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Biomimetic Nanoparticles for the Treatment of Hematologic Malignancies

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Hematologic malignancies are a prevalent group of cancers that originate from abnormal hematopoietic stem cells (HSCs) in the bone marrow. As these cells differentiate to produce all blood cell types, their mutation and/or abnormal differentiation results in a wide range of diseases and complications. Current treatments for hematologic maligancies include chemotherapy and HSC transplants, both of which engender detrimental side effects that the patient must endure, and the end result is still often death. Thus, there exists a dire need for alternative methods to treat hematologic malignancies. Researchers have recently begun to explore the use of biomimetic nanotherapeutic to treat these cancers and mitigate their side effects, with promising results. Biomimetic nanoparticles (NPs) imitate naturally occurring structures such as cells through various techniques to avoid immune recognition and target specific locations in the body; by exploiting cells' expression of "self-recognition" molecules and their unique homing abilities, biomimetic NPs can deliver therapeutic cargo precisely to diseased cells while minimizing risks of toxicity. Herein, several biomimetic nanomedicines are reviewed that are investigated as treatments for hematologic malignancies and offers perspective on the future of this approach as a therapeutic strategy.

1. Introduction

Hematologic malignancies are a collection of cancers including leukemias, lymphomas, and multiple myelomas (MMs) that stem from the abnormal differentiation of hematopoietic stem cells (HSCs) in the bone marrow (**Figure 1** and **2**).[1] HSCs are multipotent cells that differentiate into myeloid or lymphoid progenitor cells that subsequently give rise to all blood cell types in the body (Figure 1). Consequently, when HSC differentiation goes awry, a broad spectrum of disorders and malignancies can develop (Figure 2). Leukemias, lymphomas, and MM affect millions of people every year and constituted 9% of all newly diagnosed cancers in the United States in 2017, with incidence rates actively rising.[2] In 2015, an estimated 1.1 million people were diagnosed with, or in remission from a form of blood cancer.[2] Unfortunately, death is a common outcome for patients with hematologic malignancies, with one of the lowest 5-year survival rates of 28% found in patients over the age of 20 diagnosed with acute myeloid leukemia.[3,4] The biology behind each of these classes of cancer is elaborated in the following paragraphs, and a comparison of these malignancies and their treatments and complications is shown in Figure 2D.

1.1. Lymphomas

Lymphomas are generally categorized into either Hodgkin's lympnoma or non-Hodgkin's lymphoma (NHL). NHL starts in B lymphocytes, white blood cells found in the bone marrow, blood, and lymph tissue. Both Hodgkin's lymphoma and NHL affect B cells, with some subtypes also affecting other white blood cells such as peripheral T-cell lymphoma, a type of NHL where T cells develop abnormally.[5,6] Hodgkin's lymphoma is distinguished by the presence of Hodgkin's and Reed–Sternberg (HRS) cells, which are derived from Epstein–Barr virus-positive B cells with rearranged and mutated *Ig V* genes (Figure 2A).[7] Hodgkin's lymphoma is less common than NHL due to the rarity of HRS cells and it spreads between lymph nodes, whereas NHL may spread more irregularly.[8] NHL has over 60 different subtypes, including Burkitt's lymphoma, a rare but aggressive disease that is most common in children in central Africa, and central nervous system (CNS) lymphoma, a subtype of diffuse large B-cell lymphoma (DLBCL) where cells spread to the brain and spinal cord. About 2% of Americans will develop some form of NHL during their lifetime, with most being over 65 years old.[9]

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DOI: 10.1002/anbr.202000047

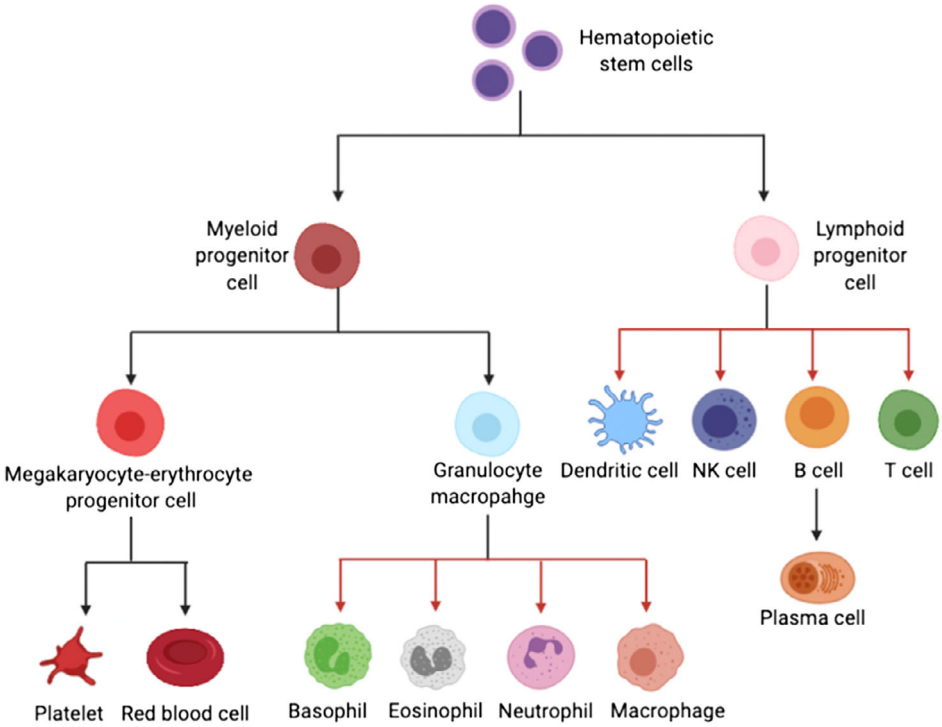


Figure 1. Schematic of healthy HSC differentiation. Abnormal HSC differentiation can lead to numerous hematologic malignancies. Created with BioRender.com.

1.2. Leukemias

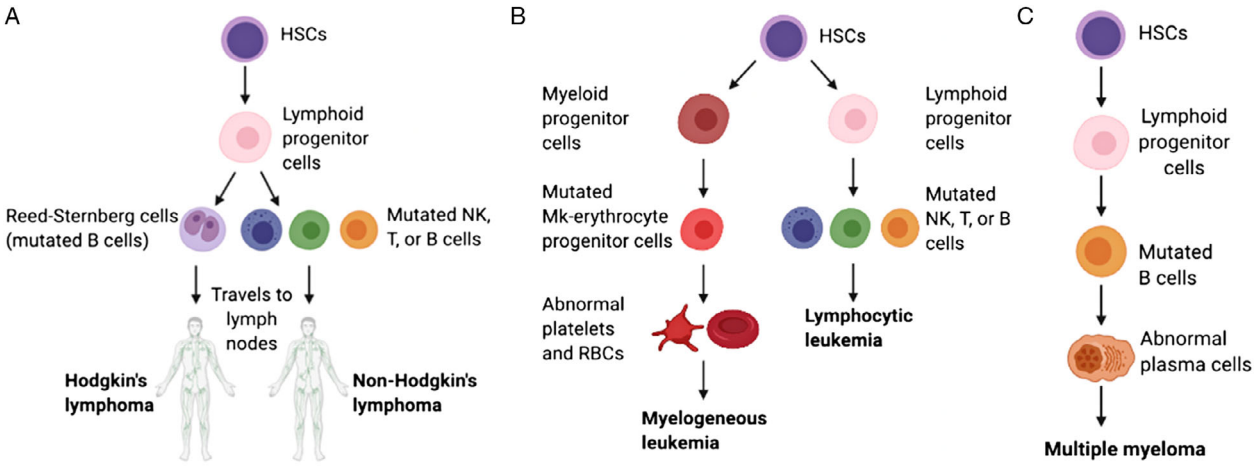
Leukemias are cancers that originate from rapid growth and accumulation of white blood cells, specifically B cells, in the blood, and bone marrow.[10] These diseased cells do not die off and become replaced with new cells, as in the typical cell cycle, so their accumulation eventually overwhelms healthy blood cells.[11] Leukemias are split into designations of acute and chronic as well as lymphocytic or myelogenous depending on the disease progression and the types of bone marrow cells involved. Acute leukemias progress rapidly in creating these immature blood cells, with acute lymphocytic, or lymphoblastic, leukemia (acute lymphoblastic leukemia [ALL]) being the most common leukemia in children. Conversely, chronic leukemias progress more slowly and are more likely to affect adults, with chronic myeloid leukemia (CML) impacting stem cells differentiating into myeloid cells (which are responsible for producing red blood cells [RBCs], platelets, and some types of white blood cells) and chronic lymphocytic leukemia (CLL) affecting B or T white blood cells (Figure 2B). Although lymphoma and leukemia can affect the same types of cells, they differ due to the location of the cancer, with lymphoma being in the lymph nodes, spleen, and other tissues and leukemia beginning in the bone marrow.

1.3. Multiple Myeloma

MM is also a B-cell malignancy that exhibits uncontrolled growth of mutated versions of these cells.[12] Specifically, MM is caused by mutations in damaged B cells' genes including, but not limited to, *KRAS, NRAS, BRAF,* and *FAM46C,* leading to abnormal and destructive growth of mutated plasma cells (Figure 2C).[12] Plasma cells are responsible for making different types of antibodies to help fight off infections and the cancerous plasma cells instead produce multiple identical abnormal antibodies, which give no benefit to the body and result in an impaired immune system. These excess proteins can cause additional problems such as hyperviscosity (thickened blood) and kidney problems.[13] In addition, the mutated plasma cells may accumulate in the bone marrow, damaging the bone itself by their presence in crowding out other cells and by sending signals for the body to break down the bone without plans to replace it, making the bone fragile and weak. MM is not considered curable, but instead treatable, with the 5-year survival rate increasing from 30% to 54% over the past 25 years.[14]

1.4. Complications of Hematologic Malignancies

Because of the HSC origin of these malignancies, it is extremely common to see additional disorders related to the blood or bone develop as a result of such cancers including anemia, thrombocytopenia, renal failure, liver failure, and bone lesions.[12,15–18] These hematologic cancers can also be side effects of other blood and autoimmune diseases, particularly human immunodeficiency virus (HIV). Interestingly, lymphomas, namely DLBCL and Burkitt's lymphoma, are common complications as HIV progresses that significantly contribute to morbidity and mortality in such patients.[19] While research has evolved to offer more treatments for these disorders and their complications, the fact that they are derived from such a vital part of the body makes them an important area to continue to study.



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Malignancy Type	Initial Tissue(s) Involved	Common Treatments [96-103]	Associated Complications [96-99,102-104]	Five-Year Survival Rate [96-97, 100,103]
Lymphoma	• Lymph nodes • Spleen • Liver • Thymus	• Chemotherapy (e.g., cyclophosphamide, cisplatin, gemcitabine) • Immunotherapy • Targeted therapy (monoclonal antibodies, kinase inhibitors, histone deacetylase inhibitors, proteasome inhibitors) • Radiation therapy • Bone marrow transplant	• Low blood cell counts • Hepatitis B virus reactivation • Neuropathy • Tumor lysis syndrome • Increased risk of infection • Excess bleeding	• 87% (Hodgkin Lymphoma) • 72% (NHL)
Leukemia	• Bone marrow • Blood	• Chemotherapy (e.g., doxorubicin, daunorubicin, cytarabine) • Immunotherapy • Targeted therapy (monoclonal antibodies, kinase inhibitors) • Radiation therapy • Bone marrow transplant	• Low blood cell counts • Lymphoma (specifically with CLL) • Kidney disfunction • Increased risk of infection • Excess bleeding	• 69% (ALL) • 28% (AML) • 85% (CLL) • 69% (CML)
Multiple Myeloma	• Bone marrow	• Chemotherapy (e.g., Doxil, cyclophosphamide, melphalan) • Immunotherapy • Targeted therapy (monoclonal antibodies, histone deacetylase inhibitors, proteasome inhibitors, bisphosphonates) • Radiation therapy • Bone marrow transplant • Corticosteroids	• Low blood cell count • Hypercalcemia • Bone-based (lesions, fractures) • Neurological-based (neuropathy, spinal cord compression) • Kidney disfunction • Increased risk of infection • Excess bleeding	• 54%

Figure 2. Schematic of the pathological differentiation of A) lymphoma, B) leukemia, C) MM, and D) a table comparing the three hematologic malignancies. Created with BioRender.com.

2. Current Treatments for Common Hematologic Cancers

Conventional treatments for lymphomas, leukemias, and MM are similar, and are shown in Figure 2D. Briefly, all treatment regimens include combination chemotherapy, with varying success rates in different populations of patients. For example, long-term chemotherapy treatment for younger patients with ALL results in complete remission rates of 85–90% and long-term survival rates of 30–50%.[20] However, most adults who relapse have a bleak prognosis with 3- to 5-year survival rates of less than 10%, due to complications related to drug resistance and treatment intensity.[20] Some types of leukemias are also treated with tyrosine kinase inhibitors,[10] and in some cases, hematopoietic stem-cell transplants (HSCTs).[21] While chemotherapy is also an essential part of the treatment for lymphoma and MM, it has limited efficacy by itself, leading to dual-treatment regimens of radiation therapy and autologous or allogeneic HSCTs, also known as bone marrow transplants (**Figure 3**).[5,6,12] Transplants are the most effective in eradicating residual disease in younger patients with complete remission rates $\geq$80%, however they are associated with higher treatment-related mortality in older patients who cannot always tolerate the high dose, systemically delivered chemotherapy required to prepare a patient for such a transplant.[21]

Despite the many significant advances in the detection and treatment of these hematologic malignancies, they still remain largely incurable.[22] Much of this is due to the fact that patients with hematologic malignancies suffer from compromised immune systems, so the nontargeted nature and unfavorable pharmacokinetics of current chemotherapy and radiation treatments oftentimes rule out these therapeutic options.[22] In addition to the lack of targeting, not all patients are eligible for bone marrow transplants, which prove to be the most effective treatments, as they require high-intensity chemotherapy delivered to the entire body and, in the case of allogeneic transplants

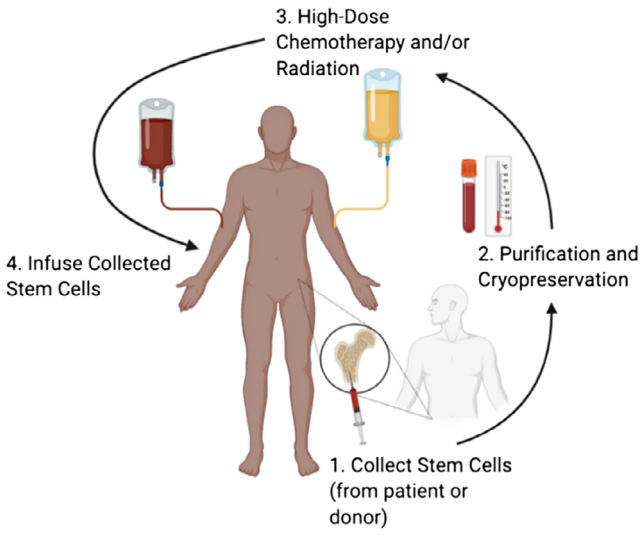

Figure 3. Depiction of the stem-cell transplant process, one of the more effective treatments for hematological malignancies. Created with BioRender.com.

they require finding a human leukocyte antigen (HLA) haplotype-matched donor, which can be difficult.[5,23] Furthermore, many malignancies are inherently drug resistant, or develop resistance over the course of treatment.[22] Recently, the development of bisphosphonate drugs, proteasome inhibitors with immunomodulatory drugs, and monoclonal antibodies are of interest in the treatment of MM and other hematologic disorders.[12] Still, many of these cancers and other blood disorders remain unresponsive to therapies or exhibit only a short-lived response with ultimately fatal consequences.[24] Thus, there is a need for new, multimodal therapies that can overcome drug resistance and reduce toxicity to the rest of the body while improving remission and survival rates of patients affected by hematologic malignancies.

One exciting new approach that may transform patient outcomes involves the application of nanotechnology. Nanotechnology allows for the potential to enhance imaging and diagnostic strategies, as well as to improve therapeutic delivery to specific disease sites in the body.[25–27] Specifically, nanoparticles (NPs), which can be synthesized from gold, polymers, lipids, and other materials, serve as excellent delivery vehicles that can encapsulate drugs, nucleic acids, and other therapeutic agents and protect them from degradation or premature clearance from the body until they reach the disease site.[28–31] NPs' success as therapeutic carriers stems from the ability to fine-tune their physiochemical characteristics, degradation, and cargo release profiles, and cell/tumor targeting and entry.[32]

Compared with freely delivered therapeutic agents, NPs offer numerous advantages. For example, NPs have improved pharmacokinetics and tissue distribution and reduced systemic toxicity.[33] Indeed, Doxil, a liposomal formulation of doxorubicin that is already on the market, has shown promise for these types of technologies to increase circulation time and improve treatment targeting. It is indicated for treatment of MM in combination with bortezomib, and has also been used successfully against other hematologic malignancies.[34] In addition, NPs can be engineered with modified surfaces decorated with antibodies, peptides, and other targeting moieties to facilitate cell-specific binding, although this strategy requires knowledge of cancer-specific biomarkers and must also account for the protein corona that rapidly forms on NPs following their administration to the bloodstream.[26,27] The following section summarizes some of the challenges that NPs must overcome to effectively treat hematologic malignancies. Then, Section 4 highlights recent examples of NP therapeutics that have begun to overcome these challenges.

3. Challenges for NP Therapeutics

For NP therapeutics to effectively treat hematologic malignancies, they must overcome a variety of challenges and biological barriers. In addition to protecting their cargo from premature degradation or release, NPs must also circulate to reach diseased cells, all while evading the body's immune response.[35,36] While NP transport in the blood is well studied, NP transport in lymphatics is less well-known, so future research aimed at advancing NPs for hematologic malignancies should consider and address this knowledge gap. As most NPs designed to treat hematologic malignancies will be administered systemically by intravenous

administration, they must have minimal harmful effects on healthy blood cells. One recent study showed that the material used to make NPs is an important factor to consider, as poly(ethylene glycol)-b-poly(lactic acid) (PEG-PLA) NPs were shown to have fewer detrimental effects on blood components than poly(-ethylene glycol)-b-poly(lactic-co-glycolic) acid (PEG-PLGA) NPs.[37] While both NP formulations left RBCs intact, plasma proteins and platelets experienced harm to their shape and function with the PEG-PLGA NP system. These results indicate that further research is needed to investigate this specific challenge when it comes to NP delivery and that the entire environment needs to be considered, not just a singular major component.

Perhaps the most significant barrier that NP systems face is clearance by the mononuclear phagocyte system (MPS).[38] Upon administration into the blood, NPs are quickly coated by opsonins and other proteins that mark them for phagocytosis by macrophages, resulting in their clearance from the blood and subsequent accumulation in the liver and spleen.[38,39] It has been reported that after just 30 s in human plasma, almost 300 proteins will be bound to a NP's surface,[40] with the specific makeup of the protein corona depending on both protein–NP and protein–protein binding kinetics.[39,41] As a result of the rapidly formed protein complex, the NPs often exhibit new or additional physiochemical identities while masking the originally engineered surface. For example, it has been shown that transferrin-conjugated NPs lose their ability to target cancer cells that overexpress transferrin receptors (TfR) after being placed in a biological environment due to the protein corona that forms and masks the targeting ligands on the NP surface.[42] As the protein corona can render the work that goes into designing actively targeted NPs futile,[39,42–44] some researchers have posed that NPs should be designed in a manner to control the makeup of the protein corona that forms around an NP, as the protein corona will ultimately define the cellular interactions of the NP (**Figure 4**). Notably, biomimetic NPs should exhibit reduced protein corona formation compared with nonbiomimetic NPs due to their unique incorporation of natural cellular structures.

Historically, poly(ethylene glycol) (PEG) has been used as a surface coating to reduce opsonization and extend the circulation half-life of NPs.[44] However, adverse effects of the use of PEG have been observed, including accumulation and formation of vacuoles in renal cells.[45,46] Notably, PEG has been demonstrated to elicit an immune response, as seen by the presence of antibodies against PEG after administration of PEGylated therapeutics.[44] For example, PEGylated asparaginase (PEG-ASNase), a treatment used for ALL, not only resulted in the presence of anti-PEG, but an undetectable level of PEG-ASNase, suggesting that the immunological response to PEG induced rapid clearance of the therapeutic itself.[47] These detrimental effects of an otherwise advantageous polymer emphasize the need for a different approach for NPs to avoid immune recognition, protect their cargo, and reach diseased cells.

4. Biomimetic Strategies and Adaptations

One innovative approach to overcome immune clearance, drug resistance, and systemic toxicity, while improving the efficacy of treatments for hematologic malignancies is to use biomimicry. Biomimetic NPs are NPs that mimic naturally occurring structures with the use of certain biomolecules, membranes, and cells.[48] These biomimetic structures are "camouflaged" from immune recognition and clearance, and some also exhibit targeting capabilities. The most widely utilized approach of biomimicry is membrane wrapping, where phospholipid membranes from specific cells are isolated and extruded with NPs to form a membrane coating around the NP core (**Figure 5**A).[17,49] Membranes derived from RBCs were the first to be used for this application.[49,50] A particular advantage of RBCs is that they express CD47, a marker-of-self, which reduces NP clearance by the immune system.[51] Impressively, it was shown that erythrocyte membrane-camouflaged poly(lactic-*co*-glycolic acid) (PLGA) NPs have improved in vivo circulation, with a blood half-life 23 h longer than that of PEG-coated NPs and increased retention in the blood at both 24 and 48 h postinjection.[52] This discovery that biomimetic NPs exhibit prolonged circulation compared with their PEGylated counterparts was a significant breakthrough in nanomedicine research.[50] This technique is now being explored using membranes derived from a variety of different cell types, which can impart the NPs with unique blood circulation and targeting capabilities.

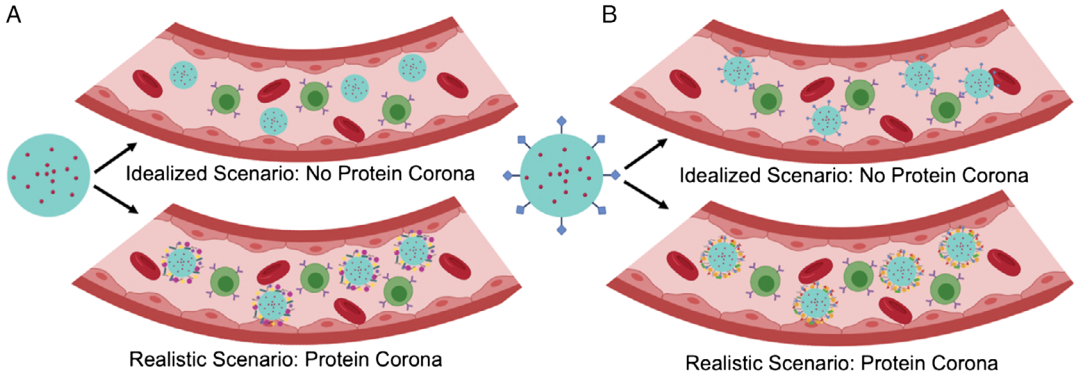

Figure 4. Scheme showing the movement of A) uncoated NPs and B) surface-modified NPs in the blood in the idealized scenario where no blood biomolecules interact with the NPs versus the more realistic scenario wherein blood biomolecules adsorb to the NPs to form a protein corona that may interfere with any designed targeting capabilities. The protein coronas in (A) and (B) are represented slightly differently as uncoated and coated NPs will be decorated by different types of proteins in the blood. Created with BioRender.com.

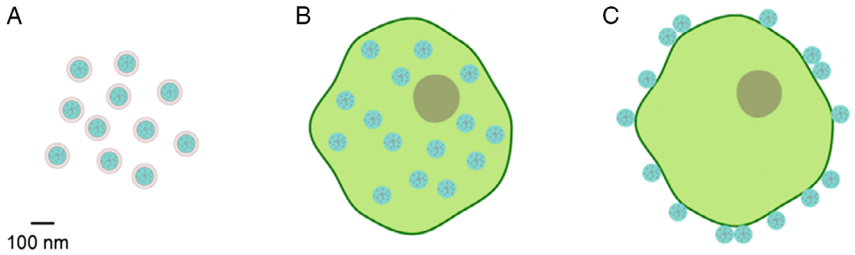

Figure 5. Illustrations of three biomimetic nanomedicine designs with a scale bar of 100 nm shown to represent the approximate diameter of the NPs. A) Membrane-wrapped NPs comprise synthetic cargo-loaded cores that are surrounded by extracted cell membranes. B) Cellular Trojan horses are cells loaded with multiple therapeutic NPs inside their interior. C) Cellular backpacks are cells that have therapeutic NPs tethered to their exterior membrane. Created with BioRender.com.

Beyond membrane wrapping, other biomimetic strategies being explored in nanomedicine include the development of cellular Trojan Horses and cellular backpacks. Whereas membrane-wrapped NPs are disguised by isolated cell membranes, Trojan Horses consist of NPs encapsulated within an intact cell; often monocytes or macrophages are used as Trojan horses because their phagocytic ability allows for easy NP loading and their innate attraction to tumor sites supports effective targeting (Figure 5B).[53,54] Alternatively, while cellular backpacks are not biomimetic in the traditional sense of covering a NP with cellular structures, they do use live cells such as macrophages as carriers by tethering cargo-loaded NPs to their exterior, as shown in Figure 5C. With this strategy, the NPs and the drugs they carry can avoid degradation that might have occurred if they were inside the cell, which also protects the cellular carrier from potential harm due to leaked drug accumulation.[55] While this Review emphasizes the use of entire cells or cell membranes as the source of biomimicry, an additional approach that has been explored with success is the development of NPs that mimic naturally occurring nanostructures such as high-density lipoprotein (HDL). Indeed, HDL-mimetic NPs have been evaluated in vitro and in vivo for the treatment of lymphomas with promise.[56,57] The following subsections will describe how each of the cell-mimetic strategies have been applied to the treatment of hematologic malignancies in preclinical studies.

4.1. Membrane-Wrapped NPs for Management of Hematologic Malignancies and Disease Complications

Membrane-wrapped NPs (Figure 5A) are novel therapeutic delivery vehicles whose synthesis involves three general steps: extracting the membranes, fabricating the NP core, and fusing the membrane around the core.[32] The specifics of each of these fabrication stages can be tailored to the application of the NP system, and the methods are reviewed in detail in previous studies.[32,52,58] The type of cellular membrane used to produce membrane-wrapped NPs is one of the most important criteria to consider in designing a treatment for hematologic malignancies. One option is to use RBC membranes, as RBC membrane-coated NPs have prolonged circulation in the blood, which could enhance cargo delivery.[50] Alternatively, platelets may be used as the membrane source, either to enable direct treatment of the disease or to enable treatment of disease complications such as the presence of antiplatelet antibodies or the formation of blood clots, as described later in this section.[16,17] Finally, membranes derived from cancerous cells can also be used to coat NPs, as this approach supports cancer cell-specific targeting due to "self-recognition molecules" that are present on cancer cell membranes.[32] Recent advances in the use of RBC, platelet, and cancer cell membrane-wrapped NPs to manage hematologic malignancies are discussed in the following paragraphs.

An early example of the use of biomimetic NPs to treat hematologic malignancies involved the development and implementation of doxorubicin-loaded RBC membrane-coated NPs (Dox RBC-NPs) to treat lymphoma.[59] Mice bearing subcutaneous EL4 lymphoma tumors were treated intravenously with either sucrose, free Dox, empty RBC-NPs, or Dox RBC-NPs every other day beginning at day 9 post-tumor implantation, with treatment continuing for 2 weeks. Impressively, the Dox RBC-NPs, dosed at 3 mg/kg, dramatically slowed tumor growth and extended survival compared with mice that received the same amount of free Dox or no treatment. Specifically, median survival in the sucrose group was 24 days, compared with 30 days for free Dox and 47 days for Dox RBC-NPs. These results suggest that the RBC-NPs were able to enhance Dox accumulation in the tumors to improve treatment outcomes. The study also showed that Dox RBC-NPs had a better safety profile than free Dox, demonstrating a further advantage of the biomimetic formulation.[59]

In addition to RBC-NPs, platelet membrane-wrapped NPs (PM-NPs) have also been used to manage hematologic malignancies and their complications. In one example, researchers showed that PM-NPs could be used to simultaneously target and treat MM and one of its treatment complications, thrombus (i.e., blood clot) formation.[16] The proteasome inhibitor bortezomib, which induces programmed cell death of MM cells, is one of the frontline therapies for MM patients, particularly in combination treatment regimens; however, its use in combination with immunomodulatory drugs has been linked with thrombus development.[60] To address this, researchers developed PM-NPs that were loaded with bortezomib and decorated with tissue plasminogen activator (tPA), a drug that catalyzes the conversion of plasminogen to plasmin, an enzyme that mediates clot dissolution.[16] The PM-NPs were also coated with alendronate (Ald) to enhance bone targeting. The overarching hypothesis was that tPA-Ald-PM-NPs could target the delivery of bortezomib to MM cells in the bone marrow environment due to the Ald modification, while also enabling delivery of tPA to sites of thrombus based on the role of platelets in thrombus development (**Figure 6**). Indeed, biodistribution studies in mice showed that

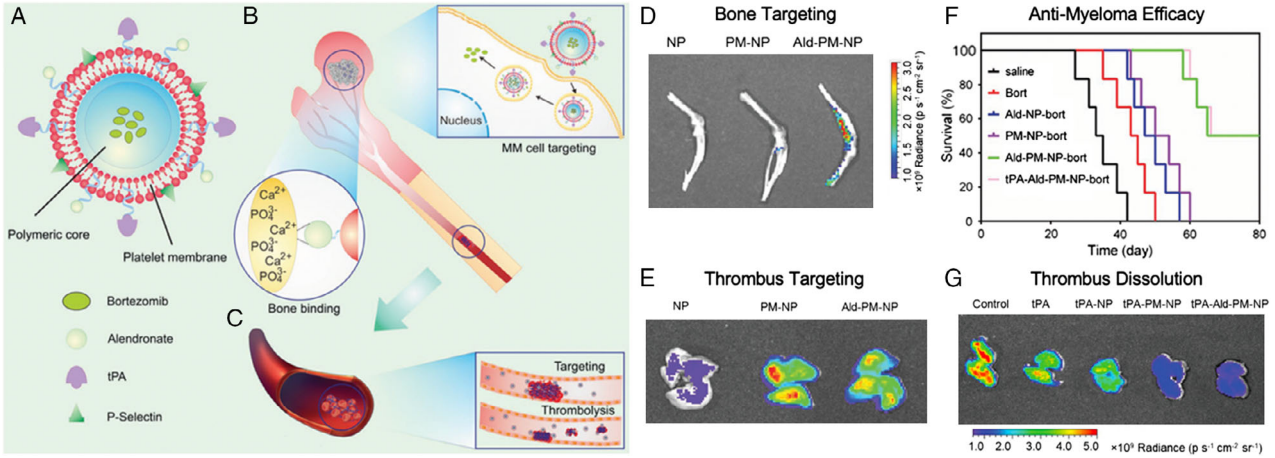

Figure 6. Representative example of the use of platelet membrane-wrapped NPs to combat hematologic malignancies. A) Depiction of the tPA-Ald-PM-NP-bort therapy, which consists of polymer NPs loaded with bortezomib, wrapped with platelet membranes, and modified with alendronate and tPA. B) The intended path of targeting of tPA-Ald-PM-NP-bort to the bone microenvironment and to MM cells via Ald and P-Selectin, respectively. C) Representation of tPA-Ald-PM-NP-bort's targeting and effect on thrombi. D) Ex vivo fluorescence imaging of murine femurs 72 h after intravenous administration of NPs, PM-NPs, and Ald-PM-NPs loaded with Cy5.5 to evaluate the bone-targeting capabilities of each formulation. E) Ex vivo fluorescence imaging of lungs from mice with lung thrombosis that received Cy5.5-loaded NPs, PM-NPs, and Ald-PM-NPs to evaluate the lung thrombus-targeting capabilities of each formulation. F) Survival times of MM-bearing NOD/SCID mice after administration of saline, bort, Ald-NP-bort, PM-NP-bort, Ald-PM-NP-bort, and tPA-Ald-PM-NP-bort. G) Fluorescence imaging of lung thrombi in mice that were administered thromboplastin and Cy5.5-labeled fibrinogen to trigger the clotting cascade. After lung thrombus formation, mice were treated with saline (control), free tPA, tPA-NP, tPA-PM-NP, or tPA-Ald-PM-NP to compare the efficacy each treatment in enhancing thrombus dissolution. The NP formulations that included platelet membranes were most effective. Reproduced with permission.[16] Copyright 2016, Wiley-VCH.

intravenously administered Ald-modified PM-NPs exhibited the highest accumulation in bone marrow (Figure 6D), and that both unmodified and Ald-modified PM-NPs could target thrombi in the lungs (formed by intravenous injection of fibrinogen and thromboplastin) due to the properties of the platelet membrane coating (Figure 6E).[16] Consequently, tPA-Ald-PM-NPs and Ald-PM-NPs containing bortezomib could effectively treat MM to extend animal survival (Figure 6F), and both tPA-PM-NPs and tPA-Ald-PM-NPs were more effective at thrombus dissolution than NPs that did not include platelet membrane coatings (Figure 6G).[16] These results demonstrate the potential of biomimetic NPs as a treatment for hematologic malignancies and their complications.

Another example of the use of PM-NPs for managing the side effects of hematologic malignancies is the development of PM-NPs as an antibody decoy to treat immune thrombocytopenia purpura (ITP).[17,61] ITP can occur in certain hematologic malignancies such as CLL as a consequence of bone marrow transplants, systemic chemotherapy, radiation, or the disease itself. ITP is characterized by the presence of antiplatelet antibodies that bind to healthy platelets and either suppress their proliferation or lead to their splenic filtration and accumulation, decreasing platelet counts in the blood and causing bleeding complications.[62] To alleviate the effects of ITP, researchers explored PM-NPs as a biomimetic therapy.[17] The authors hypothesized that PM-NPs would demonstrate prolonged circulation due to their outward appearance as a platelet and provided a natural substrate for the antiplatelet antibodies, diverting them away from healthy platelets and neutralizing the pathological antibodies. When examined in a murine model of immune thrombocytopenia in which mice received a bolus dose of antiplatelet antibodies, followed by either a blank solution, PM-NPs, or PEG-coated NPs, the PM-NPs successfully preserved 70% of the platelets compared with prechallenge values. By comparison, the PEG-NPs had no effect, showing a 93% decrease in platelet count. This study demonstrates that PM-NPs having the biological identity of platelets can be effective against ITP therapeutically. In the future, researchers should examine whether PM-NP antibody decoys can be used in conjunction with standard cancer treatments to manage hematologic cancers while minimizing the risk of ITP and other side effects that decrease healthy platelet levels.

In addition to facilitating the tumor-specific delivery of common chemotherapeutic drugs, PM-NPs have also been explored as tools that can encapsulate photosensitizers to mediate photodynamic therapy (PDT) and photothermal therapy (PTT). In PTT, materials embedded in tumors absorb externally applied light and convert it into heat to destroy cancer cells, whereas in PDT photosensitizers transfer absorbed light energy to adjacent ground-state tissue oxygen molecules to produce toxic singlet oxygen.[63–65] To enable dual PDT/PTT treatment of Burkitt's lymphoma in mice, one group developed PM-NPs coloaded with $W_{18}O_{49}$, a tungsten-based photosensitizer, and Metformin (Met).[66] The rationale for this design was that the effectiveness of $W_{18}O_{49}$-mediated PDT and PPT has been limited by both rapid clearance and tumor hypoxia, which arises from a lack of oxygen associated with tumor progression and resistance to therapies.[66–69] Met, a hypoglycemic drug traditionally used for diabetes treatment, has been demonstrated to alleviate tumor hypoxia and is thus expected to improve PDT treatment by

reducing oxygen consumption of the tumor.[66] The researchers found that PM-NPs encapsulating both $W_{18}O_{49}$ and Met and exposed to light reduced tumor volume to a greater extent than PM-NPs containing either agent alone or than freely delivered $W_{18}O_{49}$ or Met.[66] Overall, due to the properties of the platelet membranes, these dual-loaded, membrane-wrapped NPs were able to bypass the immune system to enhance PDT/PTT, indicating this is a promising approach to treat lymphoma and potentially other cancers.

Finally, in addition to RBC and platelet membranes, cancer cell-derived membranes can also be utilized to coat cargo-loaded NPs and enhance the treatment of hematologic malignancies. In a recent study, leukemia cell membrane-coated mesoporous silica NPs coloaded with the chemotherapeutic agent daunorubicin and TGFßRII neutralizing antibodies were developed to both directly eliminate ALL cells (via daunorubicin delivery) and overcome chemoresistance arising from leukemia propagating cells (LPCs) in the therapy-induced niche (TI-niche), a "refuge" in the bone marrow microenvironment for cells that remain after treatment.[70] Specifically, the TGFßRII neutralizing antibodies in this platform serve to block interactions between leukemia cells and niche cells to overcome chemoresistance. The researchers termed this nanosystem "DA_{azo}@CMSN" and showed that the leukemic cell membrane coating increased the ALL cell targeting and uptake of the NPs by 91% compared with PEGylated MSNs. Most importantly, compared with various control treatments, the DA_{azo}@CMSN treatment exhibited the greatest inhibition of NALM-6 tumors in nonobese diabetic/severe combined immunodeficiency (NOD/SCID) mice, with median survival of 27 days compared with 18 days for saline-treated mice.[70] These results demonstrate that leukemia cell-mimetic NPs containing proper cargo can precisely target the tumor site, overcome chemoresistance by bypassing TI-niche protection of residual LPCs, and attenuate systemic burden of disease to improve survival rates.

Beyond the aforementioned examples, researchers have also shown that membrane-wrapped NPs can be used to manage liver failure associated with hematologic malignancies[71] or to reduce HIV infectivity,[72] which is important as HIV is associated with the development of malignancies including DLBCL and Burkitt's lymphoma. For example, a recent report showed that CD4 + T-cell membrane-coated NPs that selectively target HIV-infected cells via gp120 could effectively neutralize 125 different HIV-1-pseudotyped viruses while also decreasing the release of HIV-1 particles from the infected cells.[73] Moreover, researchers have shown that NPs can be designed to mimic other structures, such HDL, using a minimum number of biological components (as opposed to entire cell membrane wrappings) to facilitate lymphoma targeting and therapy.[56,57] Such strategies are exciting approaches in this rapidly evolving field. While biomimetic NPs exhibit substantial promise, there are still concerns that remain to be addressed, such as the potential for immunostimulatory reactions that may result from introducing foreign cell-derived material into the body.[32] In addition, the manufacturing scalability of biomimetic membrane-wrapped NPs needs to be addressed.[32] Ultimately, research effort devoted to these topics will enhance scientists' understanding of these systems and increase the likelihood that they will successfully translate to the clinic.

4.2. Cellular Trojan Horses

Unlike membrane-wrapped NPs, which comprise singular NPs that are coated with a cell-derived membrane, cellular Trojan horses consist of single, intact cells that encapsulate multiple NPs to facilitate their delivery to desired sites (Figure 5B).[48] These types of carriers are advantageous due to the fact that there is no loss in structural or functional components of the cell.[74] Cellular Trojan horses have been developed from mesenchymal stem cells (MSCs), T cells, and macrophages, all of which possess natural tumor homing capabilities that improve cargo delivery and therapeutic efficacy.[74–77] For the treatment of hematologic cancers, T-cell-based Trojan horses are the most widely explored, as they migrate to tumors due to tumor-associated chemokines, and they exhibit lower clearance from circulation than other nanomaterials since T cells are part of the immune system and thus not recognized as foreign.[77] In addition, T cells are often favored over macrophages as they are able to be isolated from the patient, expanded in vitro, and transferred back into the patient with relative ease.[77,78]

One of the earliest studies in this field utilized T cells as a Trojan horse to enhance gold NP (AuNP) delivery to large cell lymphoma (LCL).[77] Typically, AuNPs (and other NPs) must passively accumulate in tumors based on the enhanced permeability and retention (EPR) effect, which may yield lower delivery efficiency than desired.[44,77] To improve AuNP delivery, researchers loaded ≈45 nm diameter AuNPs into activated T cells.[77] Importantly, in vitro tests demonstrated T-cell viability and function was unaltered by AuNP internalization, and in vivo studies confirmed that T cells maintained their inherent ability to migrate to tumors. Accordingly, the T-cell Trojan horses increased AuNP delivery to subcutaneous LCL tumors by more than fourfold compared with freely delivered PEGylated AuNPs (**Figure 7**). This enhanced delivery demonstrates the exciting potential of Trojan horse therapeutics for the management of hematologic cancers.

Building on the observation that T cells are effective Trojan horses, researchers have subsequently begun to evaluate their utility as drug carriers for treatment of hematologic cancers. Chemotherapy is often ineffective and poorly tolerated due to the suboptimal pharmacokinetics and low specificity of systemically administered drugs.[6,79] Further, hematological toxicity is commonly observed after combination chemotherapy because drugs fail to distinguish malignant from normal cells.[6] One group hypothesized that Trojan horses loaded with drug-carrying NPs could reduce toxicity by trafficking to tumors, where they would release the drugs as the carriers die due to the effects of the loaded chemotherapy. This hypothesis was supported by in vitro data that showed T cells and Jurkat cells, a human leukemic T lymphoblast cell line, could be loaded with TargetMAG NPs (magnetite NPs coated with doxorubicin [Dox]), resulting in destruction of ≈60% of the total loaded cells after 15 h to yield time-dependent drug release.[80] In vivo experiments were not presented, but the researchers postulated this would be enough time to allow for cell migration to tumor sites prior to drug release. This intriguing concept requires further evaluation to validate the approach. Notably, a separate study demonstrated that RBCs loaded with L-asparaginase (a common

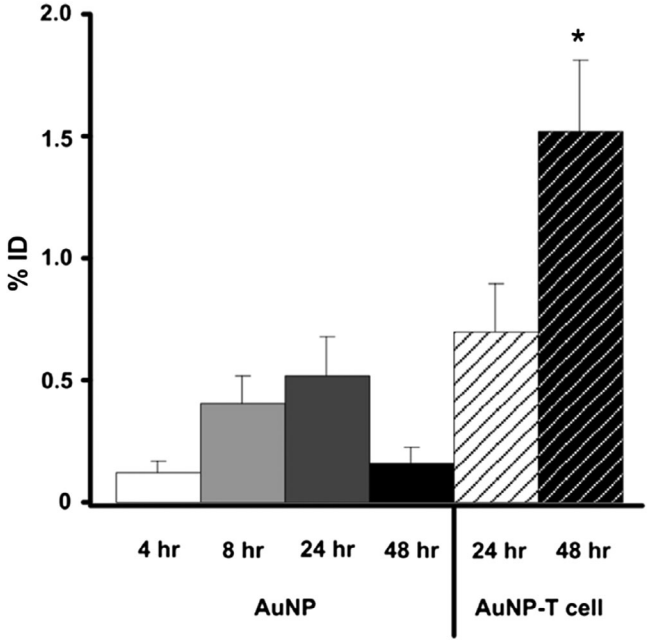

Figure 7. Cellular Trojan horses enhance AuNP delivery to lymphoma tumors. Mice bearing subcutaneous LCL tumors received injections of either PEGylated AuNPs (AuNP) or AuNP-loaded T-cell Trojan horses (AuNP-T cell), then inductively coupled plasma mass spectrometry was used to measure gold content from resected tumors at various time points. This analysis demonstrated that T-cell Trojan horses increase AuNP delivery to LCL tumors by fourfold. %ID = percent injected dose. Reproduced under the terms and conditions of the Creative Commons Attribution license 2.0.[77] Copyright 2011, The Authors, published by Springer Nature.

drug used in the treatment of ALL) could extend the survival of DBA/2 mice bearing L5178Y lymphoma tumors by 44% relative to mice that receive saline injections.[81] While this study did not incorporate NPs, it provides proof-of-principle that NP-loaded cells can enhance treatment outcomes.

It should be noted that cellular Trojan horses containing drug-loaded NPs may be damaged by the cargo they encapsulate, and it is currently unknown whether the death of cellular Trojan horses or the premature leakage of the drugs they carry prior to arriving at the tumor site could lead to detrimental side effects. As an alternative strategy, Trojan horses could be loaded with photothermally active NPs to mediate PTT of hematologic malignancies as has been demonstrated in other forms of cancer.[53,82,83] As most photothermally active NPs are biologically inert, this approach may have less risk of off-target effects or unintended damage of the cellular carrier.

Overall, NP-loaded Trojan horses represent an important development in the field of nanomedicine that may improve the management of hematologic malignancies. With further optimization, Trojan horses may become valuable tools in the fight against cancer.

4.3. Cellular Backpacks

In another method of NP delivery, cellular backpacks, or cellular patches (Figure 5C), have been used to transport NPs to diseased sites by binding the particles to the surface of intact T cells, MSCs, or macrophages.[78,79,84–87] Compared with Trojan horses, these systems have the advantage that the therapeutic agents pose less risk to the carrier cell, while still maintaining the tumor homing abilities of the cell. However, as the cargo carried by these biomimetic vehicles is exposed to the body, it is at risk of immune recognition resulting in clearance and/or degradation.[48] In addition, NPs tethered to the surface of cells may be removed due to the sheer stress encountered in fluid flow. However, as described in one of the examples below, this can be exploited for therapeutic delivery.

The development of cellular backpacks was pioneered in the early 2000s, when it was reported that retroviral particles could be tethered to T cells to facilitate treatment of metastatic melanoma.[78] This approach has subsequently been applied to hematologic malignancies such as lymphoma.[79,84] For example, by encapsulating a potent chemotherapy drug, SN-38, in multilamellar lipid nanocapsules (NCs) and conjugating these NCs to T-cell surfaces (designated SN-38 NC-T), scientists showed that Burkitt's lymphoma treatment could be significantly improved in a murine model.[79] SN-38 NC-T showed the most tumor eradication compared with phosphate buffered saline (PBS), free SN-38, and SN-38 NCs (**Figure 8**). This success was attributed to better biodistribution due to the tumoritropic properties of T cells and the resultant enhanced effect of SN-38, which was unhindered by the usually poor pharmacokinetics of systemically delivered chemotherapy. Impressively, cell-mediated delivery yielded 90-fold greater SN-38 in lymph nodes than free drug administered at 10-fold higher doses.[79] This demonstrates the excellent delivery capabilities of cellular backpacks.

Another exciting demonstration of the potential of cellular backpacks showed that multiple different types of NPs (including liposomes, multilamellar lipid NPs, and lipid-coated polymer NPs) could be attached to the surface of T lymphocytes or HSCs without altering the viability or function of the cells.[84] In a murine model of lymphoma, it was shown that NPs accumulated 176-fold more efficiently at the tumor site when they were attached to the surface of T cells as compared with freely infused NPs.[84] Moreover, T cells conjugated with cytokine-loaded NPs could eradicate melanoma in C57BL/6 mice. This study also evaluated the potential for cellular backpacks to enhance HSC transplants, which are often used to treat and sometimes cure hematological malignancies. Prior to transplantation, HSCs were coated with multilamellar lipid NPs encapsulating the glycogen synthase kinase-3ß inhibitor, TWS119, which can enhance repopulation kinetics of HSCs.[84] Remarkably, the in vivo reconstruction, as quantified through the bioluminescence of GFP + HSCs, was increased 5.7-fold compared with systemic TWS119 injection.[84] The prolonged accumulation, retention, and cargo release without interruption of normal cellular function, and the significant improvement of HSC graft growth makes this an exciting achievement with substantial potential to improve transplant outcomes.

In addition to showing potential as anticancer regimens, cellular backpacks have also demonstrated promise as tools to mitigate complications of hematological malignancies. As noted previously, thrombosis is a common and sometimes fatal complication of hematological malignancies such as MM.[16] Fortunately, researchers have recently demonstrated the ability

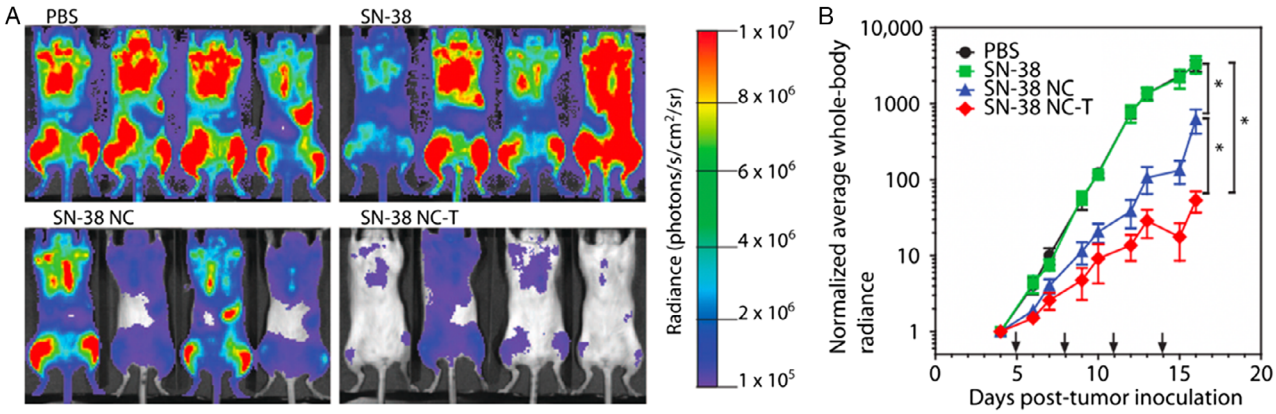

Figure 8. T-cell backpacks carrying SN-38 NCs enable potent lymphoma treatment. Mice injected with Eμ-myc cells to induce B-cell lymphoma/leukemia-like malignancy received treatment with either PBS (control), free SN-38, SN-38 NCs, or SN-38 NC-T cells. A) Bioluminescence images of tumor burden 16 days post-treatment. B) Quantified bioluminescence of the Eμ-myc cells over time (normalized to signal at the start of therapy). Arrows indicate days of treatment. $*p < 0.01$. Reproduced with permission.[79] Copyright 2015, American Association for the Advancement of Science.

to use RBC backpacks for antithrombus therapy.[85] Specifically, crosslinked polymer NPs (cNPs) loaded with heparin, an anticoagulant, were adsorbed to the surface of RBCs, which are an excellent cellular backpack for NP and drug delivery due to their long circulation time and minimal clearance toward the use of cellular backpacks to manage thrombosis and other complications of hematological malignancies.

Ultimately, cellular backpacks require much more investigation before they can be applied to clinical scenarios. Although cellular backpacks do not disguise their NP cargo from the immune system as other biomimetic strategies do, they do maintain the host cell's normal biodistribution and function, which enables enhanced delivery. Importantly, as cellular backpacks do not phagocytose the NPs they are carrying due to the attachment chemistry utilized, they may be less susceptible to damage than cellular Trojan horses, notably in the concern of premature drug release inside the carrier cells; this remains to be validated in further studies. Overall, cellular backpacks are promising therapeutics that are worthy of further evaluation against hematological cancers.

5. Conclusion: Challenges Facing Development and Considerations of Future Directions

Moving forward, there are still several challenges and barriers that must be further researched and overcome for biomimetic NPs to be used clinically against hematologic malignancies. For example, researchers have reported extravascular barriers to passive targeting where NPs face difficulty in extravasation, as passive tumor accumulation depends highly on permeability and blood flow rate.[88] It is also not uncommon for NPs to be unable to penetrate deeply into the tumor microenvironment, which reduces the efficacy of treatment.[88] Further complicating clinical translation, there are numerous biological disparities between animal models and human patients. Some research suggests that the EPR effect is prominent in animals, but much less evident in humans, making it an unreliable mechanism for NP delivery, accumulation, and retention.[89,90] Recently, new research has postulated that NPs primarily enter tumors through transendothelial transport,[91] so future work must evaluate how the biological identity of membrane-wrapped NPs, Trojan horses, and cellular backpacks changes as they go through this process. Notably, Stephan et al. began to explore this, as they showed that T-cell backpacks carrying 100 multilammelar lipid NPs per cell retained 83% (± 3%) of their cargo after crossing endothelial barriers in in vitro migration assays.[84] Interestingly, PLGA NPs were not retained by transmigrating T cells as well as liposomes and lipid-coated PLGA particles,[84] suggesting that the material used in preparing cellular backpacks is an important consideration for retaining biological identity after extravasation.

Even if the EPR effect and transendothelial transport are present in humans, there is high variability among patients with respect to their disease, tumor, and physiology, which will make the development of a single universal therapeutic difficult, if not impossible, to achieve. Moreover, clinical translation of nanotherapeutics requires scalability of the NPs and approval through government regulations, which is a difficult and lengthy process due to the gaps and novelty of nanomedicine, overall making the transition from bench to bedside a challenging task.[92] With respect to biomimetic NPs, the regulation and batch-to-batch reproducibility of these materials, which include human-derived cell components, will need to be addressed.

Despite these challenges, nanomedicine holds promise for the treatment of numerous malignancies. One important future direction for biomimetic NPs is the delivery of RNA or DNA for gene regulation. While nucleic acid-mediated gene regulation is a promising strategy for the treatment of a number of diseases, these molecules are unstable in the bloodstream, which has limited their clinical applications.[93] Future investigations should include developing biomimetic RNA- or DNA-loaded NPs for the treatment of hematologic malignancies.

Biomimetic NPs are also attractive delivery agents for the future of cancer vaccines and immunotherapy. By being able to modify the surfaces, as well as carry and deliver different

cargos inside, NPs offer a wide range of formulations and uses as vaccines. For example, Ma et al. formulated biomimetic NPs coated with membranes isolated from the fusion of dendritic cells and cancer cells.[94] These antigen-presenting NPs, which could also encapsulate immune adjuvants, were able to penetrate immune organs and activate cytotoxic T cells, which allowed them to work as both a preventative measure and as a therapeutic for established tumors. While this study was not conducted using blood cancer models, it shows the potential of biomimetic NPs for cancer vaccines, which is one of the directions that nanomedicine is moving toward in the future.

With an estimated 180 000 people expected to be diagnosed with leukemia, lymphoma, or myeloma in 2020, and a third of them expected to die from their disease, the need for new treatment options is clear.[95] Biomimetic NPs are a remarkable technology that, with further research and continued technological advances, could revolutionize the way we treat these hematologic malignancies in the future.

Acknowledgements

Funding was provided by the National Science Foundation under award number DMR-1752009 and by the University City Science Center under award number QED 1903. E.H.P. received support from the University of Delaware Summer Scholars Program.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

biomimicry, blood, cancer, nanomedicines, stem cells

Received: October 13, 2020
Revised: December 4, 2020
Published online:

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