivity to the chemotherapeutic agent. This research demonstrated the therapeutic effect of Tf-modified NPs in cell and animal models of leukemia, and highlight their favorable biodistribution, pharmacokinetic features, and therapeutic effects in mice [27]. ②Controlled release of drugs: Nanomaterials can also be designed to release drugs in a controlled manner, which can prolong the drug's activity and reduce the frequency of drug administration. For instance, gold nanoparticles coated with a temperature-sensitive polymer can release doxorubicin, a chemotherapy drug, in response to mild hyperthermia generated by laser irradiation. This approach has been shown to enhance drug uptake and cytotoxicity in leukemia cells without affecting healthy cells [28]. ③Imaging of leukemia cells: Nanomaterials can be used as contrast agents for imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT). The unique properties of nanomaterials, such as their magnetic, optical, and fluorescent properties, can enhance the sensitivity and specificity of cancer detection. For example, ultra-small superparamagnetic iron oxide (USPIO) can be conjugated with leukemia-specific antibodies to target leukemic cells and improve the accuracy of MRI diagnosis [29]. Similarly, gold nanoparticles can be functionalized with leukemia-specific peptides to enable CT imaging of cancer cells [30]. ④Overcoming multidrug resistance: Multidrug resistance (MDR) is a major challenge in leukemia treatment, as cancer cells can develop resistance to multiple chemotherapy drugs and evade cell death. Nanomaterials can overcome MDR by enhancing drug uptake and transport across cell membranes. For instance, polymeric nanoparticles coated with P-glycoprotein inhibitors can inhibit drug efflux pumps and increase the intracellular concentration of chemotherapy drugs in leukemia cells [31].

Nanomaterials are the application of nanotechnology in the field of medicine, dedicated to the use of finely constructed nanomaterial systems to develop more efficient means of disease treatment. Nanomaterials are mainly divided into organic nanomaterials and inorganic nanomaterials. Organic nanoparticles mainly include carbon-based nanomaterials (graphene, etc.), lipid materials (such as liposomes, phospholipids, etc.), polymers (such as polyethylene glycol, amphiphilic polymers, gelatin, microspheres, etc.), Inorganic nanoparticles mainly include precious metal nanoparticles (gold and silver nanoparticles, etc.), magnetic nanoparticles (such as magnetic spheres), hollow mesoporous materials (such as mesoporous silicon dioxide nanoparticles), etc. Researchers can change some aspects of the performance of nanomaterials by changing their composition, structure, particle size, etc., to meet the corresponding demand for drug carriers. In addition to a single nanoparticle, there are a variety of mixed nanoparticles, which combine two or more multifunctional nanoparticles, making it possible to detect and treat cancer simultaneously (therapeutic diagnostics), and in order to improve the therapeutic effect of disease, combining two or more therapies (drug delivery, gene delivery, heat therapy, Photodynamic therapy, sequential delivery of therapeutic agents, etc.) have also made significant advances. At present, there are various methods to construct mixed nanoparticles, among which the use of inorganic nanoparticle nuclei and organic nanoparticle shells with good biological compatibility (such as polymers, liposomes, proteins, etc.) have been widely applied.

Inorganic nanocarries have shown great potential in drug delivery systems due to their high surface area per unit volume, optical, magnetic and enzymatic properties, and the ability to be functionalized with a large number of ligands to enhance their affinity for drugs. Compared with organic nanocarriers, inorganic nanocarriers exhibit diverse physicochemical properties closely related to size and composition, and have gradually been developed for biomedical applications beyond carrier functions. However, inorganic nanocarriers are not biodegradable and lack high drug loading capacity, so they must be used in combination with organic materials in most cases. Common inorganic nano materials such as gold nano materials, silicon nanomaterials, iron nano materials, etc.

2.1. Organic nanoparticles

Organic nanoparticles are nano-sized particles made of organic materials, such as lipids, proteins, and carbohydrates. They have several advantages over inorganic nanoparticles, such as biocompatibility, biodegradability, and low toxicity. The potential risks of organic nanoparticles involve complex interactions with cellular components that may induce immune reactions or unforeseeable side

effects, which undoubtedly increases the uncertainty of their application. In addition, the lack of targeted delivery efficiency, i.e., the absence of effective targeting, further limits the potential of organic nanoparticles in practical applications. These issues need to be addressed urgently to ensure the safe and effective application of organic nanoparticles in medicine, biotechnology, and other fields. Organic nanoparticles can be engineered to have specific properties, such as targeting ligands, imaging agents, and drug delivery systems. Therefore, they have the potential to revolutionize the diagnosis and treatment of leukemia. They have emerged as promising candidates for leukemia diagnosis and targeted therapy.

2.1.1. Carbon-based nanomaterials

Carbon-based nanomaterials have emerged as promising candidates in the targeted treatment of leukemia due to their unique physicochemical properties and biocompatibility. One of the key advantages of carbon-based nanomaterials is their ability to interact with biological systems at the molecular level. Through functionalization with specific ligands or antibodies, these antibodies can selectively bind to overexpressed receptors on leukemia cells, allowing for precise targeting of cancer cells with drugs. This unique targeted delivery method not only significantly increases the concentration of drugs in the tumor site, but also minimizes the exposure of drugs to healthy cells, greatly enhancing the therapeutic effect. These superior properties such as high surface area, tunable surface chemistry, and excellent biocompatibility, which make them ideal candidates for various biomedical applications, including drug delivery.

One of the major advantages of carbon-based nanomaterials in the targeted treatment of leukemia is their ability to selectively target cancer cells. Carbon-based nanomaterials can be functionalized with targeting ligands, such as antibodies or peptides, that can recognize and bind to specific receptors present on the surface of cancer cells. This targeted delivery approach ensures that the drug payload is delivered specifically to the cancer cells, while sparing the healthy cells, thereby minimizing side effects. For instance, Khan et al. conjured a recombinant fragment of human surface active protein D (rfhSP-D) with carboxymethyl cellulose (CMC) CNT (CMC-CNT) to form leukemia-targeting CNT + rfhSP-D. Experiments showed that the cell viability of leukemia cells decreased after 24 h of culture with CNT + rfhSP-D, and CNT + rfhSP-D treated leukemia cells also showed higher cell cycle inhibitor mRNA expression. This

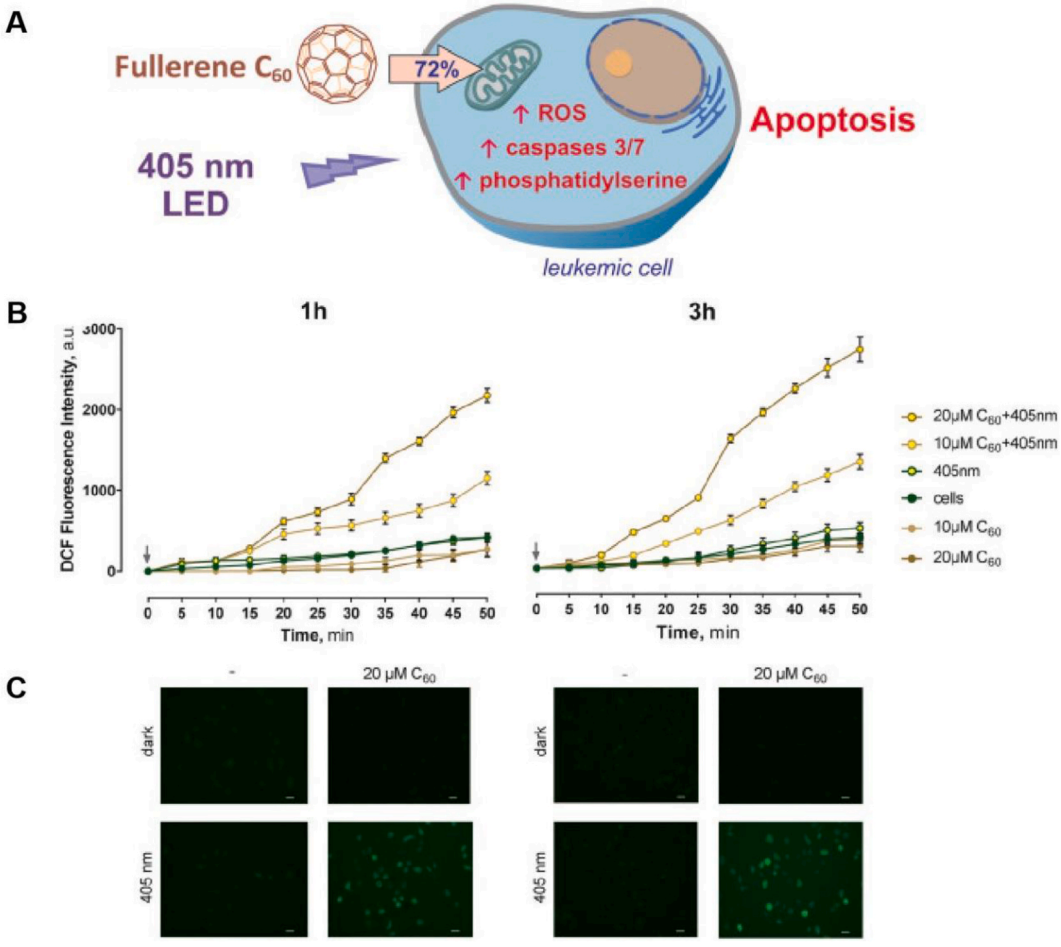


Fig. 2. A. C60 combined with LED photodynamic therapy for leukemia. B. Reactive oxygen species generation in CCRF-CEM cells and C.fluorescent microscopy images at 1 h and 3 h after treatment with either C60fullerene or irradiation alone or their combination [35].

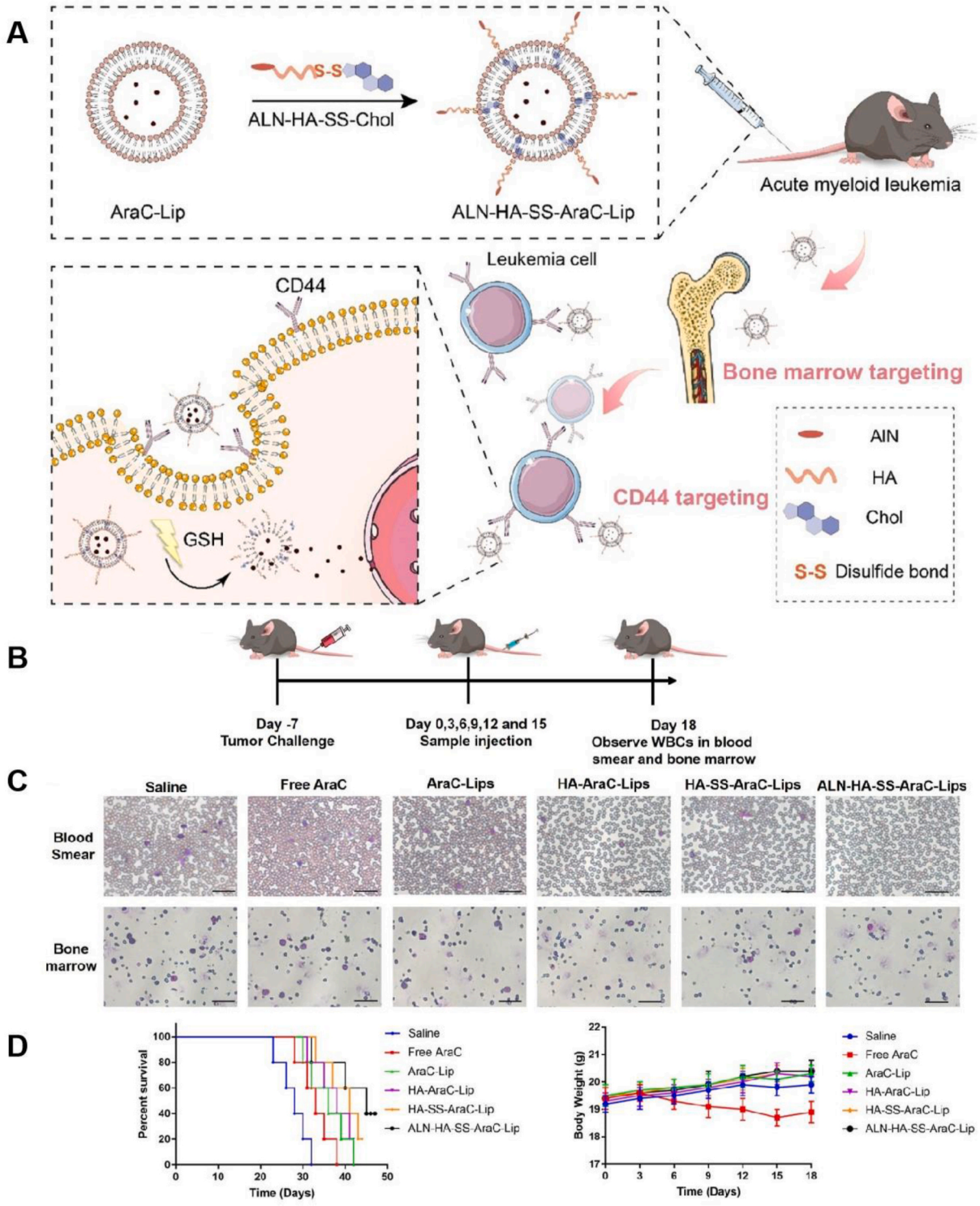


Fig. 3. A. Illustration of bone-targeting liposomes system for AML therapy. B. Treatment schedules for free AraC and AraC-loaded liposomes. C. Wright-Giemsa staining of blood smear and bone marrow in each group, purple stoods for WBCs. D. The survival curve of leukemia-bearing mice calculated by Kaplan–Meier estimate. E. Mean weight of mice after the treatment [37].

suggests that CNT + rfhSP-D enhances apoptosis and immunotherapeutic properties of leukemia cell lines, and CNT + rfhSP-D has therapeutic potential in targeting leukemia cells [32].

Another advantage of carbon-based nanomaterials is their ability to overcome drug resistance. Many cancer cells develop resistance to chemotherapy drugs, leading to treatment failure [33]. Carbon-based nanomaterials can be functionalized with multiple drugs and delivered simultaneously to the cancer cells, leading to a synergistic effect that can overcome drug resistance. For example, Zhang et al. prepared a graphene-gold nanocomposite (GGN)loaded with daunoruthromycin (DNR) for the treatment of leukemia as a drug delivery vector, which has the properties of targeting and binding drug-resistant leukemia cell (KA), inducing apoptosis of leukemia cells and inhibiting tumor growth in nude mice. The results show that GGN nanocomposites containing DNR can effectively overcome the inhibition of tumor growth induced by drug-resistant leukemia cells in KA nude mice. This nanocomposite enhances the possibility of regulating apoptosis of cancer cells and inhibiting tumor growth, indicating that this nanocomposite has broad application prospects in effective multifunctional therapy [34].

Carbon-based nanomaterials also offer the advantage of controlled drug release. The surface chemistry and morphology of these materials can be tuned to achieve controlled drug release kinetics. Carbon-based nanomaterials can be engineered to release drugs in response to specific stimuli, such as pH, temperature, or enzymes, which are present in the tumor microenvironment. This controlled release approach ensures that the drug is released at the site of the cancer cells, leading to improved therapeutic efficacy. As shown in Fig. 2, Grebinyk et al. analyzed the phototoxicity of C60 fullerene on human leukemia cells by using Light Emitting Diode (LED) of different wavelengths. The results showed that neither C60 fullerene nor 405 nm LED light affected the cell vitality, but after the combination of the two, the cell vitality of 50 % was reduced by 46 %. Reactive oxygen species production increased 10-fold. The data show that the use of C60 fullerenes and 405 nm high-power leds is an effective method for photodynamic treatment of leukemia.

Furthermore, carbon-based nanomaterials offer the advantage of real-time imaging and monitoring of the treatment response. These materials can be functionalized with imaging agents, such as fluorescent dyes or magnetic nanoparticles, that can enable real-time imaging of the cancer cells and monitoring of the treatment response. This imaging approach can provide valuable information on the efficacy of the treatment and help in optimizing the treatment regimen. For example, fullerene C60 functionalized with magnetic nanoparticles and fluorescent dyes have been shown to enable real-time imaging and monitoring of leukemia cells in vivo [35] (Fig. 2).

2.1.2. Lipid materials

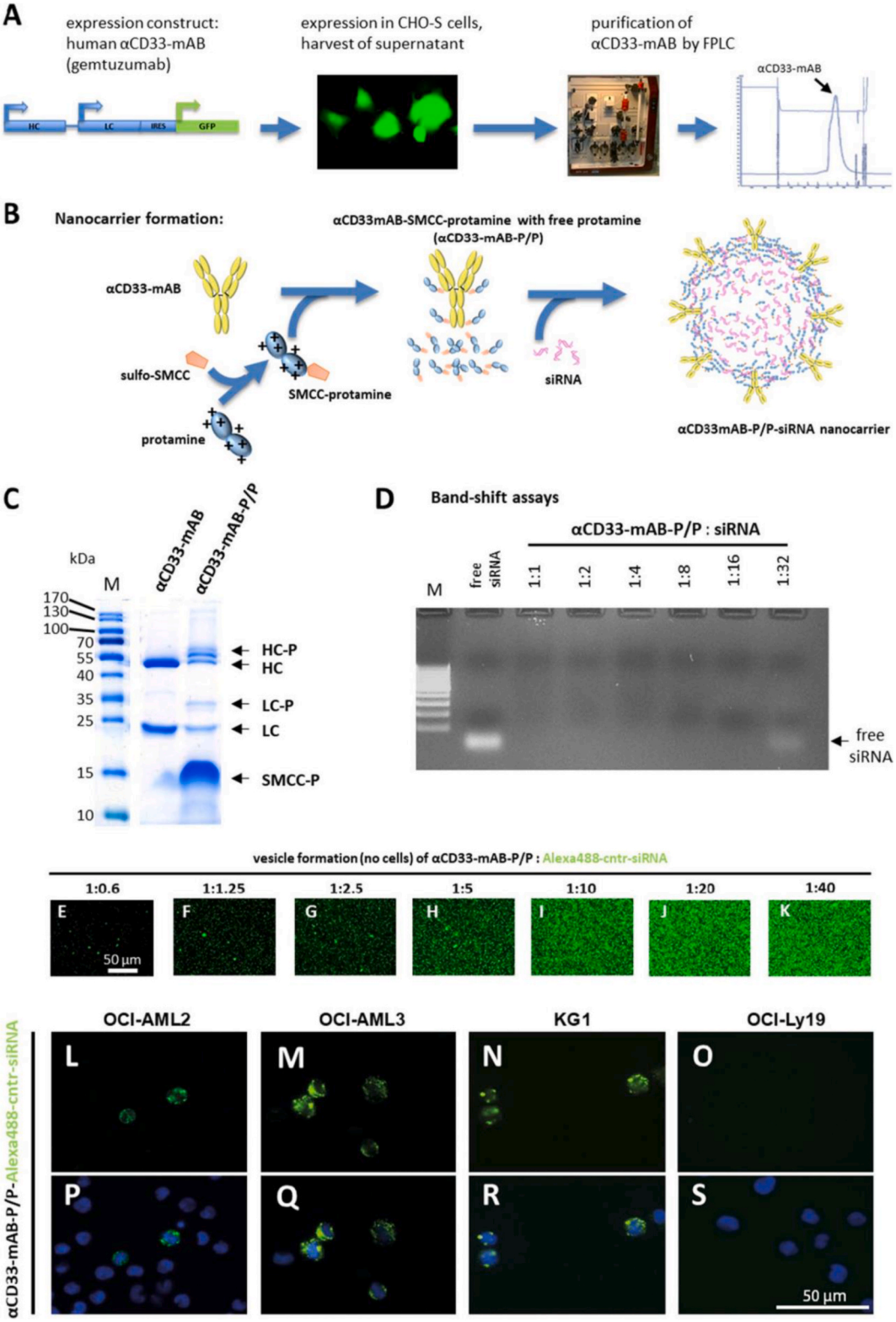
Liposomes are microspheroids with a straight diameter of 50–1000 nm made from phospholipids, cholesterol and other lipids. They have a membrane-like structure, low toxicity and no immunogenicity. The composition of phospholipid membrane is flexible and can be made into a variety of types, large and small. Lipids are essential components of cell membranes and are involved in many cellular processes, including cell signaling, energy storage, and insulation [36]. Lipid materials can be used to encapsulate drugs or other therapeutic agents, allowing them to be delivered selectively to cancer cells. Lipid materials have unique advantages for targeted therapy of leukemia.

First, liposomes can selectively target cancer cells. Lipid materials can be designed to target specific types of cancer cells based on their molecular characteristics. For example, lipid substances can be functionalized with ligands that bind to specific receptors on the surface of cancer cells, allowing them to be selectively absorbed by these cells. This selective targeting reduces the toxicity of the drug to normal cells and improves the efficacy of the drug against cancer cells.

Secondly, liposomes can enhance the solubility and stability of drugs. Many drugs used to treat cancer have poor solubility and stability, which limits their effectiveness and causes side effects. Lipid materials can be used to encapsulate these drugs, improve their solubility and stability, and reduce their toxicity. Lipid substances can also protect the drug from degradation by enzymes or other factors in the body, thus allowing the drug to be delivered in a more efficient and controlled manner. Liposomes also have the advantage of controlling drug release. Lipid materials can be designed to release the drug in a controlled manner, allowing continuous administration over time. This is particularly beneficial in the treatment of leukemia, where repeated doses of the drug may be needed to achieve therapeutic results. Controlled drug release also reduces the risk of toxicity and side effects associated with higher doses of drugs.

Liposomes have excellent biocompatibility and biodegradability. Lipid materials are biocompatible and biodegradable, which means they are well tolerated by the human body and can be broken down into harmless by-products. This reduces the risk of adverse reactions to these substances and allows them to be safely eliminated from the body. Finally, liposomes are easy to synthesize and functionalize. Lipid materials are relatively easy to synthesize and functionalize, allowing the development of a wide range of materials with different properties and functions. This flexibility makes lipid materials a common platform for the development of targeted therapies for leukemia and other types of cancer. For example, as shown in Fig. 3, Wu et al. decorated CD44 and bone-targeting liposome delivery systems with REDOX lyable polymers. First, AlN-HA was obtained by amination between Alendronate (ALN) and hyaluronic acid (HA), and cholesterol (Chol) was coupled to the target polymer ALN-HA–SS–CHOL by a bioreductive disulfide bond (–SS–), modifying the liposomes loaded with cytarabine (AraC). ALN-HA–SS–AraC-Lip's REDOX sensitive bone and CD44 dual targeting liposomes can target leukemia stem cell regions, which are then taken up by tumor cells to treat AML [37]. Houshmand et al. designed an immune liposome (IL-VX) containing Venetoclax. By using this system, selective elimination of CD26 + CML LSCs/progenitor cells can be obtained in vitro, which may reduce side effects in CML patients in vivo and obtain treatment-free long-term remission. Compared to free Venetoclax, this system showed a higher ability to induce cell death. At the same time, treating patient samples with IL-VX significantly reduced CD26 + cells in stem and progenitor cell populations, reducing side effects in vivo and achieving long-term remission in CML patients [38].

Despite the numerous benefits of lipid materials in targeted therapy for leukemia, there exist several potential risks and limitations worthy of consideration. For instance, lipid delivery systems have the potential to elicit immune responses, possibly leading to



(caption on next page)

Fig. 4. The αCD33-monoclonal antibody (mAB) gemtuzumab-protamine (αCD33-mAB-P/P) conjugates bind and transport siRNA only into CD33-positive cells. A. Representative elution profile (right panel). IRES, internal ribosomal entry side; GFP, green fluorescent protein. B. Synthesis of αCD33-mAB-P/P-siRNA nanocarrier. C. The shift of molecular weight after protamine conjugation via sulfo-SMCC to the αCD33-mAB can be seen for the heavy chain (HC–P) and for the light chain (LC-P). SMCC-P, unbound SMCC-protamine. D. Band-shift assay. Agarose gel-electrophoretic analysis of the binding capacity of siRNA to the αCD33-mAB-P/P complex. E–K. Fluorescence microscopy of nanocarriers. L–S. Fluorescence microscopy analysis of siRNA internalization mediated by αCD33-mAB-P/P-siRNA complex into CD33-positive cells (L-N and P–R) but not into negative control cells (O and S) [41].

antibody formation or allergic reactions, thereby limiting their long-term use. Additionally, the stability of lipid-based systems may be compromised by their sensitivity to temperature, pH, and other environmental factors, which can affect drug concentration and efficacy. While lipids offer the potential for selective targeting of cancer cells, there remains a risk of off-target effects, potentially leading to side effects and toxicity. Furthermore, the synthesis and functionalization of lipids are challenging and costly, limiting their widespread adoption.

In summary, lipid materials offer several advantages for targeted therapy of leukemia, including selective targeting of cancer cells, enhanced drug solubility and stability, controlled drug release, biocompatibility and biodegradability, and ease of synthesis and functionalization. These advantages make lipid materials a promising platform for the development of effective and safe therapies for leukemia and other types of cancer. Through in vitro experiments, animal experiments and clinical trials, liposome has many advantages in the treatment of leukemia, and has a good application prospect. It is believed that it will become an effective and widely used new drug delivery vector in future clinical applications.

2.1.3. Polymer nanocarrier

The common polymer nanocarriers are polymer micelles. Polymer micelles are usually composed of a hydrophilic shell and a hydrophobic core, which are usually formed by self-assembly of amphiphilic biblock or triblock copolymers in water, and its size is generally 10–200 nm. The hydrophilic segment of the polymer micelle is generally composed of polyethylene glycol (PEG), because PEG's hydrophilicity can form a protective film on the surface of the micelle, which can prevent micelle aggregation and promote uniform drug dispersion. The hydrophilic segment can also prevent the micelle from being destroyed by the components in the plasma, thereby improving the stability of its circulation in the body and prolonging the circulation time of drugs in the body [39]. The hydrophobic segment of the polymer micelle is generally composed of polyamino acids and hydrophobic elements with good biocompatibility [40], because the main chain of these polymers contains ester or amide bonds, which can support some hydrophobic chemotherapeutic drugs or nucleic acid drugs through physical, chemical or electrostatic interactions, and they can be degraded into small molecules by human enzymes. Thus, endows micelles with good biocompatibility. Polymer nanocarriers have emerged as a promising approach for targeted treatment of leukemia due to their unique properties such as biocompatibility, biodegradability, and tunable size, shape, and surface chemistry.

A noteworthy perk of polymer nanocarriers lies in their exceptional capacity to enhance drug delivery precision to designated sites. These nanocarriers can be meticulously crafted to release drugs in a controlled manner, thereby bolstering the therapeutic outcomes. Moreover, they act as shields, safeguarding drugs from immune system-induced degradation and elimination, cc ultimately leading to prolonged drug circulation and a substantial increase in bioavailability. Particularly in the realm of leukemia, polymer nanocarriers demonstrate their proficiency by delivering chemotherapy drugs directly to leukemic cells, sparing healthy cells in the process. This precision delivery is achieved by decorating the nanocarrier surfaces with ligands that possess a high affinity for receptors present on leukemic cell surfaces. For example, folic acid-conjugated polymer nanocarriers have been shown to selectively target leukemic cells that overexpress the folate receptor, resulting in improved therapeutic efficacy and reduced toxicity to healthy cells. Baumer et al. designed an AML targeting system consisting of endogenous anti-CD33 antibody-protamine conjugate that spontaneously assembled-together with anionic molecules (such as siRNA or ibrutinib-Cy3.5) and cationic free protamine in aqueous solution into sac-like nano callers. CD33 was expressed on 90 % of AML cells, but not on normal hematopoietic stem cells and mature granulocytes. Therefore, it is expected to become an obvious target for AML targeted therapy. This technique can reduce drug toxicity by effectively targeting to treat AML [41] (Fig. 4). Despite its potential, the use of αCD33-monoclonal antibody (mAB) gemtuzumab-protamine (αCD33-mAB-P/P) conjugates raises concerns and challenges. One limitation is immunogenicity, which can lead to reduced efficacy or toxicity. The specificity of the anti-CD33 antibody is another challenge, as it can affect non-malignant cells and cause side effects. Additionally, the stability and bioavailability of the nano capsules in vivo need to be evaluated. Finally, the efficacy of the drug payload delivered by the nano capsules must be thoroughly assessed to determine the therapeutic outcome.

Another advantage of polymer nanocarriers in targeted treatment of leukemia is their ability to overcome drug resistance. Drug resistance is a common problem in the treatment of leukemia, where leukemic cells become resistant to chemotherapy drugs, resulting in treatment failure and disease relapse. Polymer nanocarriers can overcome drug resistance by delivering multiple drugs simultaneously or by delivering drugs that target different pathways involved in leukemic cell survival. For example, polymer nanocarriers can be designed to deliver both chemotherapy drugs and small interfering RNA (siRNA) that target specific genes involved in drug resistance. The siRNA can silence the expression of these genes, resulting in increased sensitivity of leukemic cells to chemotherapy drugs [42]. Moreover, the nanocarriers can be designed to release the drugs in a sequential manner, which can further enhance their therapeutic efficacy and overcome drug resistance.

The use of chemotherapy drugs in the treatment of leukemia is associated with several side effects such as nausea, vomiting, hair loss, and immunosuppression. These side effects are caused by the toxicity of the drugs to healthy cells. Polymer nanocarriers can reduce the toxicity of chemotherapy drugs by selectively delivering them to leukemic cells, while sparing healthy cells. For example,

polymer nanocarriers functionalized with antibodies that specifically bind to leukemic cells have been shown to reduce the toxicity of chemotherapy drugs to healthy cells [43]. The nanocarriers can also be designed to release the drugs in a targeted manner, which can further reduce their toxicity to healthy cells.

Polymer nanocarriers can also be used for imaging and diagnosis of leukemia. The nanocarriers can be functionalized with imaging agents such as fluorescent dyes, magnetic nanoparticles, or radioactive isotopes, which can enable the visualization of leukemic cells in vivo. This can help in the early detection and monitoring of leukemia, as well as in the evaluation of the therapeutic efficacy of the treatment. For example, polymer nanocarriers functionalized with fluorescent dyes have been used for the imaging of leukemic cells in vivo. The nanocarriers can selectively accumulate in leukemic cells, resulting in specific fluorescence signals that can be detected by imaging techniques such as fluorescence microscopy or positron emission tomography (PET).

In conclusion, polymer nanocarriers have several advantages in targeted treatment of leukemia. These include improved drug delivery, overcoming drug resistance, reduction of toxicity, and imaging and diagnosis. The use of polymer nanocarriers in the treatment of leukemia is a promising approach that can enhance the therapeutic efficacy of the treatment and reduce its side effects. However, further research is needed to optimize the design and application of polymer nanocarriers in the treatment of leukemia.

2.2. Inorganic nanoparticles

In recent years, the application of inorganic nanoparticles (NPs) in the treatment of leukemia has gained considerable attention due to their unique properties, such as high surface-to-volume ratio, biocompatibility, and the ability to be targeted to specific cells or tissues. Inorganic NPs have been shown to have several advantages over traditional chemotherapy drugs, including enhanced drug delivery, prolonged circulation, and reduced side effects. Their ability to target specific cells, overcome MDR, improve pharmacokinetics, and enable imaging and diagnosis make them a promising approach for the treatment of leukemia. Additionally, their potential for combination therapy offers a new strategy for improving the efficacy of chemotherapy drugs.

2.2.1. Noble metal nanoparticles

A novel approach is the use of metal nanoparticles for targeted treatment of leukemia. Noble metal nanoparticles are tiny particles made from metals such as gold, silver and platinum. They have unique physical, chemical, and biological properties that make them attractive for use in medical applications. In recent years, metal nanoparticles have emerged as a promising tool for the treatment of cancer, including leukemia. For example, gold nanoparticles play an important role in the treatment of AML as the carrier of nanomaterials delivery system. Through chemical, physical or biological methods, gold nanoparticles of various shapes and sizes can be synthesized. Zuo et al. synthesized gold nanoparticle - CS nanocomposites by in-situ deposition of bio-reduced gold nanoparticles on chitosan (Fig. 5). The study found that Au NPs-CS nanocomposites have outstanding potential in regulating the key targets of leukemia, which is comparable to the standard leukemia drug daunorubicin, and can inhibit the growth of leukemia cells to treat leukemia [44]. One of the major advantages of noble metal nanoparticles in the treatment of leukemia is their ability to selectively target cancer cells.

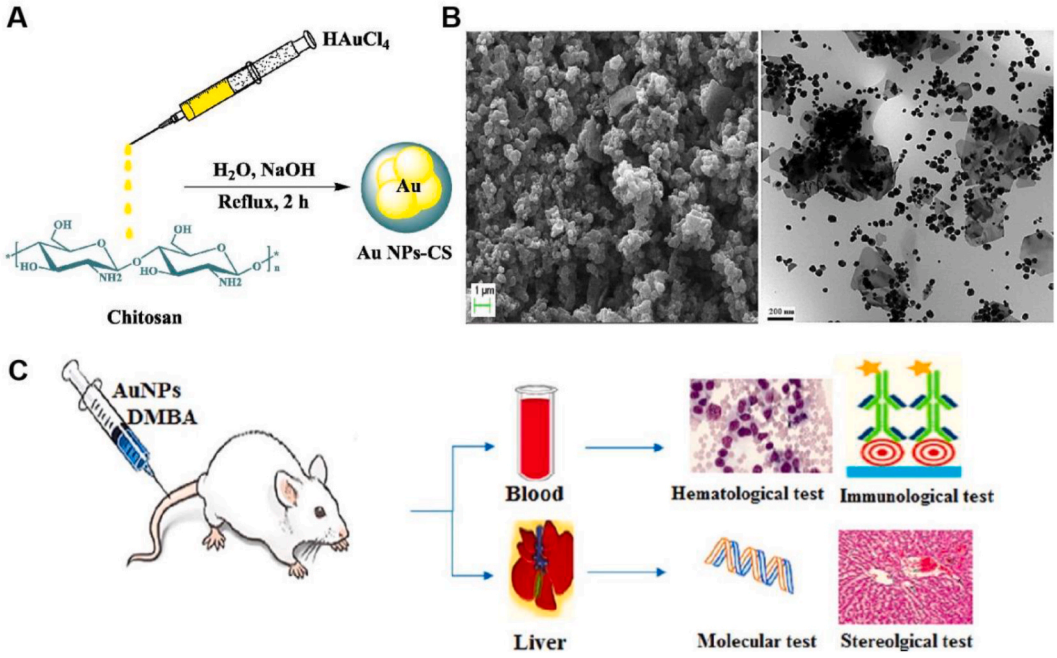


Fig. 5. Application of Au NPS-chitosan nanocomposites in the treatment of acute myeloid leukemia. A. Synthesis of Au NPs-CS nanocomposite. B. FE-SEM and TEM analysis of the Au NPs-CS nanocomposite. C. Therapeutic effect of gold NPS-Chitosan nanocomposites in vivo [44].

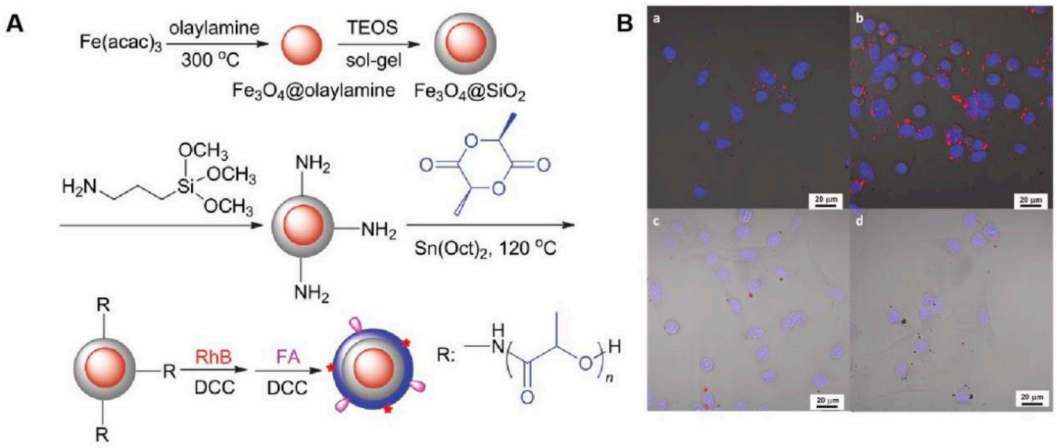


Fig. 6. Synthesis of magnetic nanions (A) and cell imaging (B) [46].

Noble metal nanoparticles can be functionalized with ligands or antibodies that specifically bind to cancer cells, while avoiding healthy cells. This targeting ability helps to minimize the damage to healthy cells and tissues, which is one of the major drawbacks of conventional chemotherapy and radiation therapy. For example, gold nanoparticles can be functionalized with antibodies that bind to specific markers on the surface of leukemia cells. Once the nanoparticles bind to the cancer cells, they can be activated by laser irradiation, which causes them to heat up and kill the cancer cells. This approach, known as photothermal therapy, has been shown to be effective in killing leukemia cells in vitro and in vivo [45] (see Fig. 6).

Another advantage of metal nanoparticles in the treatment of leukemia is their ability to enhance drug delivery. Noble metal nanoparticles can be used as carriers for drugs, which can be released selectively at the site of the cancer cells. This targeted drug delivery approach helps to increase the concentration of the drug at the site of the cancer cells, while minimizing the exposure of healthy cells to the drug. For example, platinum nanoparticles can be used as carriers for chemotherapy drugs such as cisplatin. The nanoparticles can be functionalized with ligands that bind specifically to leukemia cells, and once they are taken up by the cancer cells, they release the chemotherapy drug, which kills the cancer cells. This approach has been shown to be effective in killing leukemia cells in vitro and in vivo [48]. Similarly, gold nanoparticles can be used as carriers for small interfering RNA (siRNA), which can be used to silence specific genes that are involved in the development and progression of leukemia. The siRNA is released selectively at the site of the cancer cells, which helps to reduce the expression of the target genes and inhibit the growth of the cancer cells [49].

In addition, another advantage of precious metal nanoparticles in the treatment of leukemia is their low toxicity and side effects. Metal nanoparticles are generally considered to be biocompatible and non-toxic, and they do not accumulate in the body for long periods of time. This helps reduce the risk of toxicity and side effects associated with traditional chemotherapy and radiation therapy. For example, gold nanoparticles are biocompatible and non-toxic, and are easily excreted through urine. This makes them an attractive option for biomedical applications, including the treatment of leukemia. Similarly, nanosilver is generally considered safe and non-toxic, and they have been shown to have antibacterial and anti-inflammatory properties. This makes them very useful for treating infections and inflammatory diseases associated with leukemia [50]. In addition, some magnetic nanomaterials also have relatively unique enzyme-like activities, which can kill leukemia cells by generating hydroxyl radicals to treat leukemia. For example, Ferumoxytol, an iron oxide nanoparticle clinically available for the treatment of iron deficiency anemia in the USA, can generate harmful reactive oxygen species (ROS) through the Fenton reaction, which effectively eliminates leukemia cells and leukemia stem cells, thereby impeding the progression of leukemia [51]. Fe_3O_4 nanoparticles and Pt nanoparticles were modified and linked by polyethylene glycol (PEG) to form a binary composite structure, and one side of Pt nanoparticles was covalently linked to CXCR4 antagonistic polypeptide (E5). A cascade nanase (Fe_3O_4@Pt@E5) capable of producing a large number of ROS was successfully prepared to induce apoptosis of AML cells, showing an ideal therapeutic effect on AML [52].

2.2.2. Magnetic nanoparticles

Magnetic nanoparticles have been widely investigated for their potential use in targeted drug delivery for the treatment of various diseases, including leukemia. Leukemia is a cancer of the blood and bone marrow that affects the production of white blood cells, leading to an impaired immune system. Treatment options for leukemia include chemotherapy, radiation therapy, and stem cell transplantation. However, these treatments can cause serious side effects and may not be effective for all patients. Magnetic nanoparticles offer a promising approach for targeted treatment of leukemia due to their unique properties.

Magnetic nanoparticles are typically composed of a magnetic core, often made of iron oxide, coated with a biocompatible material. The magnetic core allows the nanoparticles to be manipulated using an external magnetic field, which can be used to guide them to specific target cells or tissues. This makes them particularly useful for targeted drug delivery, as they can be directed to cancer cells while avoiding healthy cells [53].

One of the main advantages of magnetic nanoparticles for targeted treatment of leukemia is their ability to penetrate the blood-

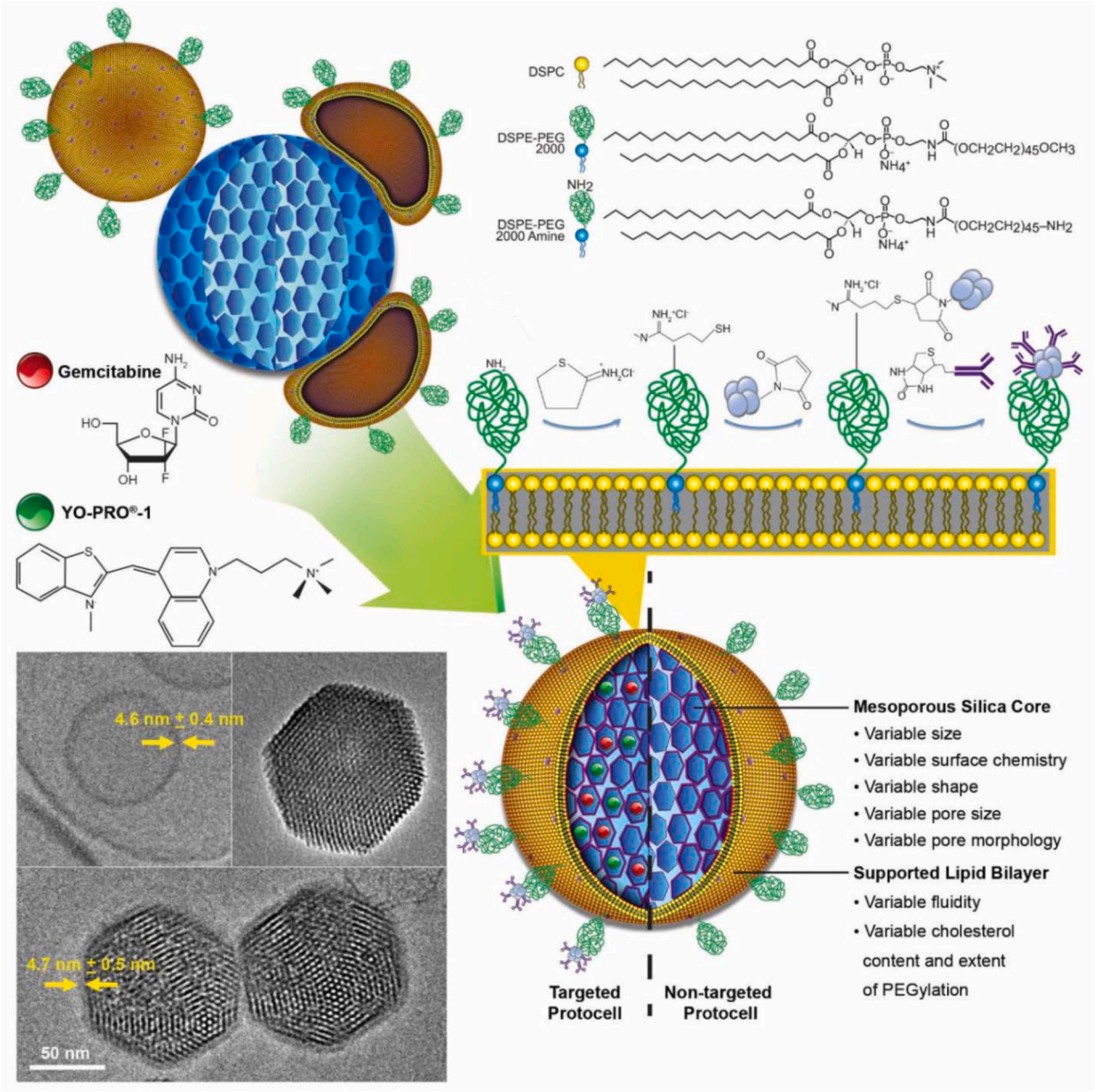


Fig. 7. Mesoporous silica nanoparticle-supported lipid bilayers (protocells) for active targeting and delivery to individual leukemia cells [47].

brain barrier. The blood-brain barrier is a specialized system of cells that protects the brain from harmful substances, but can also prevent drugs from reaching brain tumors. Magnetic nanoparticles can be coated with a material that allows them to cross the blood-brain barrier and deliver drugs directly to the tumor site. This approach has been demonstrated in preclinical studies using magnetic nanoparticles to deliver chemotherapeutic agents to brain tumors in animal models. Another advantage of magnetic nanoparticles is their ability to enhance the effectiveness of chemotherapy. Chemotherapy drugs can have toxic effects on healthy cells, leading to side effects such as hair loss, nausea, and fatigue. Magnetic nanoparticles can be loaded with chemotherapy drugs and directed to cancer cells using an external magnetic field, reducing the amount of drug that is needed and minimizing the toxic effects on healthy cells. This approach has been shown to be effective in preclinical studies using magnetic nanoparticles to deliver chemotherapy drugs to leukemia cells in vitro and in animal models [54]. Magnetic nanoparticles can also be used for imaging and diagnosis of leukemia. Magnetic resonance imaging (MRI) is a noninvasive imaging technique that uses magnetic fields and radio waves to create detailed images of the body. Magnetic nanoparticles can be used as contrast agents for MRI, allowing for more accurate detection and monitoring of leukemia. Additionally, magnetic nanoparticles can be coated with antibodies or other targeting agents to specifically bind to leukemia cells, allowing for more precise diagnosis and monitoring of the disease. For example, Zhou et al. by combining magnetic nanoparticles with folic acid (FA) and Rhodamine B-pairs to form multifunctional fluorescent magnetic nanoparticles with cell recognition capability

(Fe_3O_4@SiO_2-PLLA-RhB/FA), these fluorescent magnetic nanoparticles have good biocompatibility. What's more, these nanoparticles can be selectively absorbed by HeLa cells (FA receptor-positive), demonstrating their potential for bioimaging applications with laser scanning confocal microscopy [46].

Magnetic nanoparticles have also been investigated for use in immunotherapy for leukemia. Immunotherapy is a type of cancer treatment that uses the body's immune system to fight cancer [55]. Magnetic nanoparticles can be coated with antigens or other immune-stimulating molecules and directed to immune cells using an external magnetic field. This approach has been shown to be effective in preclinical studies using magnetic nanoparticles to deliver antigens to dendritic cells, which are key players in the immune response to cancer. By the way, iron oxide nanoparticles can be functionalized with ligands that bind to leukemia cells. Once the nanoparticles are taken up by the cancer cells, they can be activated by a magnetic field, which causes them to generate heat and kill the cancer cells. This approach, known as magnetic hyperthermia, has also been shown to be effective in killing leukemia cells.

2.2.3. Hollow mesoporous materials

Hollow mesoporous materials (HMMs) have been paid close attention by researchers for their special structures, excellent properties and potential applications. HMMs are not only a kind of porous materials, but also have the characteristics of high specific surface area, regular and ordered pore structure, and adjustable pore size. In addition, due to the existence of the pore structure, the HMMs can be used as a carrier, and some uniform and stable materials with nanometer scale can be assembled in the pore to become multi-functional composite materials [56]. Due to their excellent structure and properties, HMMs have been widely used in electrode materials, microelectronics, optoelectronic devices, nonlinear optical materials, chemical sensors, biomedicine and other fields, and the application of HMMs in the biomedical field and even cancer treatment is one of the current research hotspots. For example, using the large specific surface area and large pore structure of HMMs, the pores are loaded with biological drugs, and the release of drugs is controlled by modifying controllable functional groups to improve the circulation time and therapeutic effect of drugs in the body. Meanwhile. Using biological targeting, drugs can be effectively enriched to cancer cells and pathological sites, giving full play to the efficacy of drugs. Bai et al. designed a novel drug delivery system of hollow mesoporous Prussian blue nanoparticles (HMPBs) loaded with anti-cancer drugs daunorubicin (DNR) and cytarabine (AraC) for targeted and synergistic photothermal treatment of AML. In vitro studies have shown that HMPBs has excellent performance in the treatment of AML: excellent biocompatibility, high drug loading, photoresponsive drug release performance, active targeting ability and good chemical photothermal synergistic therapeutic effect. It was explored the potential of using HMMs as a platform for targeted treatment of leukemia, due to their unique properties and ability to deliver therapeutic agents directly to cancer cells [57].

One of the most significant advantages of HMMs in targeted treatment of leukemia is their high drug loading capacity. HMMs are characterized by their unique structure, which consists of a hollow core surrounded by a mesoporous shell. This structure provides a large surface area for the adsorption of drugs and other therapeutic agents, allowing for high drug loading capacity and efficient delivery to cancer cells. In addition, the mesoporous shell of HMMs can be functionalized with a variety of targeting ligands, such as antibodies or peptides, which can enhance the selectivity and specificity of drug delivery to cancer cells while reducing the risk of off-target effects. This targeted delivery approach can help to minimize the amount of drug required to achieve a therapeutic effect, reducing the risk of toxicity and side effects.

Another advantage of HMMs in targeted treatment of leukemia is their tunable pore size. The pore size of HMMs can be precisely controlled during their synthesis, allowing for the development of customized drug delivery systems that can accommodate a wide range of therapeutic agents, including small molecules, proteins, and nucleic acids. This tunability also allows for the development of HMMs with specific properties, such as pH or temperature sensitivity, which can enhance drug release and improve therapeutic efficacy. For example, HMMs can be designed to release drugs in response to the acidic environment of cancer cells, enhancing the specificity of drug delivery and reducing the risk of off-target effects. Ultav et al. prepared PH-sensitive chitosan polyethylene glycol (Cs-PEG) coated with doxorubicin-loaded hollow mesoporous silica nanoparticles (C-HMSN-DN), a system that extends blood circulation time through Cs-PEG coating and efficiently delivers drugs through PH-sensitive drug release and endosome escape for AML treatment [47].

HMMs also have the advantage of enhancing drug stability and bioavailability. Many therapeutic agents, such as small molecules or proteins, have poor stability and bioavailability when administered alone, leading to rapid clearance from the bloodstream and limited efficacy [58]. However, when these agents are encapsulated within HMMs, they are protected from degradation and can remain in circulation for a longer period, increasing their bioavailability and therapeutic efficacy. In addition, the hollow core of HMMs can be used to encapsulate multiple drugs or therapeutic agents, allowing for the development of combination therapies that can target multiple pathways or mechanisms of disease.

In conclusion, HMMs have several advantages in targeted treatment of leukemia, including their high drug loading capacity, tunable pore size, and ability to enhance drug stability and bioavailability. These properties make HMMs an attractive platform for the development of customized drug delivery systems that can deliver therapeutic agents directly to cancer cells, while minimizing the risk of off-target effects and reducing the amount of drug required to achieve a therapeutic effect [59]. While there are still challenges to be addressed in the development of HMM-based therapies, such as optimizing their pharmacokinetics and toxicity profiles, the potential of these materials in the treatment of leukemia and other cancers is promising, and further research in this area is warranted.

3. Conclusion

This study summarizes the nanomedicine for the targeted therapy of leukemia and its advantages and specific applications. Nanomedicine delivery systems can have a profound impact on the therapeutic effectiveness of drugs. The powerful platform of the

nanomedicine delivery system enables leukemia treatment drugs to have multiple functions to achieve better therapeutic effects. It is not only the integration of chemical drugs, but also the integration of chemical drugs and targeted therapeutic drugs or immunotherapeutic drugs. Nanomedical drug delivery system has strong therapeutic potential, and plays a unique advantage in prolonging drug cycle time, improving bioavailability, increasing tumor site retention, reducing drug resistance, and reducing adverse reactions of anticancer drugs. The design of targeted drugs is aimed at interfering with specific molecular targets within leukemia cells, in order to avoid the development of drug resistance that traditional drugs may experience. This unique strategy not only highlights the enormous potential of targeted therapy in overcoming resistance mechanisms, but also demonstrates significant benefits when used in combination with traditional drugs or other targeted drugs, in improving treatment efficacy and enhancing patients' quality of life.

At present, the design idea of nanodrug delivery system is mainly based on the direct interaction between nanodrug delivery system and AML cells, but there are still many problems to be solved in the complex physiological environment. For example, in vivo, proteins and other biomolecules will cover the surface of nanocarriers to form protein crowns; Similarly, nanocarriers can also be swallowed by various immune cells during blood circulation, thus affecting their efficacy. To date, a variety of nano-drug delivery systems have shown promise in both in vitro studies and small animal models. However, only a select few nano-materials, such as iron oxide nanoparticles and PEGylated nanoparticles, have advanced to clinical trials or $CaCO_3$ was employed for delivering antibodies in preclinical studies involving monkeys. The intricate design of most nanodrug delivery systems presents a barrier to their translation from the laboratory to clinical settings. Despite the phased research progress achieved by nanodrug delivery systems in treating AML, they continue to encounter numerous challenges that must be addressed in the ongoing advancement of clinical medicine, cell biology, nanomaterials, and related disciplines.

Data availability statement

All the data analysis results obtained during this study are included in the manuscript. The original contributions presented in this study can be obtained upon request by contacting the corresponding author via email.

CRediT authorship contribution statement

Suying Qian: Writing – original draft, Methodology, Data curation. **Cuiping Zheng:** Writing – review & editing, Visualization, Validation. **Yanfang Wu:** Writing – review & editing, Formal analysis. **Huiyan Huang:** Writing – review & editing, Conceptualization. **Gongqiang Wu:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Junyu Zhang:** Project administration, Funding acquisition.

Declaration of competing interest

The authors declared that they do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, Ca - Cancer J. Clin. 71 (3) (2021) 209–249.
[2] A. Jemal, R. Siegel, E. Ward, T. Murray, J. Xu, M.J. Thun, Cancer statistics, 2007, Ca - Cancer J. Clin. 57 (1) (2007) 43–66.
[3] L. Drgona, C. Gudiol, S. Lanini, B. Salzberger, G. Ippolito, M. Mikulska, ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4), Clin. Microbiol. Infect. 24 (Suppl 2) (2018) S83–S94.
[4] D. Cunningham, W.H. Allum, S.P. Stenning, J.N. Thompson, C.J. Van de Velde, M. Nicolson, J.H. Scarffe, F.J. Lofts, S.J. Falk, T.J. Iveson, D.B. Smith, R. E. Langley, M. Verma, S. Weeden, Y.J. Chua, MAGIC Trial Participants, Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer, N. Engl. J. Med. 355 (1) (2006) 11–20.
[5] Z. Chen, Z. Yue, K. Yang, C. Shen, Z. Cheng, X. Zhou, S. Li, Four ounces can move a thousand pounds: the enormous value of nanomaterials in tumor immunotherapy, Adv. Healthcare Mater. 12 (26) (2023 Oct) e2300882.
[6] P.N. Durfee, Y.S. Lin, D.R. Dunphy, A.J. Muñiz, K.S. Butler, K.R. Humphrey, A.J. Lokke, J.O. Agola, S.S. Chou, I.M. Chen, W. Wharton, J.L. Townson, C. L. Willman, C.J. Brinker, Mesoporous silica nanoparticle-supported lipid bilayers (protocells) for active targeting and delivery to individual leukemia cells, ACS Nano 10 (9) (2016) 8325–8345.
[7] V. Kuek, A.M. Hughes, R.S. Kotecha, L.C. Cheung, Therapeutic targeting of the leukaemia microenvironment, Int. J. Mol. Sci. 22 (13) (2021) 6888.
[8] Z. Fang, X. Wang, Y. Sun, R. Fan, Z. Liu, R. Guo, D. Xie, Sgc8 aptamer targeted glutathione-responsive nanoassemblies containing Ara-C prodrug for the treatment of acute lymphoblastic leukemia, Nanoscale 11 (47) (2019) 23000–23012.
[9] J.H. Park, I. Rivière, M. Gonen, X. Wang, B. Sénéchal, K.J. Curran, C. Sauter, Y. Wang, B. Santomasso, E. Mead, M. Roshal, P. Maslak, M. Davila, R.J. Brentjens, M. Sadelain, Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia, N. Engl. J. Med. 378 (5) (2018) 449–459.
[10] Y. Zhou, L. Guan, W. Li, R. Jia, L. Jia, Y. Zhang, X. Wen, S. Meng, D. Ma, N. Zhang, M. Ji, Y. Liu, C. Ji, DT7 peptide-modified lecithin nanoparticles co-loaded with γ-secretase inhibitor and dexamethasone efficiently inhibit T-cell acute lymphoblastic leukemia and reduce gastrointestinal toxicity, Cancer Lett. 533 (2022) 215608.
[11] D. Walker, Y. Li, Á. Roxin, P. Schaffer, M.J. Adam, D.M. Perrin, Facile synthesis and 18F-radiolabeling of α4β1-specific LLP2A-aryltrifluoroborate peptidomimetic conjugates, Bioorg. Med. Chem. Lett. 26 (20) (2016) 5126–5131.
[12] W.J. Geldenhuys, R.R. Nair, D. Piktel, K.H. Martin, L.F. Gibson, The MitoNEET ligand NL-1 mediates antileukemic activity in drug-resistant B-cell acute lymphoblastic leukemia, J. Pharmacol. Exp. Therapeut. 370 (1) (2019) 25–34.
[13] D.J. Weiss, Flow cytometric and immunophenotypic evaluation of acute lymphocytic leukemia in dog bone marrow, J. Vet. Intern. Med. 15 (6) (2001) 589–594.
[14] A. Dasargyri, C.D. Kümin, J.C. Leroux, Targeting nanocarriers with anisamide: fact or artifact? Adv. Mater. 29 (7) (2017) 1603451.
[15] F.M. Uckun, P. Goodman, H. Ma, I. Dibirdik, S. Qazi, CD22 EXON 12 deletion as a pathogenic mechanism of human B-precursor leukemia, Proc. Natl. Acad. Sci. U.S.A. 107 (39) (2010) 16852–16857.

[16] F.M. Uckun, B.A. Roers, B. Waurzyniak, X.P. Liu, M. Cetkovic-Cvrlje, Janus kinase 3 inhibitor WHI-P131/JANEX-1 prevents graft-versus-host disease but spares the graft-versus-leukemia function of the bone marrow allografts in a murine bone marrow transplantation model, Blood 99 (11) (2002) 4192–4199.

[17] C. Li, X. You, X. Xu, B. Wu, Y. Liu, T. Tong, J. Chen, Y. Li, C. Dai, Z. Ye, X. Tian, Y. Wei, Z. Hao, L. Jiang, J. Wu, M. Zhao, A metabolic reprogramming amino acid polymer as an immunosurveillance activator and leukemia targeting drug carrier for T-cell acute lymphoblastic leukemia, Adv. Sci. 9 (9) (2022) e2104134.

[18] S. Laukkanen, A. Veloso, C. Yan, L. Oksa, E.J. Alpert, D. Do, N. Hyvärinen, K. McCarthy, A. Adhikari, Q. Yang, S. Iyer, S.P. Garcia, A. Pello, T. Ruokoranta, S. Moisio, S. Adhikari, J.A. Yoder, K. Gallagher, L. Whelton, J.R. Allen, A.H. Jin, S. Loontiens, M. Heinäniemi, M. Kelliher, C.A. Heckman, O. Lohi, D. M. Langenau, Therapeutic targeting of LCK tyrosine kinase and mTOR signaling in T-cell acute lymphoblastic leukemia, Blood 140 (17) (2022) 1891–1906.

[19] S. Misra, V.C. Hascall, R.R. Markwald, S. Ghatak, Interactions between hyaluronan and its receptors (CD44, RHAMM) regulate the activities of inflammation and cancer, Front. Immunol. 6 (2015 May 6) 201.

[20] E.L. Atallah, J.J. Orozco, M. Craig, et al., A Phase 2 study of actinium-225 (225Ac)-lintuzumab in older patients with untreated acute myeloid leukemia (AML) - interim analysis of 1.5 μci/Kg/dose, Blood 132 (2018) 1457.

[21] A. Marchese, C. Raiborg, F. Santini, J.H. Keen, H. Stenmark, J.L. Benovic, The E3 ubiquitin ligase AIP4 mediates ubiquitination and sorting of the G protein-coupled receptor CXCR4, Dev. Cell 5 (5) (2003) 709–722.

[22] P.N. Durfee, Y.S. Lin, D.R. Dunphy, A.J. Muñiz, K.S. Butler, K.R. Humphrey, A.J. Lokke, J.O. Agola, S.S. Chou, I.M. Chen, W. Wharton, J.L. Townson, C. L. Willman, C.J. Brinker, Mesoporous silica nanoparticle-supported lipid bilayers (protocells) for active targeting and delivery to individual leukemia cells, ACS Nano 10 (9) (2016) 8325–8345.

[23] J. Guo, E.G. Russell, R. Darcy, T.G. Cotter, S.L. McKenna, M.R. Cahill, C.M. O'Driscoll, Antibody-targeted cyclodextrin-based nanoparticles for siRNA delivery in the treatment of acute myeloid leukemia: physicochemical characteristics, in vitro mechanistic studies, and ex vivo patient derived therapeutic efficacy, Mol. Pharm. 14 (3) (2017) 940–952.

[24] X. Zhu, S. Li, Nanomaterials in tumor immunotherapy: new strategies and challenges, Mol. Cancer 22 (1) (2023 Jun 13) 94.

[25] Z. Chen, Z. Yue, K. Yang, S. Li, Nanomaterials: small particles show huge possibilities for cancer immunotherapy, J. Nanobiotechnol. 20 (1) (2022 Nov 16) 484.

[26] R. Khademi, Z. Mohammadi, R. Khademi, A. Saghazadeh, N. Rezaei, Nanotechnology-based diagnostics and therapeutics in acute lymphoblastic leukemia: a systematic review of preclinical studies, Nanoscale Adv. 5 (3) (2023) 571–595.

[27] L. Guo, H. Zhang, F. Wang, P. Liu, Y. Wang, G. Xia, R. Liu, X. Li, H. Yin, H. Jiang, B. Chen, Targeted multidrug-resistance reversal in tumor based on PEG-PLL-PLGA polymer nano drug delivery system, Int. J. Nanomed. 10 (2015 Jul 16) 4535–4547.

[28] Y. Ma, F. He, A.F. El-kott, A.S. Alshehri, a Zein, A.M. Eldib, Synthesis of gold nanoparticles encapsulated chitosan/gelatin polymers for the treatment of several types of leukemia, J. Inorg. Organomet. Polym. 34 (1) (2023) 100–109, 2024.

[29] F. Valdora, G. Cutrona, S. Matis, F. Morabito, C. Massucco, L. Emionite, S. Boccardo, L. Basso, A.G. Recchia, S. Salvi, F. Rosa, M. Gentile, M. Ravina, D. Pace, A. Castronovo, M. Cilli, M. Truini, M. Calabrese, A. Neri, C.E. Neumaier, F. Fais, G. Baio, M. Ferrarini, A non-invasive approach to monitor chronic lymphocytic leukemia engraftment in a xenograft mouse model using ultra-small superparamagnetic iron oxide-magnetic resonance imaging (USPIO-MRI), Clin. Immunol. 172 (2016) 52–60.

[30] I. Yasinska, B. Gibbs, L. Varani, R. Hussain, G. Siligardi, E. Fasler-Kan, L. Calzolai L, V. Sumbayev, Highly specific targeting of human acute myeloid leukaemia (AML) cells using functionalised gold nanoparticles, ESMO Open 3 (2) (2018) 463.

[31] J.C.K. Amerigos Daddy, M. Chen, F. Raza, Y. Xiao, Z. Su, Q. Ping, Co-encapsulation of mitoxantrone and β-elemene in solid lipid nanoparticles to overcome multidrug resistance in leukemia, Pharmaceutics 12 (2) (2020) 191.

[32] X. Guo, C. Gao, D.H. Yang, S. Li, Exosomal circular RNAs: a chief culprit in cancer chemotherapy resistance, Drug Resist. Updates 67 (2023) 100937.

[33] Khan HA, Kishore U, Alsulami HM, Alrokayan SH. Pro-apoptotic and immunotherapeutic effects of carbon nanotubes functionalized with recombinant human surfactant protein D on leukemic cells. Int. J. Mol. Sci. 202;22(19):10445.

[34] G. Zhang, H. Chang, C. Amatore, Y. Chen, H. Jiang, X. Wang, Apoptosis induction and inhibition of drug resistant tumor growth in vivo involving daunorubicin-loaded graphene-gold composites, J. Mater. Chem. B 1 (4) (2013) 493–499.

[35] D. Franskevych, K. Palyvoda, D. Petukhov, S. Prylutska, I. Grynyuk, C. Schuetze, L. Drobot, O. Matyshevska, U. Ritter, Fullerene C60 penetration into leukemic cells and its photoinduced cytotoxic effects, Nanoscale Res. Lett. 12 (1) (2017) 40.

[36] X. Cheng, J. Gao, Y. Ding, Y. Lu, Q. Wei, D. Cui, J. Fan, X. Li, E. Zhu, Y. Lu, Q. Wu, L. Li, W. Huang, Multi-functional liposome: a powerful theranostic nano-platform enhancing photodynamic therapy, Adv. Sci. 8 (16) (2021) e2100876.

[37] H. Wu, Y. Gao, J. Ma, M. Hu, J. Xia, S. Bao, Y. Liu, K. Feng, Cytarabine delivered by CD44 and bone targeting redox-sensitive liposomes for treatment of acute myelogenous leukemia, Regen Biomater 9 (2022) rbac058.

[38] M. Houshmand, F. Garello, R. Stefania, V. Gaidano, A. Cignetti, M. Spinelli, C. Fava, M. Nikougoftar Zarif, S. Galimberti, E. Pungolino, M. Annunziata, L. Luciano, G. Specchia, M. Bocchia, G. Binotto, M. Bonifacio, B. Martino, P. Pregno, F. Stagno, A. Iurlo, S. Russo, S. Aime, P. Circosta, G. Saglio, Targeting chronic myeloid leukemia stem/progenitor cells using venetoclax-loaded immunoliposome, Cancers 13 (6) (2021) 1311.

[39] M. Zhang, Y. Ge, S. Xu, X. Fang, J. Meng, L. Yu, C. Wang, J. Liu, T. Wen, Y. Yang, C. Wang, H. Xu, Nanomicelles co-loading CXCR4 antagonist and doxorubicin combat the refractory acute myeloid leukemia, Pharmacol. Res. 185 (2022) 106503.

[40] T.D. Langridge, R.A. Gemeinhart, Toward understanding polymer micelle stability: density ultracentrifugation offers insight into polymer micelle stability in human fluids, J. Contr. Release 319 (2020) 157–167.

[41] N. Bäumer, A. Scheller, L. Wittmann, A. Faust, M. Apel, S.C. Nimmagadda, C. Geyer, K. Grunert, N. Kellmann, M. Peipp, S. Kailayangiri, M.E. Gutierrez Suburu, C.A. Strassert, M. Schenk, L. Greune, C. Rüter, P. Dersch, W. Hartmann, C. Rossig, D. Neri, C. Müller-Tidow, C. Schwöppe, C. Schliemann, C. Khandanpour, G. Lenz, W.E. Berdel, S. Bäumer, Electrostatic anti-CD33-antibody-protamine nanocarriers as platform for a targeted treatment of acute myeloid leukemia, J. Hematol. Oncol. 15 (1) (2022) 171.

[42] Y. Zhang, R. Cai, H. Li, Y. Duan, Y. Zhang, W. Jing, S. Lv, X. Chu, Z. Cao, L. Yang, L. Ming, Construction of a target MSNs drugcarrier loaded with siRNAGLI1 and siRNASMO aim at hedgehog signal pathway and the pharmacodynamic study of drug-carriers in the treatment of leukemia stem cells, Drug Deliv Transl Res 12 (10) (2022) 2463–2473.

[43] T.T. Smith, S.B. Stephan, H.F. Moffett, L.E. McKnight, W. Ji, D. Reiman, E. Bonagofski, M.E. Wohlfahrt, S.P.S. Pillai, M.T. Stephan, In situ programming of leukaemia-specific T cells using synthetic DNA nanocarriers, Nat. Nanotechnol. 12 (8) (2017) 813–820.

[44] W. Zuo, M. Shahriari, M. Javadi, H. Mohebi, N. Abbasi, H. Ghaneialvar, Synthesis and application of Au NPs-chitosan nanocomposite in the treatment of acute myeloid leukemia in vitro and in vivo, Arab. J. Chem. 14 (2) (2021) 102929.

[45] A.V. Liopo, A. Conjusteau, M. Konopleva, M. Andreeff, A.A. Oraevsky, Laser nanothermolysis of human leukemia cells using functionalized plasmonic nanoparticles, Nano Biomed Eng. 4 (2) (2012) 66–75.

[46] Y. Kang, S. Li, Nanomaterials: breaking through the bottleneck of tumor immunotherapy, Int. J. Biol. Macromol. 230 (2023) 123159.

[47] G. Ultav, H. Tonbul, E. Tavukcuoglu, S.C. Ozturk, S. Akbas, A. Sahin, G. Esendagli, Y. Capan, pH-sensitive chitosan-PEG-decorated hollow mesoporous silica nanoparticles could be an effective treatment for acute myeloid leukemia (AML), J Nanopart Res 24 (2) (2022) 40.

[48] B. Fu, M. Dang, J. Tao, Y. Li, Y. Tang, Mesoporous platinum nanoparticle-based nanoplatforms for combined chemo-photothermal breast cancer therapy, J. Colloid Interface Sci. 570 (2020) 197–204.

[49] F. Perche, Y. Yi, L. Hespel, P. Mi, A. Dirisala, H. Cabral, K. Miyata, K. Kataoka, Hydroxychloroquine-conjugated gold nanoparticles for improved siRNA activity, Biomaterials 90 (2016) 62–71.

[50] A.K. Mittal, U.C. Banerjee, In vivo safety, toxicity, biocompatibility and anti-tumour efficacy of bioinspired silver and selenium nanoparticles, Mater. Today Commun. 26 (2021) 102001.

[51] V. Trujillo-Alonso, E.C. Pratt, H. Zong, A. Lara-Martinez, C. Kaittanis, M.O. Rabie, V. Longo, M.W. Becker, G.J. Roboz, J. Grimm, M.L. Guzman, FDA-approved ferumoxytol displays anti-leukaemia efficacy against cells with low ferroportin levels, Nat. Nanotechnol. 14 (6) (2019) 616–622.

[52] F. Kong, H. Bai, M. Ma, C. Wang, H. Xu, N. Gu, Y. Zhang, Fe_3O_4@Pt nanozymes combining with CXCR4antagonists to synergistically treat acute myeloid leukemia, Nano Today 37 (2021) 101106.

[53] B. Chen, Y. Liang, W. Wu, J. Cheng, G. Xia, F. Gao, J. Ding, C. Gao, Z. Shao, G. Li, W. Chen, W. Xu, X. Sun, L. Liu, X. Li, X. Wang, Synergistic effect of magnetic nanoparticles of Fe(3)O(4) with gambogic acid on apoptosis of K562 leukemia cells, Int. J. Nanomed. 4 (2009) 251–259.
[54] J. Cheng, J. Wang, B. Chen, G. Xia, X. Cai, R. Liu, Y. Ren, W. Bao, X. Wang, A promising strategy for overcoming MDR in tumor by magnetic iron oxide nanoparticles co-loaded with daunorubicin and 5-bromotetrandrin, Int. J. Nanomed. 6 (2011) 2123–2131.
[55] A. Iscaro, N.F. Howard, M. Muthana, Nanoparticles: properties and applications in cancer immunotherapy, Curr. Pharmaceut. Des. 25 (17) (2019) 1962–1979.
[56] P.N. Durfee, Y.S. Lin, D.R. Dunphy, A.J. Muñiz, K.S. Butler, K.R. Humphrey, A.J. Lokke, J.O. Agola, S.S. Chou, I.M. Chen, W. Wharton, J.L. Townson, C. L. Willman, C.J. Brinker, Mesoporous silica nanoparticle-supported lipid bilayers (protocells) for active targeting and delivery to individual leukemia cells, ACS Nano 10 (9) (2016) 8325–8345.
[57] H. Bai, Q. Sun, F. Kong, H. Dong, M. Ma, F. Liu, C. Wang, H. Xu, N. Gu, Y. Zhang, Zwitterion-functionalized hollow mesoporous Prussian blue nanoparticles for targeted and synergetic chemo-photothermal treatment of acute myeloid leukemia, J. Mater. Chem. B 9 (26) (2021) 5245–5254.
[58] Q.L. Guo, X.L. Dai, M.Y. Yin, H.W. Cheng, H.S. Qian, H. Wang, D.M. Zhu, X.W. Wang, Nanosensitizers for sonodynamic therapy for glioblastoma multiforme: current progress and future perspectives, Mil Med Res 9 (1) (2022) 26.
[59] C.X. Li, J.S. Wang, W.N. Wang, D.K. Xu, Y.T. Zhou, F.Z. Sun, Y.Q. Li, F.Z. Guo, J.L. Ma, X.Y. Zhang, M.J. Chang, B.H. Xu, F. Ma, H.L. Qian, Expression dynamics of periodic transcripts during cancer cell cycle progression and their correlation with anticancer drug sensitivity, Mil Med Res 9 (1) (2022) 71.