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## Advances in targeted therapies and emerging strategies for blood cancer treatment

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Blood cancers, including leukemia, lymphoma, and multiple myeloma, originate within the bone marrow, where the intricate microenvironment presents considerable challenges for conventional therapies such as chemotherapy, immunotherapy, radiotherapy, and hematopoietic stem cell transplantation. These approaches often suffer from poor specificity, low bioavailability, and systemic toxicity, resulting in suboptimal treatment outcomes. In response, significant advances in targeted drug delivery systems, including liposomes, pegylated formulations, and polymeric nanoparticles have been developed to enhance drug stability, prolong circulation time, and improve tumor accumulation while reducing off-target effects. This review provides a comprehensive overview of recent innovations in ligand-directed drug delivery systems for blood cancers. Emphasis is placed on systems functionalized with antibodies, peptides, aptamers, and proteins designed to overcome the barriers of the bone marrow niche and enable selective delivery to malignant cells. Notably, leukemia has emerged as a key model for evaluating these technologies, with promising preclinical and clinical results. However, despite technological progress, critical translational challenges remain. These include biological heterogeneity, variability in target receptor expression, immunogenicity of nanoparticles, and the complexity of scaling multifunctional delivery systems under clinical conditions. Furthermore, current *in vitro* and *in vivo* models fail to accurately recapitulate the bone marrow's dynamic physiology, underscoring the need for improved predictive systems. Future perspectives suggest the integration of personalized nanomedicine approaches that adapt to patient-specific genetic profiles and disease states. Additionally, artificial intelligence (AI) and big data analytics are expected to revolutionize delivery optimization, biomarker discovery, and therapy customization. Ultimately, interdisciplinary collaboration is required to bridge the gap between bench and bedside. By addressing current limitations and embracing innovation, the field moves closer to realizing safe, precise, and effective therapies for patients with hematologic malignancies.

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### 1. Introduction

Blood cancer is a type of cancer caused by mutations in the deoxyribonucleic acid (DNA) complex within blood cells causing abnormalities.<sup>1</sup> Contrary to other cancers that manifest in other organs as solid tumors, blood cancer manifests as liquid tumors in the lymphatic system or bone marrow.<sup>2</sup> Leukemia, lymphoma, and multiple myeloma are the most common forms of blood cancer (Fig. 1), each characterized by distinct symptoms, treatments, and prognoses.<sup>1</sup> Leukemia emanates from the uncontrollable proliferation of mutant pro-

genitors, caused by a hematopoiesis dysfunction, leading to the generation of large quantities of abnormal leukocytes in peripheral blood, bone marrow, and other organs.<sup>3</sup> Moreover, leukemia is further classified into various subtypes depending on the mutant progenitor cell type (*i.e.*, lymphoid or myeloid) and the disease onset (*i.e.*, acute or chronic).<sup>1,3</sup>

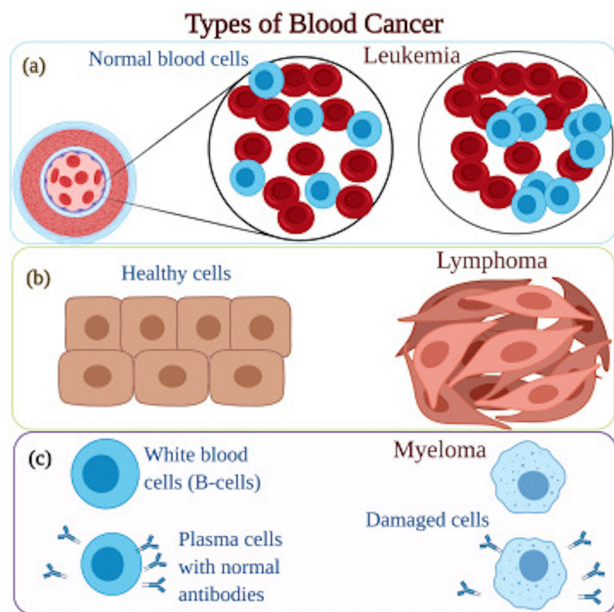
The common subtypes of leukemia include acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myeloid leukemia, and chronic myeloid leukemia.<sup>3</sup> Accordingly, approximately 2.5% of all cancer cases are attributed to leukemia, with more than 470 000 patients diagnosed globally in 2020.<sup>4</sup> Meanwhile, another type of blood cancer, multiple myeloma (MM) is characterized as a hematological malignancy of plasma cells localized in the bone marrow. This form of blood cancer is the second most prevalent hematological malignancy, and is considered incurable, with relapse rates of more than 90%.<sup>5</sup> Various risk factors have been implicated in MM, including age, sex, ethnicity, and family history, with

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**Fig. 1** Graphical depiction of the most common types of blood cancer. Adapted with permission from.<sup>11</sup>

multiple related complications such as bone defects, kidney problems, and anemia.<sup>6</sup> More than 34 000 new cases and 12 000 deaths related to MM were reported in 2022.<sup>1</sup>

Additionally, lymphoma which are heterogenous lymphoid tumors emanating from a malignant transformation of peripheral lymphocytes during differentiation.<sup>7</sup> Malignant lymphomas can be classified as Hodgkin lymphomas (HL), which are relatively rare, or non-Hodgkin lymphomas (NHL), which are the most prevalent. NHL further comprise various subtypes such as diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, and marginal zone lymphoma.<sup>8</sup> In 2022, about 80 910 new cases and 21 000 lymphoma-related deaths were reported.<sup>1</sup>

Current treatments for blood cancer remain unsatisfactory due to off-target effects and drug resistance.<sup>9</sup> Chemotherapy, immunotherapy, radiotherapy, and bone marrow transplantation are the current treatment modalities for blood cancer. However, these modalities present with limited therapeutic efficacy and mostly accompanied by treatment-associated toxicity.<sup>10</sup> Although, various chemotherapeutic drugs are currently in use, their therapeutic efficacy is compromised by dose-related cytotoxicity and lack of tumor cell specificity.<sup>1,11</sup> Moreover, the poor bioavailability and non-specificity of current chemotherapeutics require frequent administration of high dosages of the drugs to achieve the required therapeutic levels in bone marrow or the lymphatic system, thus causing increased adverse effects and patient intolerance.<sup>1,7</sup>

Moreover, it is challenging to achieve adequate therapeutic dosages of anticancer therapeutics at tumor sites within the lymphatic system and bone marrow using conventional systematic administration.<sup>12</sup> Additionally, the bone marrow microenvironment presents with high numbers of progenitor cells which are resistant to chemotherapeutics, and promote disease

relapse.<sup>1,12</sup> As such, there have been extensive efforts made in developing advanced and clinically effective drug delivery systems to deliver anticancer drugs with improved therapeutic efficacy, bioavailability, and minimal cytotoxicity. This review provides a comprehensive synthesis of current and emerging targeted drug delivery strategies for blood cancer, highlighting a critical shift from conventional systemic therapies toward more refined, ligand-directed nanocarrier approaches. The key novel insight lies in its focused examination of how targeted delivery systems—including liposomes, pegylated drugs, and polymeric nanoparticles functionalized with ligands like antibodies, peptides, and aptamers—are designed to overcome the intrinsic barriers of the bone marrow microenvironment, which remains a major site of therapeutic resistance. Furthermore, the review contributes to the field by identifying and addressing several unmet needs and translational challenges including clinical translation, barriers to commercialization, unmet research needs and personalized and adaptive delivery systems. While numerous ligand-targeted nanocarriers have demonstrated promising preclinical efficacy, very few have successfully transitioned into routine clinical practice.<sup>13</sup> This is largely due to the biological complexity of haematological malignancies and the heterogeneity in receptor expression, which limits the universal applicability of single ligand targeting strategies. Also, the logistical and regulatory hurdles associated with manufacturing and scaling advanced delivery systems, particularly polymeric nanoparticles and multifunctional platforms, which require rigorous quality control, reproducibility, and stability under clinical conditions are highlighted. A significant gap identified is the limited understanding of how the dynamic interactions within the bone marrow niche—including immune suppression, hypoxia, and stromal support—affect nanoparticle transport, cellular uptake, and drug release. Furthermore, current models do not adequately simulate the physiological complexity of the human bone marrow, suggesting a need for improved *in vitro* and *in vivo* systems that better predict clinical outcomes. The review calls attention to the need for customizable platforms that adapt to disease stage, patient-specific biomarkers, and resistance mechanisms. There is also a compelling need for theranostic systems that combine diagnostic imaging and therapy for real-time monitoring of treatment response in hematologic cancers. In a nutshell, the review advances the field by synthesizing recent innovations in blood cancer drug delivery while clearly articulating the biological, technological, and translational barriers that must be addressed to realize the full therapeutic potential of these approaches. It serves as a roadmap for researchers and clinicians aiming to bridge the bench-to bedside gap in blood cancer therapy.

## 2. Blood cancer variations and related complications

### 2.1 Leukemia

Leukemia is primarily characterized by the uncontrollable proliferation of mutant progenitors as a result of hematopoiesis



dysfunction, generating a large number of ab-normal leukocytes which accumulate in peripheral blood, bone marrow, and spleen.<sup>3</sup> Essentially, leukemia halts the production of normal blood cells, leading to anemia, coagulation disorders, as well as high risk of infection.<sup>3,14</sup> The current traditional treatment modalities for leukemia include chemotherapy, radiotherapy, and immunotherapy.<sup>3</sup> Unfortunately, these traditional treatments have been shown to be unsatisfactory, particularly for the acute forms in adults, with the 5-year survival rate of acute leukemia often recorded at 30–50%, with a decrease to 17% for acute lymphoblastic leukemia, and 7% for acute myeloid leukemia.<sup>3,15</sup>

The unsatisfactory prognosis is mainly related to treatment-aligned toxicity and disease relapse.<sup>3,15</sup> Essentially, the majority of drugs used to treat leukemia suffer from non-specificity, leading to off-target complications and drug resistance.<sup>3</sup> On the other hand, the prevalence of minimal residual disease (MRD) during therapy often leads to higher chances of relapse in both adults and children, with around 56–100% 5-year relapse rate for MRD-positive patients.<sup>15</sup> As such, targeted therapies offer a promising avenue for attaining deeper first remissions, while preventing relapse.<sup>15</sup>

## 2.2 Multiple myeloma

Multiple myeloma (MM) is a clonal plasma cell neoplasm, characterized by hypercalcemia, renal insufficiency, and bone destruction.<sup>6</sup> It is localized in the bone marrow, and remains incurable with over 90% relapse rates.<sup>5</sup> The complexity of MM, perpetuated by disease heterogeneity, drug resistance, and relapse, continues to affect the treatment outcomes from current therapies.<sup>16</sup> MM is a highly heterogeneous disease, and the intra and inter-patient heterogeneity complicates treatment approaches and fosters the survival of MRD, leading to relapse. The majority of MM patients experience relapse from the emergence of resistant myeloma clones, which evolve to escape the cytotoxic drugs and render current treatments ineffective.<sup>6,16</sup> As such, most patients often experience relapse even after achieving remission. Moreover, the microenvironmental influence by the bone marrow microenvironment plays a significant role in the growth and survival of myeloma cells.<sup>16</sup> Particularly, the bone marrow microenvironment can also stimulate angiogenesis while inhibiting immune responses, resulting in therapies being ineffective and contribute to resistance.<sup>16</sup>

## 2.3 Lymphoma

Lymphomas represent the most prevalent form of hematological malignancies which arise from a malignant transformation of precursor or peripheral lymphocytes when undergoing different states of differentiation.<sup>7</sup> Lymphomas consist of two subtypes; Hodgkin lymphoma, which are rare aggressive malignancies of B-cell origin, and non-Hodgkin lymphomas, which represent the most common subtype of lymphomas.<sup>7,8</sup> The front-line therapy for lymphomas remains chemotherapy, with the use of genotoxic cytostatic drugs, such as alkylating agents, nucleoside analogs, anthracyclines, topoisomerase inhibitors, as well as vinca alkaloids.<sup>7</sup> However, lymphomas

still present a number of challenges in treatment, contributing to the limitations and ineffectiveness of current therapies.<sup>17</sup> Despite advancements in treatment protocols, several key issues remain unresolved, leading to suboptimal outcomes for many patients.<sup>17</sup> One of the most significant complications in lymphoma treatment is the development of resistance to therapies. Lymphoma cells can develop mutations or alter their signalling pathways, enabling them to evade destruction by chemotherapy and radiation.<sup>6,17</sup>

## 3. Current therapeutic approaches to treat blood cancers

Therapies that are currently available for the treatment of blood cancer include chemotherapy, immunotherapy, radiotherapy, as well as hematopoietic stem cell transplantation. These have undergone relatively notable advancements over the years, although still presenting with some clinical limitations such as toxicity and side effects, rapid clearance, as well as interference with bone marrow.<sup>10</sup> The specific limitations from the current therapeutic approaches are discussed in the sections below. Moreover, leukemia, lymphoma, and multiple myeloma possess significant challenges when it comes to treatment, owing to heterogeneity and the complex interplay of genetic and molecular factors.<sup>1,10,18</sup> Accordingly, although the current conventional therapies have been a crucial component of the blood cancer treatment arsenal, providing strategies to control blood cancer severity, alleviate symptoms, and improve the patients' overall quality of life,<sup>3</sup> more advanced drug delivery strategies are still required to improve the efficacy of these therapies.

### 3.1 Chemotherapy

Chemotherapy is one of the earliest interventions of blood cancer, with mustargen first approved in 1949 by the U.S. Food and Drug Administration (FDA) as a chemotherapeutic drug for the treatment of leukemia, lymphosarcoma, and Hodgkin's disease.<sup>3</sup> Subsequently, more chemotherapy drugs have been approved and prescribed as first-line drugs in the treatment of blood cancers. Presented in Table 1 is a summary of the FDA-approved chemotherapeutic drugs for application in blood cancer treatment. The dominance of chemotherapy in blood cancer management has been evident for over 40 years, but the severe adverse effects caused by the indiscriminate toxicity of the drugs to both cancer cells and healthy tissue remains a daunting drawback.<sup>19</sup> In addition, the pathophysiology of bone marrow in blood cancer patients, particularly leukemia, may induce chemoresistance of leukemia cells *via* specific cellular interactions, weakening the cytotoxicity of chemotherapeutic drugs.<sup>3,19</sup> Thus, the development of advanced drug delivery systems for improving targeting ability and limiting drug resistance remains crucial in blood cancer treatment.

### 3.2 Immunotherapy

Over the years, immunotherapy has undoubtedly gained importance in the treatment of blood cancers.<sup>37</sup> Advanced



Table 1 List of common FDA-approved chemotherapeutic drugs for blood cancers

Drug	Mechanisms of action	Type of blood cancer	Delivery route(s)	Challenge(s)	Ref.
Imatinib (Gleevec)	Tyrosine kinase inhibitor	Chronic myeloid leukemia	Oral	Delayed liver toxicity	20–22
Dasatinib (Sprycel)	Tyrosine kinase inhibitor	Chronic myeloid leukemia Acute lymphoblastic leukemia	Oral	Drug resistance/intolerance	20 and 23
Nilotinib (Tasigna)	Tyrosine kinase inhibitor	Chronic myeloid leukemia	Oral	Adverse drug reactions	20 and 24
Bosutinib (Bosulif)	Tyrosine kinase inhibitor	Chronic myeloid leukemia	Oral	Adverse drug reactions	20 and 25
Ponatinib (Iclusig)	Tyrosine kinase inhibitor	Chronic myeloid leukemia Acute lymphoblastic leukemia	Oral	Reduced selectivity	20
Cyclophosphamide (Cytosan)	Alkylating agent	Leukemia Lymphoma	Oral Intravenous	Bladder and gonadal toxicity	26 and 27
Doxorubicin (Adriamycin)	Intercalating agent	Multiple myeloma Leukemia Lymphoma	Intravenous	Drug resistance and cardiotoxicity	26 and 28
Methotrexate	Antimetabolite	Multiple myeloma Leukemia Lymphoma	Oral Subcutaneous Intravenous	Drug resistance	29–31
Fludarabine (Fludara)	Antimetabolite	Chronic lymphocytic leukemia	Oral Intravenous	Non-specificity	32 and 33
Bendamustine (Treanda)	Alkylating agent	Non-Hodgkin lymphoma Chronic lymphocytic lymphoma	Intravenous	Adverse toxicity and opportunistic infections	34 and 35
Daunorubicin (Cerubidine)	Intercalating agent	Acute myeloid leukemia	Intravenous	Adverse drug reactions and non-specificity	36
Cytarabine (Cytosar-U)	DNA/RNA synthesis inhibitor	Acute myeloid leukemia	Intravenous Subcutaneous Intrathecal	Adverse drug reactions	36

immunotherapeutic approaches involving checkpoint inhibitors, cell-based therapies, and vaccines have been used and successfully integrated into standard regimen. These immunotherapies harness the immune system to eradicate blood cancers, and prevent the spread of cancerous cells beyond the primary site.<sup>37</sup> Checkpoint inhibitors are a common immunotherapeutic strategy that blocks the immune suppression pathways used by cancer cells to evade the attack by the cytotoxic T-cells.<sup>38</sup> Particularly, it has been shown that Reed-Sternberg cells of Hodgkin lymphoma make use of the programmed death 1 (PD-1) checkpoint to escape immune detection, and thus anti-PD-1 checkpoint inhibitors have been used in therapy for patients with Hodgkin lymphoma. Also, cytotoxic T-lymphocyte antigen (CTLA-4) checkpoint inhibitors are currently clinically investigated, with promising results.<sup>37,38</sup>

On the other hand, cell-based therapies have shown potential as a promising therapy for blood cancers, and chimeric antigen receptor (CAR) T cells have garnered a massive interest.<sup>37</sup> The first CAR T cell-based therapies were approved in 2017 for the treatment of advanced lymphoma in adults and acute lymphocytic leukemia in children.<sup>38,39</sup> The two FDA-approved cell-based therapies for acute lymphocytic leukemia, tisagenlecleucel and brexucabtagene autoleucel are CD-19 directed, and the former is also approved for treatment of diffuse large B cell non-Hodgkin lymphoma.<sup>39</sup> More antigen receptors, including CD-17, CD-13, and CD-70-specific are being investigated, and significant efforts have been made to improve the design and therapeutic efficacy of CAR T cell-based therapies.<sup>40</sup> Likewise, cell-based vaccines have been devised for multiple myeloma, categorized as either vaccines that use antigen-presenting cells generated *ex vivo* or vaccines that use whole tumor cells.<sup>41</sup> Accordingly, the application of GVAX vaccine combined with lenalidomide in myeloma patients in near complete remission yield a robust immunity with a durable disease control.<sup>42</sup>

### 3.3 Radiotherapy

Radiotherapy is one of the conventional treatment modalities for blood cancers, primarily utilized for localized disease control or as part of the comprehensive conditioning regimen.<sup>10</sup> Essentially, the precise application of radiotherapy is dependent on the type and stage of the blood cancer, and the overall intervention plan.<sup>43</sup> Particularly, in Hodgkin lymphoma, radiotherapy is often utilized to precisely deliver radiation to areas where cancerous cells are concentrated, consequently eradicating tumors, alleviating symptoms, and achieving remission.<sup>44</sup> Importantly, radiotherapy has proven to be more beneficial in cases where the cancer is confined to a limited region of the body. Moreover, radiotherapy may be applied in combination with other interventions for beneficial outcomes. Accordingly, during stem cell transplantation, radiotherapy may be administered to destroy cancerous cells and suppress the immune system to make it receptive to the transplanted stem cells.<sup>43,44</sup> This further minimizes the risk of graft rejection, while increasing the chances of a successful transplant.<sup>44</sup>



### 3.4 Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT), generally known as bone marrow transplantation is an available treatment option for lymphoma, leukemia, and multiple myeloma.<sup>45</sup> HSCT involves intravenous infusion of normal hematopoietic stem cells, responsible for blood cells production, to repair the damaged hematopoiesis and immune functionality.<sup>3</sup> HSCT can be categorized as allogeneic or autologous stem cell transplantation, with the former being the most widely used form involving donors which are usually relatives with matching bone marrow types, meanwhile the latter involves the use of stem cells derived from the patient's own bone marrow.<sup>46</sup> Fundamentally, HSCT presents a vital approach for completely curing certain types of blood cancers, such as leukemia, with reported 5-year survival rates of more than 70% and complete remission.<sup>47</sup> However, there exists some drawbacks from HSCT, including high risk of graft-versus-host disease occurrence, and severe immune disorders from graft rejection.<sup>3</sup>

## 4. Current drug delivery systems for improved blood cancer treatment

Certain drug delivery systems have been devised to enhance the bioavailability of the drugs and the pharmacokinetics thereof, to improve the treatment outcomes in blood cancer.<sup>48</sup> These systems are capable of shielding the drugs from rapid metabolism and elimination by the liver and kidneys, while increasing blood circulation time and biodistribution<sup>48</sup> (Table 2). The currently available drug delivery systems include liposomes, pegylated drug systems, and polymeric nanoparticles, and these are undoubtedly the fastest developed in the translation pipeline.<sup>3</sup> Highlighted in Table 2 are FDA-approved and clinical trial product representatives of these systems.

### 4.1 Liposomes

Liposomal drug delivery systems stand out amongst the other types of current drug delivery systems, owing to their desirable

biological properties and advantageous technological aspects<sup>3</sup> (Table 3 and Fig. 2). Accordingly, various liposomal drug delivery systems for numerous anticancer drugs used in blood cancer intervention, including doxorubicin, vincristine, annamycin, daunorubicin, and cytarabine, have been formulated and demonstrate enhanced *in vivo* pharmacokinetics and therapeutic efficacy.<sup>8,49</sup> One representative system that stands out is the liposomal formulation (CPX-351) co-loaded with daunorubicin and cytarabine approved in 2017.<sup>50</sup> The system yielded a prolonged circulation time of the loaded drugs with improved accumulation in bone marrow, and maximally enhanced synergistic anti-tumor efficiency. Moreover, the liposomal system significantly increased the terminal half-life of daunorubicin (18.5 h) and cytarabine (1–3 h) to 31.5 h and 40.4 h, respectively.<sup>50</sup> Interestingly, the overall survival from the treatment with CPX-351 was found to be 9.6 months, higher than the 6.0 months reported from the standard chemotherapy. The system further alleviated the side effects of the drugs, such as gastrointestinal complications and hair loss.<sup>50</sup>

#### 4.1.1 Mechanisms of action of liposomal drug delivery systems in the treatment of acute myeloid leukemia (AML).

Vyxeos® (CPX-351) is a U.S. FDA-approved liposomal chemotherapy formulation specifically designed for the treatment of high-risk acute myeloid leukemia (AML), including therapy-related AML (t-AML) and AML with myelodysplasia-related changes (AML-MRC). This nanomedicine co-encapsulates two synergistic chemotherapeutic agents, daunorubicin and cytarabine, at a fixed 1:5 molar ratio, an optimal ratio established through preclinical studies to maximize antileukemic efficacy while minimizing systemic toxicity.<sup>51</sup> The liposomal delivery system plays a crucial role in enhancing the pharmacological performance of the drug combination. It ensures prolonged circulation time, targeted accumulation in the bone marrow, where leukemic cells predominantly reside, and controlled, sustained drug release. This improves therapeutic selectivity and reduces exposure to healthy tissues, thereby limiting adverse effects often associated with conventional chemotherapy.

Within the liposome, daunorubicin, an anthracycline antibiotic, intercalates into DNA and inhibits topoisomerase II, resulting in the formation of double-strand DNA breaks and

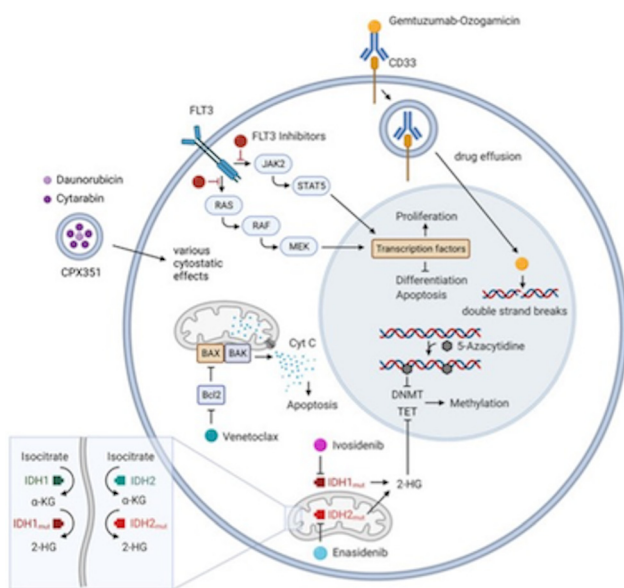
**Table 2** Overview of the FDA-approved and under clinical trial representative drug delivery systems derived from liposomes, pegylated drug systems, and nanoparticles<sup>3</sup>

System	Product name	Drug	Status
Liposome	Vyxeos	Daunorubicin Cytarabine	Approved
Liposome	Marqibo kit	Vincristine	Approved
Liposome	Doxil	Doxorubicin	Phase II
Liposome	DepoCyte	Cytarabine	Phase II
Liposome	BP1001	Grb2 antisense oligonucleotide	Phase II
Liposome	—	Annamycin	Phase II
Liposome	—	Mitoxantrone	Phase I
Pegylated drug	Asparlas	Asparaginase homotetramer	Approved
Pegylated drug	Oncaspar	Pegaspargase	Approved
Pegylated drug	—	Interferon-alpha	Phase III
Nanoparticle	—	Barasertib	Phase I



**Table 3** Comparative overview of targeted drug delivery platforms in blood cancer therapy: efficacy, scalability, limitations, and translational outlook

Delivery strategy	Efficacy	Scalability	Limitations	Translational potential
Liposomes	<b>Moderate to high:</b> enables encapsulation of hydrophilic and hydrophobic drugs; improves drug stability and circulation time	<b>High:</b> scalable <i>via</i> established industrial processes ( <i>e.g.</i> , extrusion, microfluidics)	Prone to leakage and fusion; rapid clearance by reticuloendothelial system (RES); limited specificity	Several FDA-approved formulations ( <i>e.g.</i> , Doxil); proven clinical translation
Polymeric nanoparticles	<b>High:</b> controlled and sustained release; tunable size and surface properties enhance targeting	<b>Moderate:</b> scalable using nanoprecipitation and emulsion methods, but batch consistency is a concern	Potential cytotoxicity from degradation products; complex synthesis	Strong preclinical data; increasing entry into clinical trials
Antibody-mediated systems	<b>Very high:</b> high specificity through antigen recognition; ideal for targeted delivery of cytotoxins ( <i>e.g.</i> , ADCs)	<b>Low to moderate:</b> production is expensive and requires complex biologics manufacturing	Immunogenicity concerns; target antigen heterogeneity; off-target toxicity	Several approved ADCs ( <i>e.g.</i> , Gemtuzumab ozogamicin for AML); growing clinical success

**Fig. 2** Mechanisms of Action of Liposomal drug delivery systems in the Treatment of Acute Myeloid Leukemia (AML). Reprinted with permission from.<sup>53</sup>

subsequent induction of apoptosis (Fig. 2). It also contributes to cellular damage by generating reactive oxygen species (ROS). Cytarabine, on the other hand, is a cytidine analog that undergoes intracellular phosphorylation to its active triphosphate form (Ara-CTP). This active metabolite competes with natural nucleotides during DNA replication, leading to premature chain termination and inhibition of DNA polymerase, thus inducing cell cycle arrest in the S-phase and promoting cell death.<sup>52</sup> The fixed molar ratio of 1 : 5 (daunorubicin to cytarabine) within the liposome allows for a synergistic interaction, significantly enhancing DNA damage and cytotoxicity in leukemic cells compared to traditional 7 + 3 regimens (seven days of cytarabine plus three days of daunorubicin). Overall, Vyxeos® represents a novel paradigm in AML treatment by integrating

optimized drug ratios with targeted, nanocarrier-based delivery to improve efficacy and patient outcomes.

#### 4.2 Pegylated drug systems

The pegylation strategy entails the modification of molecules by polyethylene glycol (PEG) chains to shield the linked drug from recognition by the immune systems while increasing the body-residence time.<sup>54,55</sup> Commonly, therapeutic proteins including the *Escherichia coli*-derived asparaginase (approved for acute lymphoblastic leukemia), are affected by short half-life and adverse allergies which limit their *in vivo* efficacy.<sup>56</sup> However, through pegylation, the elimination half-life of asparaginase could be significantly enhanced, elevating it from 26–30 h to 5.5–7 days, resulting in reduced dosage and administration frequency.<sup>3</sup> The pegylation technique has also been applied to avert the rapid clearance of naïve IFN- $\alpha$  by modification with monomethoxy polyethylene glycol (mPEG) chains, leading to improve *in vivo* activity and pharmacokinetics. Currently, pegylated IFN- $\alpha$  (Pegasys) is in Phase III clinical trial (NCT02736721) for the treatment of chronic myeloid leukemia.<sup>53</sup>

#### 4.3 Polymeric nanoparticles

The therapeutic potency of nanoparticle-based delivery systems in blood cancer treatment is governed by their exclusive advantages, such as improved stability and biocompatibility, high permeability, enhanced retention and precise targeting, and reduced drug toxicity (Fig. 3) (Table 2).<sup>57</sup> Accordingly, in addition to current liposomal and pegylated drug delivery systems, there is a polymeric nanoparticle-based barasertib (AZD2811) delivery system currently in clinical trial (NCT03217838) as a potential blood cancer nanomedicine.<sup>58,59</sup> Essentially, barasertib is an Aurora kinase B inhibitor capable of arresting the cell cycle and inducing chromosome misalignments, leading to cell death.<sup>60</sup> As such, in this formulated nanoparticle delivery system, AZD2811 is encapsulated in poly(D,L-lactide)-poly(ethylene glycol) (PLGA-PEG) nanoparticles using an *in situ* ion pairing technique. The system reportedly exhibited a sustained delivery



## Nanoparticle-based drug delivery - specific advantages

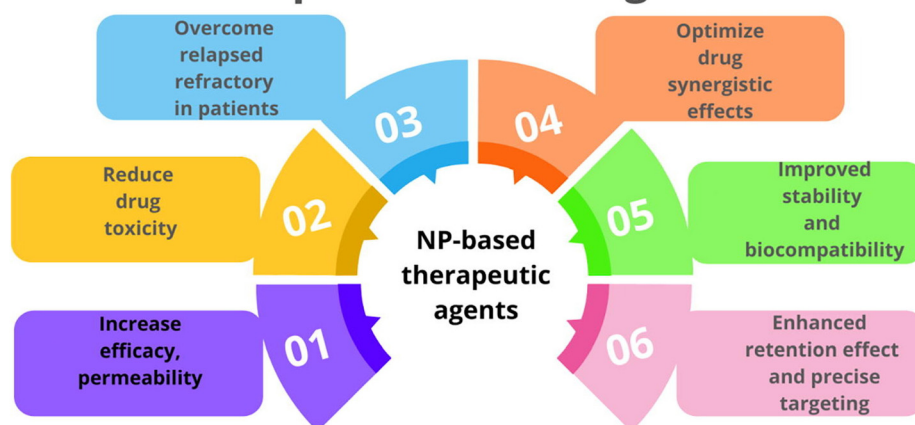


Fig. 3 Outline of specific advantages of nanoparticle-based drug delivery systems for blood cancer treatment. Adapted with permission from,<sup>57</sup> published under a Creative Commons License.

of AZD2811 for more than one week, and 93% tumor regression at 19 days, in preclinical models of acute myeloid leukemia.<sup>58</sup> Currently, more studies exploiting the specific properties of polymeric nanoparticles for drug delivery in cancer treatment are underway, and envisaged to yield positive outcomes.<sup>57</sup>

### 5. New drug delivery systems developed for blood cancer treatment

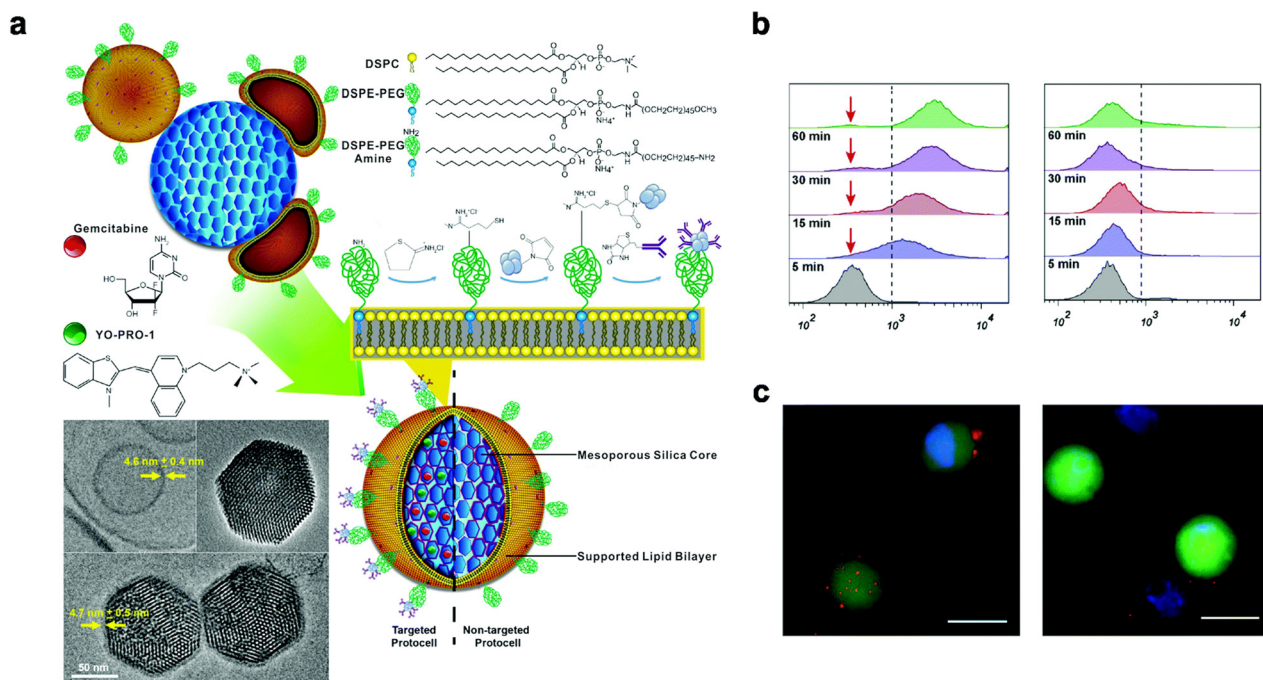
Various novel targeted drug delivery systems are being developed and investigated for blood cancer treatment to enhance

accumulation in the tumor site (*i.e.*, bone marrow and lymphatic system) and improve the efficacy and safety of the drugs.<sup>1</sup> Although, the bone marrow is the most complex system, its microenvironment comprises different cell types that can be targeted either passively or actively.<sup>1</sup> Essentially, passive targeting is achieved through leaky vasculatures, allowing drug accumulation at tumor sites, mean-while active targeting depends on the specific surface biomarkers expressed by blood cancer cells which bind the ligands from the drug delivery system.<sup>61</sup> Accordingly, the latter has been the most widely explored technique for developing targeted drug delivery systems for blood cancer treatment. Amongst these systems

Table 4 Comparative analysis of targeted drug delivery platforms for blood cancer therapy—mechanisms, clinical status, and translational potential

Delivery system	Targeting mechanism	Key components	Clinical status	Advantages	Disadvantages	Ref.
Antibody-modified nanosystems	Monoclonal antibodies recognize and bind specific antigens on cancer cells	Liposomes, polymeric nanoparticles + antibodies ( <i>e.g.</i> , anti-CD33, anti-CD19)	Some in clinical use ( <i>e.g.</i> , gemtuzumab ozogamicin for AML)	High specificity-proven efficacy in hematological cancers-established in clinical oncology	High cost-potential immunogenicity-limited tumor penetration	57
Peptide-mediated targeted systems	Short peptide ligands bind to overexpressed receptors on malignant cells	SLNs, liposomes, dendrimers + targeting peptides ( <i>e.g.</i> , RGD, NGR)	Preclinical to early-phase trials	Easier synthesis and modification-lower immunogenicity-good tissue penetration	Less stable than antibodies-susceptible to enzymatic degradation	1 and 62
Aptamer-mediated targeted systems	DNA/RNA aptamers bind to specific cell surface markers <i>via</i> 3D structures	Polymeric nanoparticles, lipid carriers + aptamers ( <i>e.g.</i> , AS1411)	Mostly preclinical	High binding affinity-chemically synthesized-lower batch-to-batch variation	Susceptible to nuclease degradation-requires chemical stabilization	63
Protein-mediated targeted systems	Use of functional proteins that naturally bind cancer cell receptors or markers	Nanogels, micelles, exosomes + proteins ( <i>e.g.</i> , transferrin, lactoferrin)	Preclinical to exploratory clinical phases	Biocompatible-can leverage natural transport pathways-multifunctional capabilities	Complex purification and formulation-risk of immune response in some cases	64 and 65





**Fig. 4** Graphical illustration of a novel antibody-mediated nanosystem for targeted gemcitabine delivery in leukemia therapy. (a) Schematic representation of mesoporous silica nanoparticles (MSNs) loaded with the chemotherapeutic agent gemcitabine and coated with a lipid bilayer functionalized with anti-epidermal growth factor receptor (EGFR) antibodies for selective targeting of EGFR-overexpressing leukemia cells. (b) Evaluation of the nanosystem's stability in physiological blood-mimicking conditions, demonstrating enhanced circulation potential and resistance to premature drug release. (c) Visualization of the targeted cellular uptake of the gemcitabine-loaded nanosystem by EGFR-positive leukemia cells, confirming effective internalization and receptor-mediated endocytosis.

are antibody-modified, peptide-mediated, aptamer-mediated, and protein-mediated targeting systems<sup>1</sup> (Table 4).

### 5.1 Antibody-modified nanosystems

Antibody-drug conjugates hold great promise in targeted drug delivery, owing to the high specificity effects of antibodies coupled with the antitumor efficacy of the cytotoxic drugs.<sup>66</sup> Consequently, the decoration of drug nanocarriers with antibodies presents an efficient drug delivery approach in blood cancer treatment. A drug delivery system for active targeting of leukemia cells was developed by Durfee *et al.*, (2016), comprising mesoporous silica nanoparticles loaded with gemcitabine and grafted with epidermal growth factor receptor (EGFR) antibody-modified lipid bilayers (Fig. 4).<sup>67</sup> This drug delivery nanosystem exhibited high stability in blood circulation, and a great targetability of leukemia cells *via* antibody-mediated interactions between the cells and the nanocarrier. Moreover, the system showed faster and enhanced internalization into EGFR-positive cells, with only minimal interaction with EGFR-negative cells, demonstrating specificity to targeted cells.<sup>67</sup> These results suggested the promising application of this antibody-mediated nanosystem in targeted therapy for leukemia. Various antigens, including CD19, CD20, CD22, CD33, and CD44 have since been proven to be over-expressed in leukemia cells, serving as potential targets in leukemia treatment.

### 5.2 Peptide-mediated targeted systems

Various studies have investigated the potential application of cell penetrating peptides with the ability to penetrate cellular membranes *via* internalization and enhance the antitumor efficacy of the drugs, for targeted treatment of blood cancers.<sup>68</sup> CPP44 is one of the peptides that has been shown to bind the M160 receptor on the acute myeloid leukemia cell surface, and has been used to formulate CP44-decorated bifunctional dendrimers containing P16INK4a payload (cytotoxic compound), as an anti-acute myeloid leukemia therapeutic system.<sup>69</sup> The system exhibited significantly higher anti-acute myeloid leukemia activity compared to the cytotoxic compound alone.<sup>69</sup> Besides cell penetrating peptides, other normal peptides can also be exploited as targeting moieties in drug delivery carriers in blood cancer. A typical example is the peptide AA13 which targets and binds low density lipoprotein receptor, over-expressed in certain types of leukemia cells.<sup>70</sup>

### 5.3 Aptamer-mediated targeted systems

Various Nucleic acid aptamers present with numerous advantages for application as targeting moieties in anticancer drug delivery systems. The advantages include, but not limited to smaller size, chemical structure stability, target specificity, lack of immunogenicity, and are easily chemically modified.<sup>71</sup> As such, these artificially synthesized DNA/RNA molecules have sparked great interest as new promising targeting



ligands. The As1411 is one of the therapeutic DNA aptamers with specific recognition for the nucleolin protein, currently explored for combination with cytarabine for the treatment of acute myeloid leukemia.<sup>72</sup> Essentially, the combination of anti-cancer drugs with aptamers can improve the targeting ability and minimize the drugs' side effects. Interestingly, Sgc8 which specifically binds protein tyrosine kinase 7 (PTK7) is the first aptamer that could be covalently linked to doxorubicin to achieve targeted cell binding for treatment of leukemia.<sup>73</sup> Moreover, the site-specific release of doxorubicin for targeted killing was observed, due to the hydrazone bond breakage in the acidic tumor microenvironment.<sup>73</sup> In another work, a DNA aptamer targeting CD177 was developed for combination with methotrexate, yielding an aptamer-drug conjugate with significant inhibition of acute myeloid leukemia cell proliferation.<sup>74</sup>

#### 5.4 Protein-mediated targeted systems

Proteins are also potential candidates for application as targeting moieties in targeted drug delivery systems.<sup>3</sup> Particularly, ferritin and transferrin, which are blood proteins containing iron have been investigated for application in protein-mediated targeting delivery systems in blood cancer.<sup>75</sup> Ferritin has been used to develop a ferritin-based trivalent arsenic nanomedicine for targeting overexpressed CD71 receptors of leukemia cells. It was discovered that the ferritin-arsenic nanocomplex resulted in notable anti-leukemia effects in different leukemia types, further exhibiting enhanced antitumor efficacy and minimal side effects compared to pristine arsenic trioxide.<sup>75</sup> Likewise, transferrin has been decorated onto different drug delivery systems to enable specific targeting of highly expressed tumor transferrin receptors (TfR) for selective uptake by cancerous cells in blood cancer treatment.<sup>75</sup> Accordingly, a TfR-targeted liposomal carrier was proposed for delivering Bcl-2-specific antisense oligodeoxyribonucleotide (G3139) for Bcl-2 protein downregulation in leukemia.<sup>75</sup> Additionally, more other proteins, including high-density lipoproteins are under investigations for tumor cell targeting in blood cancer treatment.<sup>3</sup>

## 6. Conclusions and future perspectives

The treatment of blood cancers such as leukemia, lymphoma, and multiple myeloma continues to face substantial challenges, primarily due to the non-specificity, poor bio-availability, and systemic toxicity of conventional therapies. Standard approaches, chemotherapy, radiotherapy, immunotherapy, and stem cell transplantation, have demonstrated limited efficacy in effectively targeting malignant cells within the bone marrow's complex and protective microenvironment. To overcome these barriers, various advanced drug delivery system, including liposomes, pegylated formulations, and polymeric nanoparticles, have been developed to improve drug stability, circulation time, and tumor retention while minimizing off-target effects. These innovations have not only opti-

mized pharmacokinetics and therapeutic index but have also provided a basis for site-specific drug delivery, thereby enhancing clinical outcomes. Notably, some of these systems have already gained regulatory approval, while others are in advanced clinical trial phases, demonstrating real translational potential.

Moreover, the integration of targeting ligands such as antibodies, peptides, aptamers, and proteins into these delivery systems has opened new pathways for precise and personalized therapeutic intervention. These ligand-directed systems enable specific recognition of cell-surface markers overexpressed on malignant cells, promoting receptor-mediated endocytosis and enhanced intracellular drug delivery. Leukemia has emerged as a key model in evaluating these strategies, with preclinical models showing significant improvements in both specificity and therapeutic efficacy.

Despite these promising advances, several translational hurdles remain. Regulatory approval, manufacturing scalability, long-term biocompatibility, and cost-effective production are critical challenges that must be addressed to accelerate the clinical translation of emerging targeted delivery systems. Additionally, variability in patient response, immune clearance of nanoparticles, and heterogeneity of tumor markers further complicate widespread application.

Personalized nanomedicine offers a promising frontier for blood cancer treatment. By tailoring delivery systems based on patient-specific biomarkers, disease subtypes, and genetic profiles, therapies can be customized to maximize effectiveness and reduce adverse effects. The future of blood cancer therapy may increasingly rely on integrating such precision medicine approaches with advanced delivery technologies.

Furthermore, the incorporation of artificial intelligence (AI) and big data analytics holds transformative potential in optimizing targeted drug delivery. AI algorithms can assist in identifying optimal drug-ligand combinations, predicting pharmacokinetics, and simulating tumor-drug interactions. Machine learning models trained on large clinical datasets may guide real-time treatment decisions, improve patient stratification, and support adaptive therapy designs.

In summary, while current progress in targeted drug delivery for blood cancers is promising, continued interdisciplinary research, merging nanotechnology, systems biology, computational science, and clinical oncology, is essential to fully realize the potential of these innovations. A future defined by personalized, AI-driven, and precisely targeted therapies is within reach, offering renewed hope for patients battling hematologic malignancies.

## Author contributions

Samson A. Adeyemi: conceptualization, literature survey, writing original draft, review & editing; Lindokuhle M. Ngema: conceptualization, literature survey, writing original draft, review & editing; Yahya E. Choonara: conceptualization, review, editing, validation, and supervision.



## Conflicts of interest

There are no conflicts to declare.

## Data availability

No primary research results have been included, and no new data were generated as part of this review.

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