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Nanotechnology based approaches for leukemia therapy

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Abstract

Leukemia, a leading cause of cancer-related morbidity and mortality, primarily affect blood-forming tissues. It is classified into four main types: acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). These subtypes vary in characteristics and prevalence, affecting different age groups, from children to adults, with prognosis heavily influenced by the type and severity of the disease. Conventional treatments for leukemia, including chemotherapy, radiation, and stem cell therapy, have notable limitations, such as non-specific targeting, high costs, drug resistance, and issues related to donor compatibility. These limitations underscore the urgent need for innovative solutions. One of the major challenges in treating leukemia with tyrosine kinase inhibitors (TKIs) is the frequent resistance due to factors like lack of specific targeting, underdosing, limited bioavailability, and severe adverse effects. Nanotechnology presents a promising solution to these challenges by utilizing nanoscale materials such as liposomes, metallic nanoparticles, polymeric nanoparticles, and biomimetic nanoparticles for targeted drug delivery. Nanoparticle-based drug delivery systems offer enhanced drug targeting, reduced systemic toxicity, and improved therapeutic efficacy. This review highlights recent advancements in nanotechnology to improve leukemia treatment.

Introduction

Leukemia is a type of cancer that affects the blood and bone marrow. It is characterized by the uncontrolled proliferation of abnormal blood cells, which crowd out healthy cells and impair their functions. These abnormal cells interfere with the production of critical blood components, such as white blood cells, red blood cells, and platelets, which are vital for immune defense, oxygen transport, and blood clotting [1]. Leukemia can originate from myeloid or lymphoblastic cells, essential to the body's immune and blood systems. This disorder impairs the normal functioning of these cells, leading to a deficiency in key components responsible for body defense, clotting, and oxygen delivery [2]. Leukemia is more prevalent in children than in adults, and its treatment often includes chemotherapy, radiation, and stem cell therapy. However, these treatments can damage healthy cells and not deliver chemotherapeutic drugs specifically to cancer cells. The limitations of anticancer drugs, such as short half-life, poor solubility, and off-target distribution, contribute to systemic toxicity and drug resistance [3].

Recent advances in targeted drug delivery, particularly through nanotechnology, offer promising alternatives. Nanotechnology aims to improve drug biocompatibility, enhance the solubility of both hydrophobic and hydrophilic compounds, and ensure more precise targeting, thereby reducing the adverse effects typically associated with conventional therapies [4].

Leukemia includes various subtypes, such as acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and chronic lymphoblastic leukemia [5]. While the exact cause of leukemia is not fully understood, genetic mutations, particularly chromosomal abnormalities like the BCR-ABL translocation between chromosomes 9 and 22, play a significant role. This translocation produces a fusion protein that drives uncontrolled cell proliferation and reduces apoptosis in leukemia cells [6]. Environmental factors, genetic predisposition, and lifestyle choices, such as exposure to radiation and certain chemicals, are also believed to contribute to the development of leukemia [7]. Common symptoms of leukemia include fatigue, bleeding, frequent infections, weight loss, poor oxygenation, delayed wound healing, and weakened immunity[8]. Diagnosis typically involves biopsy, blood tests, and cytogenetic analysis [9].

New treatment strategies for leukemia are being explored, emphasizing improving targeted delivery methods to enhance treatment efficacy. Conventional therapies such as chemotherapy, radiation, and stem cell transplantation have been used for decades but face challenges due to side effects, drug overdose, and limited effectiveness [10]. Nanotechnology is emerging as a promising approach for the delivery of anticancer drugs, offering benefits such as controlled drug release, prolonged circulation time, enhanced targeting, and improved therapeutic outcomes [11].

Basics of Leukemia

Leukemia encompasses several distinct types, including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). While the precise causes of leukemia remain unclear, genetic mutations at the chromosomal level are often implicated in the development of these cancers.

Acute Lymphoblastic Leukemia (ALL) is a cancer that affects white blood cells, specifically leading to the production of immature lymphocytes that cannot function properly. ALL is more common in children and adults over 50, resulting in fewer healthy cells and a weakened immune system. This disorder impairs the body's ability to fight infections. Diagnosis is made through blood tests and bone marrow biopsies, which help detect genetic abnormalities such as the Philadelphia chromosome and ETV6/RUNX1 translocations [12].

Chronic Lymphocytic Leukemia (CLL) is a cancer marked by the overproduction of abnormal white blood cells in the bone marrow, which hinders the production of healthy blood cells, including white blood cells, red blood cells, and platelets [13]. This disease can affect children and adults, impairing the immune response and making the body more susceptible to infections. Blood cells develop in the hematopoietic bone marrow, where myeloid cells form red blood cells and platelets, while lymphoid cells mature into immune cells such as lymphocytes [14]. Genetic mutations, including those in proto-oncogenes, tumor suppressor genes, and microRNAs, contribute to these blood cells' abnormal proliferation and dysfunction [15].

Acute Myeloid Leukemia (AML) is a rapidly progressing cancer characterized by the abnormal proliferation of myeloid cells, precursors to red blood cells, white blood cells, and platelets. AML primarily

affects adults over the age of 60, with both men and women being equally impacted. Symptoms include fever, weight loss, anemia, liver inflammation, and headaches [16]. Diagnosis is made through blood tests that reveal elevated levels of immature myeloid cells and low levels of red blood cells and platelets, alongside bone marrow biopsies. Cytogenetic testing is vital, as it can identify chromosomal abnormalities such as the translocation t(15;17) in acute promyelocytic leukemia (APL) [17], as well as mutations in FLT3 and NPM1, which influence prognosis and treatment strategies [18].

Chronic Myeloid Leukemia (CML) is characterized by the overproduction of myeloid cells. A hallmark of CML is the Philadelphia chromosome, a genetic abnormality caused by a translocation between chromosomes 9 and 22 [19]. This translocation results in the formation of the BCR-ABL fusion gene, which produces a protein that drives the proliferation of abnormal cells [20]. The BCR-ABL fusion gene is critical for diagnosing and treating CML, as it plays a key role in disease progression and directly influences patient outcomes. Understanding this genetic component is essential for effectively managing the condition [21].

Diagnosis of Leukemia

The leukemia diagnosis varies depending on the type, as each leukemia subtype is characterized by specific morphological, chromosomal, and cytogenetic alterations [22]. Genetic mutations and chromosomal abnormalities lead to the expression of markers associated with the disease [9]. Accurate diagnosis is critical for understanding the underlying causes of leukemia and determining the most effective treatment strategy [23]. The diagnostic process typically includes flow cytometry to assess surface markers, immunohistochemistry to evaluate specific protein expressions (e.g., dim CD3 expression), and cytogenetic analysis to identify key mutations such as BCR-ABL [24]. Fluorescence in situ hybridization (FISH) is commonly used to detect chromosomal mutations, translocations, and other structural changes [25]

Diagnosing ALL involves examining cell morphology, identifying chromosomal abnormalities using FISH, and conducting immunophenotyping. If abnormalities are detected, reverse transcription polymerase chain reaction (RT-PCR) and next-generation sequencing may be employed to further analyze genetic changes [26]. In AML, diagnosis is based on the morphological examination of blast cells and immunophenotyping using flow cytometry. Cytogenetic analysis is essential for identifying gene rearrangements and chromosomal abnormalities [27]. CLL is primarily diagnosed using flow cytometry to analyze B lymphocytes. Blood tests often reveal abnormalities, such as the presence of small, irregular, and immature cells [28]. CML diagnosis is based on the detection of chromosomal abnormalities through RT-PCR, specifically identifying the Philadelphia chromosome, a common genetic abnormality associated with CML. The presence of 22q- or BCR-ABL1 transcripts in peripheral blood or bone marrow cells is typically conclusive for diagnosing CML [29].

Conventional Treatment of Leukemia

Conventional treatment for leukemia primarily involves the use of FDA-approved anticancer drugs that target enzymes responsible for cell proliferation. These drugs are commonly employed in leukemia therapy [30]. Leukemia chemotherapy typically involves administering high doses of anticancer drugs to eliminate or inhibit the growth of cancerous cells. However, this treatment also damages healthy cells. For example, doxorubicin is frequently used in chemotherapy for leukemia [31].

The specific treatment approach depends on the type and subtype of leukemia. Selecting the appropriate frontline therapy is essential for effective treatment outcomes. In younger patients, chemotherapy is generally preferred. Medications like Imatinib, which inhibits the tyrosine kinase enzyme involved in cancer cell proliferation, effectively reduce tumor growth [32]. Tyrosine Kinase Inhibitors (TKIs) are targeted therapy drugs that specifically block the action of abnormal tyrosine kinases enzymes that regulate cell growth. In leukemia, particularly CML, the BCR-ABL fusion protein created by the Philadelphia chromosome translocation results in the constitutive activation of tyrosine kinases, driving uncontrolled cell proliferation. TKIs, such as Imatinib, dasatinib, and nilotinib, target and inhibit the BCR-ABL protein, preventing the abnormal signaling that leads to the proliferation of cancer cells [33]. These inhibitors have significantly improved the prognosis for CML patients, leading to higher remission rates and reducing the need for stem cell transplants.

Some treatments are designed to activate specific T-cells and B-cells, triggering a therapeutic immune response against leukemic cells. For instance, blinatumomab targets CD19 and activates T-cells,

inducing cytotoxicity against the cancer cells [34]. Combining TKIs with chemotherapy has improved remission rates. Studies indicate that patients who received hyper-CVAD therapy in combination with ponatinib had an 84% complete molecular remission (CMR) rate and a 5-year survival rate of 73%-86%, with or without allogeneic stem cell transplantation (alloSCT) [35].

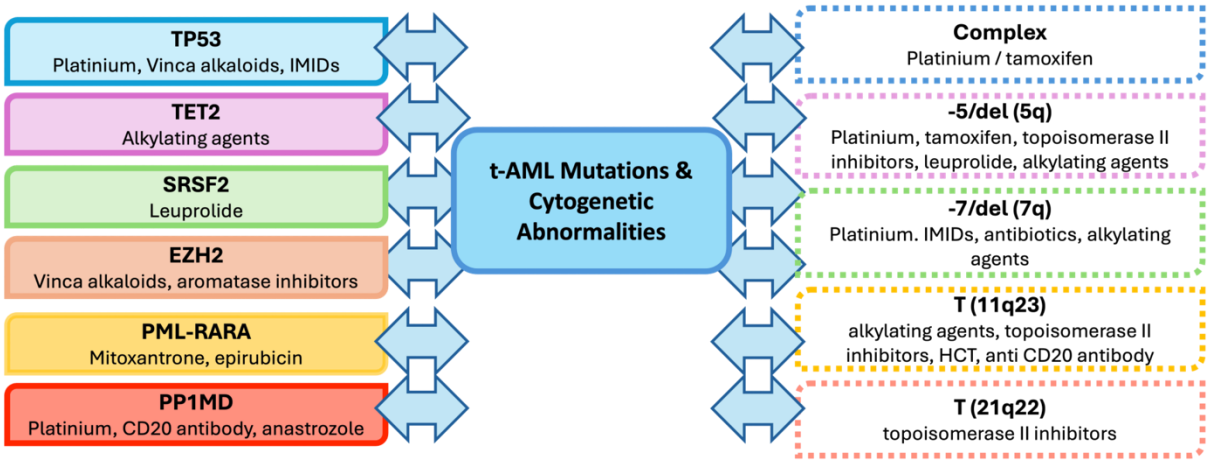

Fig. 1: Mutations and cytogenetic abnormalities in therapy-related complications

Advancements in leukemia treatment continue to focus on enhancing therapeutic efficacy. The effectiveness of chemotherapy has been improved by combining multiple anticancer drugs, although the damage to healthy cells remains a significant challenge, and these treatments still have considerable side effects **(Fig. 1)** [36]. Radiation therapy, which uses high-energy radio waves to damage and kill cancer cells, can also induce apoptosis in leukemia cells. Stem cell therapy is another approach wherein cancer cells are eradicated through chemotherapy and radiation, followed by the introduction of new stem cells to repair the system and regenerate healthy blood cells [37]. However, these treatments also lead to off-target effects, damaging healthy tissues and compromising the immune system [38].

Allogeneic stem cell transplantation (alloSCT) involves infusing healthy donor stem cells into the patient's body. To ensure the success of this treatment, high doses of chemotherapy are used to eliminate the patient's cancerous cells. However, this procedure is associated with significant side effects, and improved treatment strategies are needed to minimize these adverse effects [39].

Introduction to Nanotechnology

Nanotechnology is the application of scientific and engineering principles at the nanoscale, typically involving materials ranging from 1 to 100 nanometers. At this scale, materials exhibit unique chemical, physical, and biological properties that differ significantly from those at larger scales [33]. Nanotechnology encompasses various fields, including organic and inorganic nanoparticles, biomimetic nanoparticles, and polymer-based nanoparticles, each offering specialized applications [40].

The term "nanotechnology" was first coined in 1959 by physicist Richard Feynman, who explored the behavior of atoms and electrons at the nanoscale, focusing on the properties of particles at atomic and subatomic levels [41]. Since then, advancements in nanotechnology have been substantial, particularly in synthesizing metallic nanoparticles through green methods, such as using plant extracts, which may also possess therapeutic properties [42]. For example, silver and zinc nanoparticles are well-known for their antibacterial effects and are widely used to treat infections [43]. However, these nanoparticles can exhibit toxicity, which limits their use in biomedical applications [44]. Fortunately, innovations in nanotechnology have led to improved biocompatibility, minimizing toxic effects, and enhancing the efficiency of targeted drug delivery. One prominent example is liposome-based mRNA vaccines, approved by the FDA during the COVID-19 pandemic for mass immunization [45].

In healthcare, nanotechnology is primarily applied to disease diagnosis and the enhancement of treatment methods, with a special focus on targeted drug delivery [46, 47]. The main objective of nanotechnology in medicine is to understand, control,

and manipulate systems at the nanoscale, enabling the repair, targeting, and interaction with biological systems **(Fig. 2)** [48]. Nanoscale materials have a significantly increased surface-to-volume ratio compared to larger molecules, enhancing their interaction surfaces and boosting therapeutic efficacy [49]. This makes them ideal for improving targeted drug delivery and controlled release, ultimately minimizing the side effects associated with off-target therapies [50]. Nanomedicine has revolutionized the treatment of diseases and the development of precise diagnostic devices, providing deeper insights into diseases and leading to better therapeutic outcomes.

A notable application of nanotechnology is by employing nanoshells, which can absorb light and generate heat. These nanoshells are particularly useful in cancer treatment, where they can be directed to cancer cells. When exposed to infrared light, the nanoshells generate heat, destroying cancer cells while minimizing damage to healthy tissue and reducing off-target effects [51].

Nanomaterials are also vital in tissue engineering and regenerative medicine as scaffolds for tissue growth. Polymeric and metallic nanoparticles are commonly used in these fields due to their low toxicity and high biocompatibility [52]. By modifying the surface chemistry of nanoparticles, researchers can achieve targeted drug delivery, improved biocompatibility, extended circulation time in the bloodstream, and reduced toxicity. Nanomedicine's applications extend across imaging, diagnostics, and therapies, enabling more precise treatment and prevention of diseases [53].

Biomimetic and bioinspired nanoparticles have gained attention for their significant roles in gene delivery, drug delivery, and therapeutic interventions [54]. These nanoparticles are often conjugated with hydrophilic groups, such as polyethylene glycol (PEG), or hydrophobic drugs like doxorubicin for targeted cancer treatment. PEG-dendritic systems, for example, enhance the circulation time of nanoparticles in the bloodstream, thereby improving the effectiveness of targeted drug delivery in cancer therapies [55].

Unique Properties of Nanomaterials

Nanomaterials possess unique properties that enhance their potential for drug delivery and cancer therapy. Their nanoscale size facilitates enhanced permeability and retention (EPR) in tumor tissues, exploiting the leaky vasculature typical of many tumors [56]. This allows nanomaterials to accumulate preferentially in tumor areas, improving therapeutic outcomes. Additionally, nanomaterials' high surface area-to-volume ratio provides significant drug-loading capacity, making them ideal for carrying large amounts of therapeutic agents [57]. This feature also allows for surface functionalization, enabling the attachment of targeting ligands such as antibodies or peptides, which enhances specificity and reduces off-target effects[58] [59]. These functionalized nanomaterials can actively target cancer cells, improving the precision and effectiveness of cancer therapies.

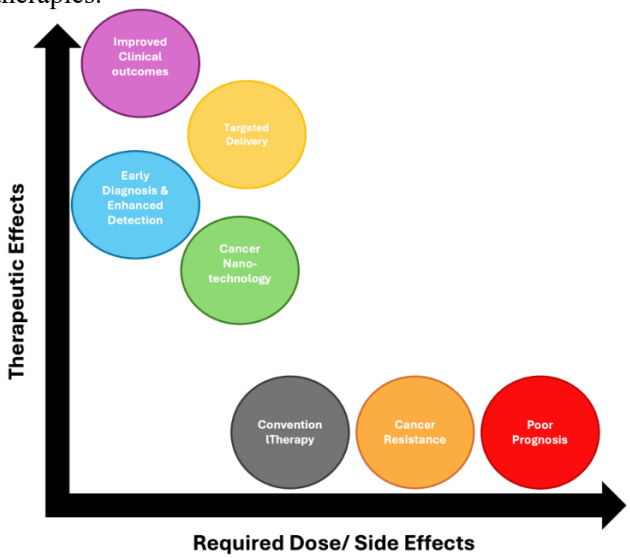

Fig. 2: Nanotechnology-based improved theranostics compared to conventional approaches

Mechanisms of Nanotechnology in Drug Delivery and Cancer Targeting

Nanotechnology offers multiple mechanisms that improve the efficacy of cancer treatments. First, the encapsulation of hydrophobic drugs within nanocarriers can significantly enhance their solubility and stability, protecting them from enzymatic degradation. This ensures the drugs remain effective throughout their delivery [60]. Second, nanomaterials can be engineered for controlled drug release, responding to specific stimuli such as changes in pH or temperature. This feature enables the delivery of drugs directly to the tumor site, minimizing the exposure of healthy tissues to toxic agents and reducing side effects [61].

Nanomaterials also utilize the EPR effect for passive targeting. Through this mechanism, nanocarriers preferentially accumulate in tumor tissues, where the

tumor's leaky blood vessels allow for greater drug concentration [62]. In addition to passive targeting, active targeting is achieved through surface functionalization with targeting moieties. These moieties direct the nanocarriers to specific cancer cell receptors, further increasing the precision and effectiveness of the treatment [63].

Moreover, some advanced nanocarriers combine therapeutic and diagnostic functions, offering a dual approach known as theranostics **(Fig. 3)** [64]. This integration allows for simultaneous treatment and real-time monitoring of cancer progression, providing valuable insights into the therapy's effectiveness and the disease status [65].

These unique properties of nanomaterials make them a promising tool in cancer treatment, improving the pharmacokinetics, targeting efficiency, and therapeutic index of anticancer agents. By overcoming challenges like drug resistance, nanotechnology holds the potential to enhance patient outcomes in cancer therapy significantly [11].

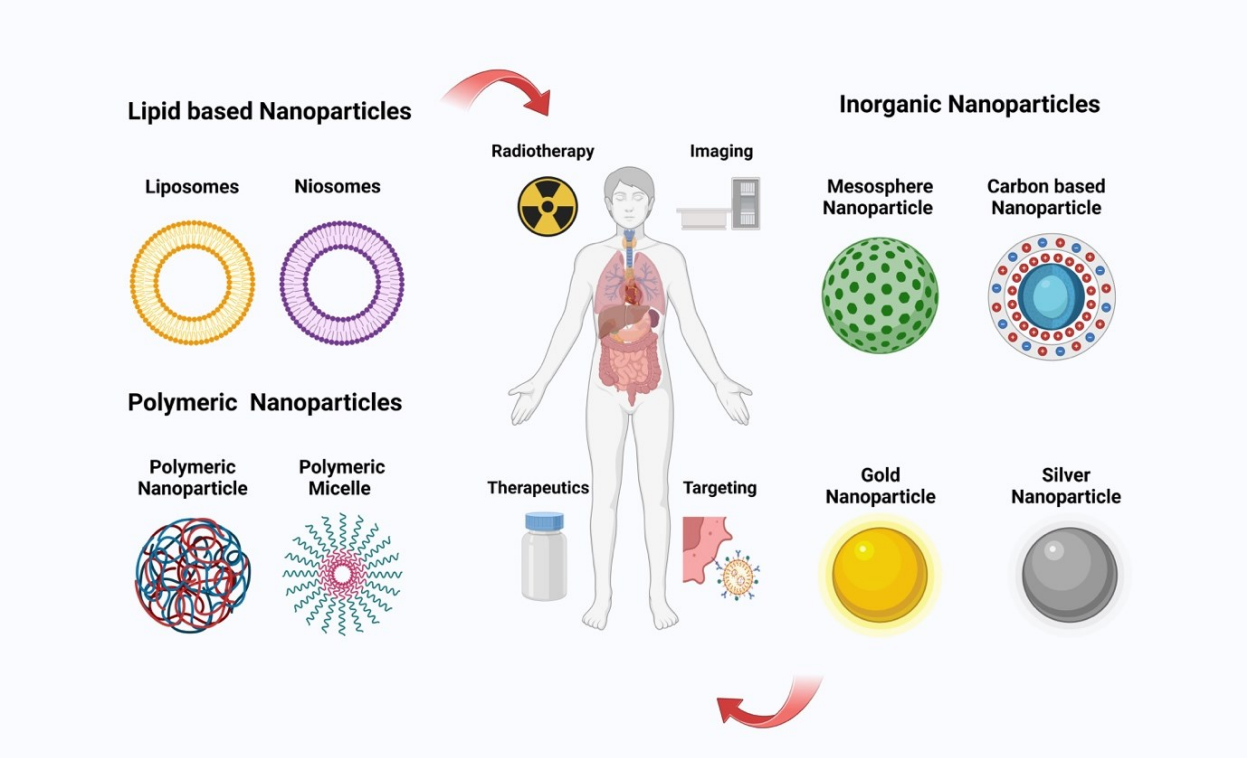

Fig. 3: Schematic representation of nanotechnology-based advancements in theranostics. The figure illustrates the integration of advanced nanomaterials in diagnostics and therapeutics, focusing on targeted drug delivery and diagnosis via bioimaging.

Nanotechnology Approach in Leukemia Treatment

Conventional treatment methods for leukemia, such as chemotherapy and radiation, are often associated with significant side effects and off-target effects, which can damage healthy cells and lead to complications like immune suppression, inflammation, and gastrointestinal infections [66]. To address these challenges, nanotechnology has emerged as a promising strategy for more effective and targeted drug delivery. Using nanoparticles, chemotherapeutic agents can be specifically delivered to the disease site, reducing the risk of harming healthy cells and improving therapeutic outcomes [67] [68].

One of the major limitations of conventional chemotherapy is the development of resistance by cancer cells, which often renders treatments ineffective [69]. This resistance can lead to suboptimal outcomes, contributing to further complications. Nanoparticle-based delivery systems help overcome these issues by enhancing the targeting of drugs and minimizing the required dosage. These systems ensure that the drug interacts specifically with its target molecules, resulting in better bioavailability and consistent distribution of therapeutic agents.

Targeted delivery through nanoparticles addresses the main drawbacks of traditional treatments like chemotherapy and radiation. While these therapies can damage healthy tissues and cause severe side effects, nanoparticle-based approaches offer a more precise and efficient method for treating and diagnosing cancer. Various types of nanoparticles, including liposomes, micelles, and polymeric nanoparticles, have been explored in cancer therapy [66].

For instance, liposomes are synthetic carriers that can be tailored to meet specific treatment requirements. Recent advancements in liposomal formulations have led to the development of drugs like MP-A08, a novel sphingosine kinase 1 (SPHK1) inhibitor used in the treatment of acute myeloid leukemia. Liposomal delivery systems help overcome the limitations of conventional chemotherapy drugs by enhancing drug efficacy and reducing side effects, thereby improving overall treatment effectiveness [70].

Polymeric nanoparticles also offer a valuable strategy for targeted drug delivery in leukemia treatment. One example is the use of polymeric nanoparticles to deliver cytarabine, an antimetabolic drug commonly used to treat leukemia. The dose-limiting toxicity associated with conventional Cytarabine therapy can be overcome by loading cytarabine onto polymeric nanoparticles, allowing for more effective treatment with fewer side effects [71].

Metallic Nanoparticles in Leukemia Treatment

Metallic nanoparticles, typically ranging in size from 1 nm to 100 nm, exhibit unique chemical and physiological properties that differentiate them from their bulk counterparts [72]. These nanoparticles are synthesized using two main approaches: bottom-up and top-down. The bottom-up approach involves assembling smaller units into nanoparticles, while the top-down approach breaks down larger materials into nanoparticle-sized components. Both methods are tailored to achieve specific characteristics depending on the intended application, allowing for the creation of nanoparticles with distinct properties **(Fig. 4)** [73].

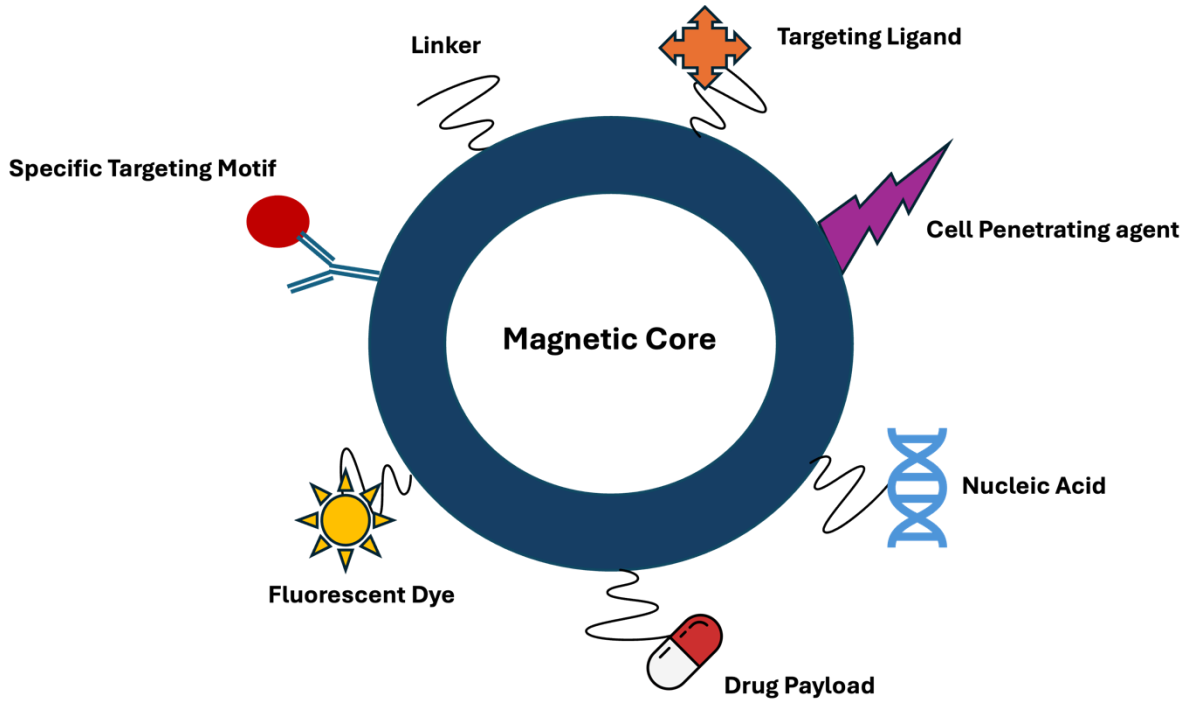

Fig. 4: Multifunctional Metallic Nanoparticles. The figure highlights the versatile roles of metallic nanoparticles in theranostic applications, focusing on their multifunctional properties.

Metallic nanoparticles are usually synthesized through chemical reduction, catalysts, stabilizers, or green synthesis methods, such as plant extracts, which also possess therapeutic properties [74]. Techniques like thermal and co-precipitation methods are often

used to control the size and shape of nanoparticles under optimal laboratory conditions [75].

In cancer treatment, metallic nanoparticles have gained attention due to their ability to induce apoptosis, or programmed cell death, in cancer cells [76]. Green biogenic nanoparticles have shown promise in treating liquid tumors such as leukemia. These nanoparticles are beneficial not only for therapy but also for the diagnosis of leukemia. Leukemia cells can produce reactive oxygen species (ROS), damaging healthy cells. Green nanoparticles have antioxidative and antitumor properties, helping protect normal cells while reducing the side effects of conventional treatments [77] [78].

Iron-based nanoparticles are widely recognized for their biocompatibility and therapeutic potential. These nanoparticles are used in diagnosing and treating cancer, including leukemia. For instance, iron oxide nanoparticles and iron folate core-shell nanoparticles have been employed in treating acute lymphoblastic leukemia (ALL) [79]. These nanoparticles have been shown to alter the expression of the BCL gene, promoting apoptosis in cancer cells. Characterization of the nanoparticles through dynamic light scattering and cytotoxicity assays, such as the MTT assay, has demonstrated their anticancer effects. These iron oxide nanoparticles help to upregulate pro-apoptotic proteins like Bax while downregulating anti-apoptotic proteins like BCL, thereby inducing cell death in leukemia cells [80].

Gold nanoparticles have also been investigated for their potential in leukemia treatment. A study using 50 nm gold nanoparticles stabilized with chitosan—a biocompatible polymer, showed enhanced therapeutic effects against leukemia cell lines. This work demonstrated how metallic nanoparticles can be effective alternatives to conventional chemotherapy drugs [81]. Additionally, iron nanoparticles have been used to overcome resistance to traditional anticancer drugs like doxorubicin. Surface modifications with iron nanoparticles enable RNA interference, reducing drug resistance and improving doxorubicin's therapeutic efficacy [82].

Silver nanoparticles have shown promise in treating acute myeloid leukemia (AML). These nanoparticles help reduce cytotoxicity to healthy cells while inducing mechanisms to target and kill cancer cells [83]. The unique chemical and physical properties of metallic nanoparticles make them versatile and promising tools for therapeutic applications in cancer treatment [84].

Likewise, titanium dioxide combined with graphene oxide (TiO2-GO) nanocomposites were used to ameliorate Ph+ leukemia by delivering the TKIs nilotinib and ponatinib. TiO2 has been reported to have a higher affinity for leukemia cells, whereas GO could enhance the drug-loading ability in K562 cells in vitro[85].

Although metallic nanoparticles have been tested in clinical and preclinical trials for cancer therapy, challenges remain, including potential side effects. However, their prospects for improving cancer treatment, particularly leukemia, are highly promising. Continued advancements in nanoparticle design and targeted delivery systems are essential to optimize their specificity and therapeutic effects [86].

Liposomes as a Drug Delivery System

Liposomes are nanoparticles with a lipid bilayer structure, forming a central core capable of encapsulating drugs, while their surface can be modified to bind specific ligands [87]. In recent years, liposomes have gained considerable attention as an effective drug delivery system, particularly in cancer treatment. Various strategies for drug delivery via liposomes are presented in **Fig. 5**. One of the most notable advancements is the encapsulation of Doxil (liposomal doxorubicin), which enhances the drug's efficacy and minimizes its side effects [88]. Additionally, surface modification of liposomes, such as coating them with polyethylene glycol (PEG), has been explored to increase their circulation time in the bloodstream and improve drug delivery efficiency.

In leukemia treatment, liposomal formulations of anticancer drugs, including mitoxantrone and flavopiridol, have shown significant promise [89]. Nanoscale drug delivery systems like liposomes aim to ensure targeted drug delivery, extend the drug's half-life, and maintain high concentrations at the intended site of action [90]. Liposomes can be surface-modified with specific ligands, such as CD19, CD20, and CD21, which are receptors expressed on leukemic cells. In 2016, the FDA approved Doxil liposomes for their enhanced therapeutic outcomes, paving the way for liposomal-based treatments for various cancers, including leukemia [91].

Liposomes have become an essential strategy for delivering anticancer drugs and transporting other therapeutic agents, including amino acids, siRNA, DNA, and plasmids, directly to target sites. Oral administration of drugs often presents challenges, such as degradation or reduced absorption in the digestive tract, which can limit their effectiveness [92]. Liposomal formulations help overcome these

limitations by improving the half-life of drugs, ensuring prolonged circulation in the bloodstream, and enabling controlled drug release at the target location.

Liposomal formulations have also been successfully used with kinase and BCL2 inhibitors, showing promising therapeutic results in cancer treatment [93]. These advancements highlight the growing potential of liposomes as a versatile and efficient drug delivery platform in treating leukemia and other cancers.

Polymeric Nanomedicines

Polymeric nanoparticles are solid structures typically ranging from 10 nm to 1000 nm in size, offering unique properties that enhance the stability and shelf life of drugs by protecting them from degradation [74]. In leukemia treatment, many anticancer drugs provoke immunogenic reactions and have short half-lives in the body, leading to higher drug concentrations to achieve therapeutic effects. However, this often results in side effects that damage healthy cells. As a result, there has been increasing interest in novel nanoscale systems designed to minimize these effects and improve the pharmacokinetics and half-life of anticancer drugs [94].

Polymeric nanoparticles have been tested in clinical trials, where drugs are encapsulated in nanocarriers such as micelles and dendrimers [95]. These nanocarriers offer several advantages, including biodegradability, biological effectiveness, and targeted delivery to specific sites. Recent advancements in polymeric nanoparticle technology have included surface modifications with peptides, ligands, antibodies, nucleic acids, and cancer cell membrane proteins [96]. These modifications help ensure that drugs are explicitly delivered to cancer cells.

Common polymeric compounds, such as polyethylene glycol (PEG), provide structural stability and facilitate tissue-specific delivery. PEG-based modifications help reduce the degradation of therapeutic compounds in aqueous environments, ensuring they reach their intended targets with minimal loss of potency [97]. Polymeric coatings also help protect drugs from premature degradation, a common problem in conventional drug delivery systems.

Nanotechnology-based polymeric systems aim to improve the efficacy of traditional drugs, which often suffer from toxicity due to high doses or systemic side effects [98]. For instance, cytarabine, an anticancer drug used for acute myeloid leukemia, has a short half-life of about 10 minutes and can cause adverse effects due to its rapid intravenous (IV) administration and poor membrane efflux. Polymeric nanoparticles (PNPs) offer a solution by enabling controlled release and targeted delivery, thereby improving the drug's pharmacokinetics, efficacy, and safety profile [99]. These advancements illustrate the potential of polymeric nanomedicines to enhance the effectiveness and safety of cancer therapies.

Biomimetic Nanoparticles

Biomimetic nanoparticles are engineered by coating synthetic nanoparticles with cell membranes, which bestow biological and artificial characteristics upon them. This hybrid nature enables these nanoparticles to exhibit beneficial properties such as biointerfacing and self-recognition, effectively navigating and bypassing cellular barriers [100]. A significant challenge synthetic nanoparticles face is their potential to be identified and eliminated as foreign particles when circulating in the bloodstream [101]. In contrast, natural carriers, such as those responsible for transporting nutrients and essential compounds between cells, are not eliminated in this manner. This biomimetic approach, which leverages cell membrane-coated nanoparticles to deliver substances like siRNA, plasmids, and drugs, represents a significant breakthrough in nanotechnology [102].

By mimicking natural cell carriers, biomimetic nanoparticles are recognized as "self" by the immune system, thus reducing the likelihood of immune system clearance. This self-recognition improves their bioavailability and target-specific delivery and reduces immunogenic responses, making them a promising tool for therapeutic applications [100].

In the context of cancer treatment, challenges such as the tumor microenvironment and chemotherapy resistance often hinder the efficacy of anticancer drugs. One approach to overcoming these challenges involves gene activation. For example, activating the STING (Stimulator of Interferon Genes) pathway can enhance the response to chemotherapy drugs and improve treatment outcomes [103]. Biomimetic nanomedicine can facilitate targeted drug delivery, such as encapsulating doxorubicin within the cell membranes of leukemia cells, enabling precise targeting of cancer cells and activation of the STING gene. Studies have shown that such targeted delivery to bone marrow (BM) can be detected via magnetic

signaling, offering a non-invasive means to monitor treatment efficacy [104].

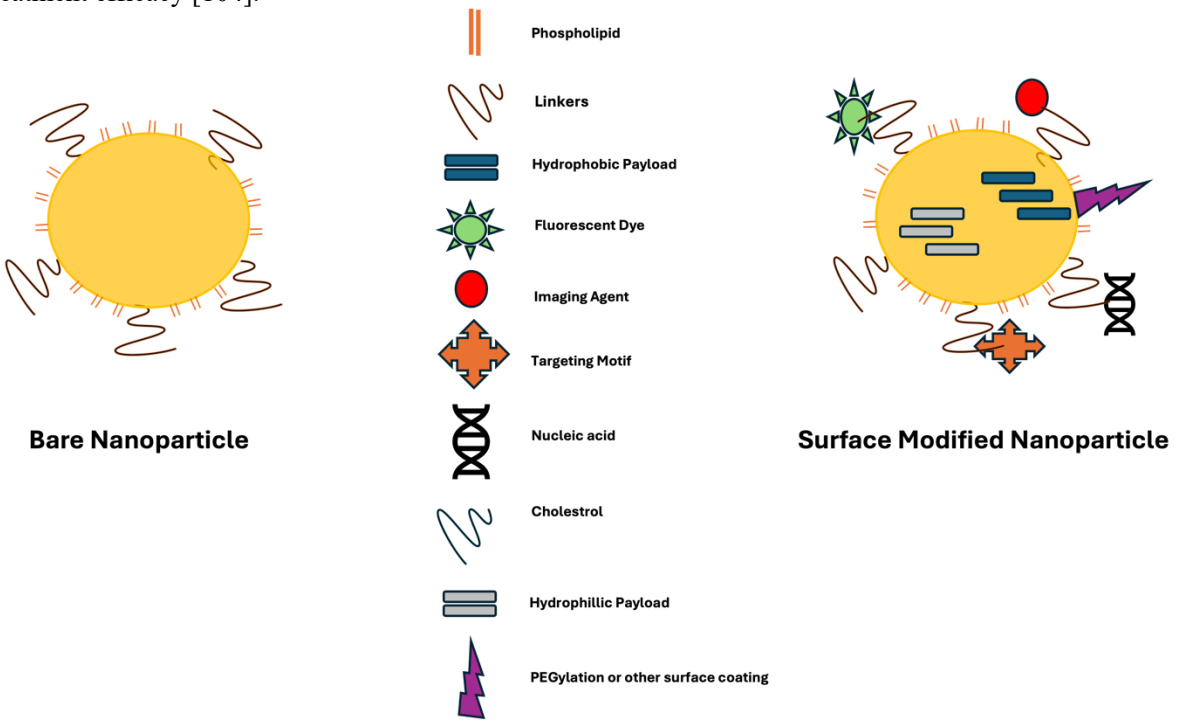

Fig. 5: Surface-Modified Liposomes for Enhanced Theranostic Applications. The figure illustrates the structure of surface-modified liposomes, emphasizing their role in theranostics.

Blood cell development begins in the bone marrow, where cells differentiate into myeloid and lymphoid cells, each playing a critical role in oxygen transport, immune defense, and clotting [105]. However, chromosomal abnormalities, such as gene translocations, can lead to uncontrolled proliferation of cancerous cells. Genetic alterations, like the BCR-ABL or RAS mutations, are known to drive the development of leukemia. At the same time, changes in tumor suppressor genes or microRNAs, such as miR-16, further contribute to disease progression [106]. Leukemia can present as acute or chronic, with acute myeloid leukemia (AML) often affecting children and caused by chromosomal translocations that disrupt normal gene function [107]. Recent advancements in nanomedicine have introduced nano-drugs, such as bimetallic metal-organic frameworks (MOFs), which have shown promise in treating AML by inducing DNA demethylation and RNA hypermethylation in AML blast cells. These epigenetic modifications allow cancer cells to be recognized by T cells, triggering apoptosis and enhancing the efficacy of the treatment [108].

Extracellular vesicles, especially exosomes, are the nanoscale membrane-bound vesicles secreted by almost all types of cells[109]. They serve as excellent platforms for drug delivery due to their intrinsic and biogenic nature to deliver various biological molecules, including but not limited to nucleic acids, proteins, enzymes, growth factors, etc. Their application in leukemia diagnosis and therapy has been intensely investigated. For instance, Qazi et al, employed TKIs (Dasatinib, Ponatinid) loaded exosomes to cure Ph+ leukemia [110].

Outlook

Nanotechnology has shown great potential in revolutionizing drug delivery systems, offering unique physicochemical properties that can significantly improve healthcare, particularly in treating various diseases. At the nanoscale, particles exhibit distinct characteristics that differ from bulk materials, such as a larger surface area, which can lead to enhanced therapeutic effects. This approach has proven particularly beneficial in treating leukemia, a type of blood cancer, with advancements in nanotechnology introducing innovative treatment strategies. Nanoscale drug delivery systems are especially promising due to their low toxicity, reduced immune response, and high efficiency in targeting

cancer cells, particularly in chemotherapy treatments. These systems offer a more precise and effective method for delivering drugs directly to cancer cells, potentially improving therapeutic outcomes while minimizing harm to healthy tissues.

As nanotechnology continues to evolve, it is expected to play an increasingly crucial role in the medical field, offering new avenues for treating leukemia and other diseases. The future of nanotechnology holds great promise in advancing disease treatment, making it an essential aspect of modern medicine.

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Conflict of interest

The authors declare no conflict of interest.

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