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Review article

Therapeutics incorporating blood constituents

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ABSTRACT

Blood deficiency and dysfunctionality can result in adverse events, which can primarily be treated by transfusion of blood or the re-introduction of properly functioning sub-components. Blood constituents can be engineered on the sub-cellular (i.e., DNA recombinant technology) and cellular level (i.e., cellular hitchhiking for drug delivery) for supplementing and enhancing therapeutic efficacy, in addition to rectifying dysfunctioning mechanisms (i.e., clotting). Herein, we report the progress of blood-based therapeutics, with an emphasis on recent applications of blood transfusion, blood cell-based therapies and biomimetic carriers. Clinically translated technologies and commercial products of blood-based therapeutics are subsequently highlighted and perspectives on challenges and future prospects are discussed.

Statement of significance

Blood-based therapeutics is a burgeoning field and has advanced considerably in recent years. Blood and its constituents, with and without modification (i.e., combinatorial), have been utilized in a broad spectrum of pre-clinical and clinically-translated treatments. This review article summarizes the most up-to-date progress of blood-based therapeutics in the following contexts: synthetic blood substitutes, acellular/non-recombinant therapies, cell-based therapies, and therapeutic sub-components. The article subsequently discusses clinically-translated technologies and future prospects thereof.

Contents

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Introduction

Bloodletting likely originated in ancient Egypt, as it was thought the act removed the illness [1]. Leeches have been used to help facilitate the bloodletting process [2]. In regards to blood transfusion, the first occurred around 1630 and the first successful blood transfusion was accomplished in 1665 in England. Blood transfusions are helpful for replacing needed red blood cells (RBC)s, for delivering anti-thrombotic clotting therapeutics and neutralizing antibodies. Before the 1970s, risks of transfusion involved infectious diseases [3] such as hepatitis B/C or HIV, and risks for cancer [4] (i.e., non-Hodgkin lymphoma (NHL) [5] and leukemia). With today's technology, the probability of having issues with blood transfusions involving blood typing, and Rh compatibility is highly unlikely when using appropriate measures. For example, the probability of contracting HIV is approximately 1 in 1 million [6]. Today, the following are generally screened for protecting transfusion recipients: HIV, hepatitis B, hepatitis C, human T-lymphotropic virus, syphilis, ABO/RhD, and other antibodies (i.e., against cytomegalovirus (CMV), hemoglobin (Hb)s, malaria).

In addition to replacing or supplementing blood and its components due to blood deficiencies and dysfunctionality, blood can be manipulated to exert supplemental therapeutic action or used to aid medical treatments, which are unrelated to natural blood-related mechanisms. This review will discuss: (1) blood-based therapeutics which serve as oxygen delivery vectors; (2) blood constituents which have an intrinsic therapeutic effect itself (i.e., clotting or immune supplementing (non-cell-based)); (3) cellular-based (including subcellular-based) entities within the blood which serve as carriers for endogenous (therapeutics naturally found within blood) or exogenous cargo (not naturally found within blood); (4) biomimetic-based technologies which incorporate blood subcomponents to enhance an endogenous or exogenous cargo's delivery efficiency by avoiding clearance mechanisms or enhancing localization; (5) clinically translated technologies or those which are in the midst of clinical trials; (6) lastly, we will discuss barriers to clinically translating blood-based technologies and potential future directions.

Due to length limitations, an in depth background discussion of drug delivery is not feasible. We therefore recommend referring to the following nanoparticle- and microparticle-based drug delivery articles: [7–15].

1. Synthetic blood substitutes

1.1. Current status of natural blood product transfusion

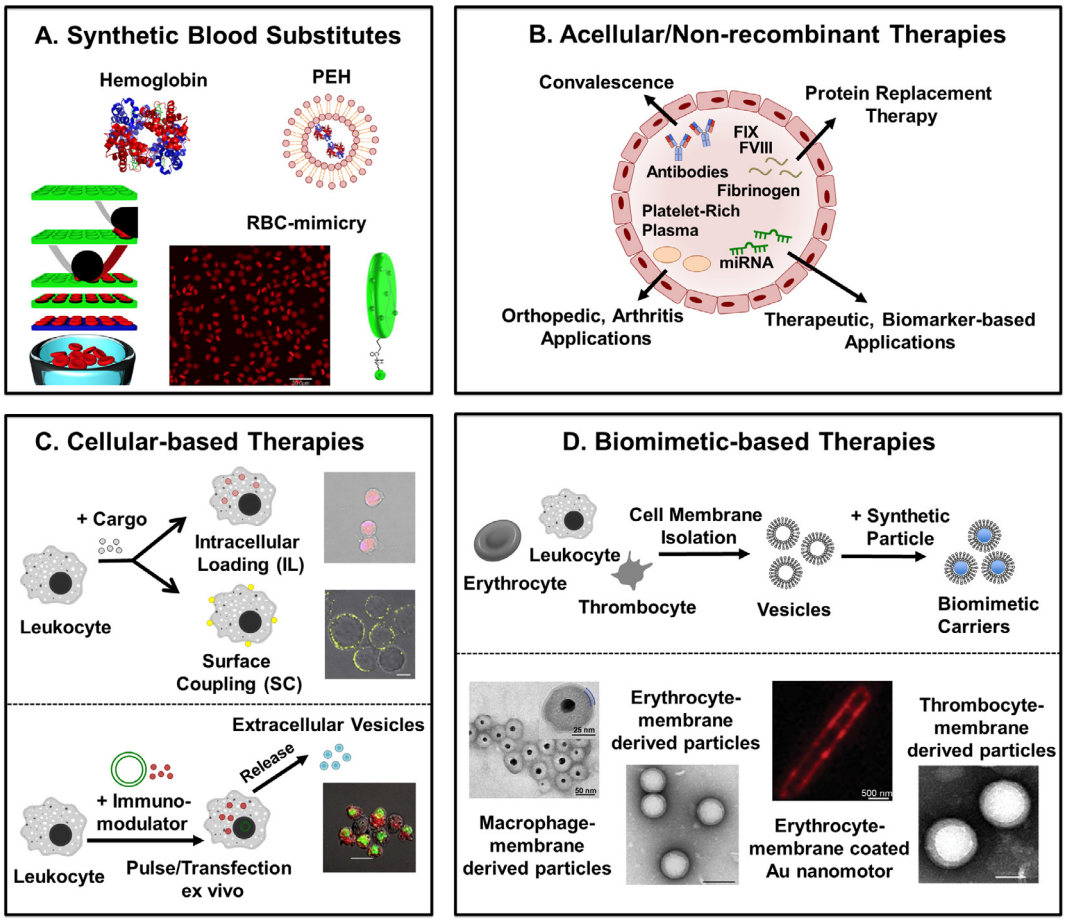
Whole blood transfusions have substantial demand in surgical procedures and in clinical use for treating traumatic injuries, anemia, and bleeding disorders. Prior to blood transfusions, rigorous screening for personal/donor history, serological testing and blood treatments are often required to minimize the risk of disease transmission. Although current blood treatments including pathogen reduction (i.e. RBC irradiation) and leukoreduction techniques have demonstrated a reduction in the donor-recipient infection rate, the efficacy and safety of certain treated blood products can still be compromised. For instance, the treatment of blood plasma and platelet products with amotosalen (which is activated via ultraviolet A light) has successfully resulted in reducing a broad spectrum of threatening pathogens and has also received U.S. FDA approval. However, the safety and efficacy of RBC and whole blood products, receiving S-303 (nucleic acid intercalator)/glutathione and riboflavin/UVB treatments have not been approved and are currently being examined in clinical trials [16]. Similarly, although the leukoreduction treatment can minimize the infection rates by removing pathogens in concentrated white blood cells (WBC)s, this treatment is often reserved for high-risk blood products such as platelet concentrate pooled from multiple donors because of its high cost and statistically marginal benefits [17].

Other issues involve transfusion-related acute lung injury (TRALI) [18] and short shelf life. In regards to short shelf life, RBCs can be stored for 20–40 days under refrigerated conditions and 3–5 days for platelets at room temperature [19]. Such limited shelf life poses difficulties for blood transportation services, particularly to remote areas. Current freeze-dried processes with an addition of stabilizers, e.g. trehalose and other effective cryoprotectants, can partially preserve RBC bioactivity and reduce RBC storage lesions but the RBC functional rate after recovery processes have not yet reached desirable levels [20–23]. Similarly, efforts to extend platelet shelf life such as using additives (i.e., glucose and acetate), utilizing homeostasis-enhancing containers or varying agitation rates during storage are not yet sufficient to suppress platelet storage lesions [24]. Ongoing efforts are seeking for technologies that can minimize issues of cross infection and increase long-term storage of natural blood products.

We recommend referring to the following review for further information regarding synthetic blood substitutes outside the scope of this review article: [25].

1.2. Synthetic products for oxygen delivery

While attempts to resolve the issues associated with natural blood products are ongoing, a parallel interest in developing blood substitutes has rapidly emerged in the past few decades. Unlike natural blood products, blood substitutes pose minimized risks for infection, do not require compatibility or blood type testing and thus would be potentially helpful for any patient. Among blood



Scheme 1. Blood-based therapeutics. (A) Synthetic blood substitutes for oxygen delivery, formulated in the forms of free hemoglobin, polymersome-encapsulated hemoglobin (PEH) and hemoglobin-loaded microgel (RBC-mimicry, prepared by PRINT) [39,40]; (B) Acellular and non-recombinant constituents found within blood used for therapeutics; (C) Living cells delivering therapeutic cargo by intracellular loading (IL) or surface coupling (SC) methods and modulated living cells bearing supplemental therapeutic actions [87,91,215]; and (D) Blood-subcomponents hybridized with other natural or synthetic materials for therapeutic delivery [74,81,163,166,178,181]. Adapted with permission from [39] (Copyright 2017 American Chemical Society); Adapted [40] (Copyright 2011 National Academy of Sciences); Adapted [91] (Copyright 2010 Nature Publishing Group).

components, synthetic plasma and synthetic RBC analogs (Scheme 1A) have made great progress and a few of these formulations have already received clinical approvals from regulatory bodies. The most studied designs of synthetic RBCs are hemoglobin-based oxygen carriers. They facilitate oxygen transport by relying on hemoglobin, which is an oxygen unit carrier for natural RBCs.

Hemoglobin-based carriers were first developed in the form of a free suspension, which is an unpurified mixture of hemoglobin (Hb) monomers and dimers derived from outdated or expired human or mammalian erythrocytes [26]. Due to the instability and natural intrinsic toxicity associated with the erythrocyte sources, many subjects treated with free Hb were reported to experience hypertension and acute renal failure [27,28]. To prevent Hbs' dissociation and increase its efficacy and safety, Hb was later reformulated into a tetrameric conformation, with chemical modifications or microencapsulation (i.e., with liposomes, polymers). Although various formulations of synthetic Hb-based carriers (synthetic RBCs) have been previously approved for clinical use, many were discontinued due to increased risks for death, myocardial infarctions and other serious adverse events without significant clinical benefit [29]. A number of cases of mortality were reported in clinical trials for blood replacement with HemAssist (a diaspirin cross-linked hemoglobin) in severe hemorrhagic shock patients [30] and Polyheme® (glutaraldehyde-polymerized hemoglobin) in trauma patients [31]. Currently, although there are no U.S. FDA-approved RBC substitute products for human applications available in the United States, a few formulations are presently used for anemia treatment in animals in the U.S. and Europe (Oxyglobin®) [32] and patients in South Africa (Hemopure®) [33].

Polymersome-encapsulated hemoglobin (PEH) is a recent formulation of synthetic RBCs. Due to self-assembly capabilities, this formulation facilitates a scaled-up manufacturing process. Although PEH's lifetime is not yet comparable to natural RBC's, PEH can be used for emergent oxygen delivery in cases of refractory hypoxemia for short-term improvements in tissue oxygenation [34]. Due to length constraints, we recommend the following articles of polymersomes, the majority of which is hemoglobin-related: [35–37].

Because the physicochemical properties of RBCs, particularly size, shape, and deformability, significantly influence their unique long circulation times, recent applications of integrating oxygen carrier units within RBC-mimicking particles have emerged [38]. Recent work from the DeSimone research group demonstrates the synthesis of microgel particles using particle replication in non-wetting templates (PRINT) technique. These RBC-mimicking particles have similar size, shape, deformability and oxygen transportability, comparable to natural RBCs (Scheme 1A) [39,40]. To date, there is still a need to improve the efficacy and safety for both natural blood products and blood substitutes. Issues of cross infection and long-term storage of natural blood products, insufficient circulation times and toxicity of synthetic RBCs must be addressed.

2. Acellular/Non-recombinant therapies

By way of background, in a healthy state, ~45% of whole blood generally constitutes erythrocytes, leukocytes (<1%), and thrombocytes (<1%); and ~55% of whole blood is plasma. Plasma, in a healthy state, is generally ~92% H_2O, 7% proteins (i.e., immunoglobulins, clotting factors, albumin (~55% of protein within blood)), and 1% of plasma contains salts, carbohydrates, lipids, hormones, enzymatic cofactors, etc.

The following section encompasses genetically unmodified therapeutics within whole blood (Scheme 1B), excluding living cells (refer to the **Cellular-based therapies** section). This section also includes RNA which is translated into protein or proteins which are mass produced via DNA recombinant technology; the overall protein sequences remain unmodified (exceptions may include histidine tags for purification), however.

2.1. Immune applications – convalescent blood products

Convalescence [41] is the practice of passively administering antibodies using whole blood or plasma from patients who have recovered from an infection or disease of interest. Convalescence was generally used when 1) the technology to mass produce the therapeutic constituent within bacteria or yeast via DNA recombinant methods or 2) when the technology to reliably isolate and purify therapeutic components within blood did not exist. For example, in the 1930s, measles and yellow fever were treated in such a manner [42]. In more technologically advanced times, when convalescence is used, it is because the outbreak is emergent and a therapeutic is needed immediately or the target antigen is unknown. For example, during the Ebola outbreak which began in 2014, whole blood and plasma convalescence was used [43]. The ability to have a therapeutic in such an expedited fashion, although not without its own risks, can be invaluable during needful times.

2.2. Blood clotting applications

Blood clotting factors [44] found within plasma are as follows: fibrinogen (factor I) or von Willebrand Factor (VWF), prothrombin (factor II), Ca^{2+} (Factor IV), proaccelerin (factor V), proconvertin (factor VII), antihemophilic factor (factor VIII; lack thereof is hemophilia A), plasma thromboplastin component (factor IX; lack thereof is hemophilia B), Stuart-Prower factor (factor X), plasma thromboplastin antecedent (factor XI), Hageman factor (factor XII), and the fibrin stabilizing factor (factor XIII). Protein replacement therapy for hemophilia has strong roots since 1984 [45]. Methods for exploring subcutaneous routes delivering factors VIII and IX to treat Hemophilia A and B have been reported by many research groups; for example, bolus injections, implanted pumps and hydrogel depots were being used to provide sustained release of these factors in tissues in 1998 [46]. Issues in regards to the formation of inhibitory antibodies against protein replacement therapies have been fully recognized within the past decade [47]. By 2010, methods to help alleviate such issues were being addressed; bioencapsulated coagulation factor IX was delivered to mice for treating hemophilia B, which helped prevent the formation of inhibitory antibodies up to 100-fold against the protein replacement, which helped alleviate risks for fatal anaphylactic reactions in a murine model [48].

To date there are only four gene therapies approved for use by the China FDA, the European Union, and the U.S. FDA. Great efforts for delivering nucleic acids (short interfering RNA, messenger RNA (mRNA), plasmid DNA, etc.) have been taken to treat and potentially cure diseases, particularly for monogenic diseases (i.e., hemophilia) [49,50]. For example, a lipid-nanoparticle-based system delivered factor IX mRNA for a protein replacement therapy using a factor IX-deficient mouse model to demonstrate safety and efficacy [51].

2.3. Blood-derived miRNA biomarker applications

Although the sequence of micro RNA (miRNA) itself could be genetically unmodified and still have therapeutic value, miRNA is generally mass-produced using DNA recombinant techniques. miRNAs can be derived from the blood or blood-derived microvesicles and have been found to have a variety of therapeutic applications, and in some cases biomarker-based applications (Scheme 1B; i.e., cardiovascular, renal, cancer [52–55]).

2.4. Therapeutic extraction process of blood constituents

Therapeutic phlebotomy may be indicated for hemochromatosis, polycythemia, and porphyries. Apheresis can be therapeutically performed for plasma (plasmapheresis) due to auto-immune complications (i.e., plasma exchange), or for leukocytes (leukapheresis) which is at times indicated for patients with acute myeloid leukemia which causes abnormally high levels of white blood cells. Of note, there are also other indications for extracting entities within the blood which are pathogenic. For example, although outside the scope of this review article, the inactivation of bacteria, viruses, or contaminating leukocytes from a plasma transfusion may provide therapeutic benefits.

2.5. Orthopedic and arthritis applications

At times, orthopedic injuries may require the promotion of angiogenesis, collagen synthesis, and cell proliferation, which can be accomplished using platelet-rich plasma (PRP) [56]. PRP is also capable of inhibiting inflammation and has been used for osteoarthritis applications [57]. Despite literature demonstrating that there are positive effects, this is a controversial topic which is outside the scope of this review article; we recommend the following article for further information: [58].

3. Cellular-based therapies

Erythrocytes, leukocytes and thrombocytes are blood components that are implicated in homeostasis and pathological progression. These blood cells possess inherent immune biocompatibility, long circulation, and homing capabilities to specific tissues via chemical and biomechanical cues, providing ideal features as self-delivery systems. Since the early 1970s, the idea of using blood sub-components as a vehicle to potentially camouflage exogenous antigenic material from the host's immune system have been implemented. Erythrocytes received early attention because of their morphology as a semipermeable elastic sac, lack of nucleus and their relatively higher intracellular loading capacity. Erythrocytes were first used in 1973 to carry enzymes, which when delivered to the reticuloendothelial system (RES), had a therapeutic effect for treating Gaucher's disease [59]. To date, a wide range of blood components, including but not limited to erythrocytes, leukocytes, thrombocytes, and exosomes, have been used as delivery systems for endogenous and exogenous agents such as: peptides, viruses, plasmid DNA, short interfering RNA (siRNA), and imaging probes for numerous applications (Tables 1–3). This section will discuss recent therapeutic applications of cellular-based (leukocytes) and subcellular-based (erythrocytes, thrombocytes, exosomes) delivery systems. If interested, detailed information on a history and a vast body of literature (before 2010s) on this subject

Table 1
Applications of erythrocyte-based delivery systems (Au: gold; Dox: doxorubicin; ICG: indocyanine green; IL: intracellular drug loading; NIR: near-infrared; PTX: paclitaxel; SC: surface coupling; USPIO: ultrasmall paramagnetic iron oxide nanoparticles).

Cargo	Applications	Studies	Refs
Loading & Release: Proofs of Concept			
Nanoparticles (SC)	Targeted delivery to lung endothelium	in vivo (mice)	[74]
Systemic Therapy			
L-asparaginase enzyme (IL)	Treat acute lymphoblastic leukemia (ALL)	in vivo (mice)	[81]
Thrombomodulin Prodrug (SC)	Treat thromboprophylaxis at the site of clot formation	in vivo (mice)	[70,120]
Fasudil hypertension drugs (IL)	Drug delivery via inhalation for pulmonary artery hypertension	in vitro, in vivo (rats)	[121]
Targeting the Reticuloendothelial System			
Amphotericin B (IL)	Delivery to RES for systemic antifungal treatment	in vitro	[80]
Ovalbumin antigen (IL) (model antigen)	Delivery of antigen to antigen-presenting cells to induce immune tolerance in mice	in vivo (mice)	[122]
Cancer Treatment			
Iron oxide nanoparticles (IL), anticancer drug (IL), Virosome (SC)	Magnetically guided and virosome-induced intracellular targeting within cancer cells	in vitro	[83]
5-Fluorouracil (IL)	Prolonged survival of hepatocarcinoma malignant ascites via intraperitoneal administration	in vitro, in vivo (mice)	[123]
NIR dye (IL), Dox (IL), RGD cancer targeting peptide (SC)	RGD-targeted and NIR-triggered release for photothermal-chemotherapy combination therapy	in vitro	[84]
Photoporphyrin X (IL)	Photosensitizers for cancer photodynamic therapy	in vitro	[124]
PTX (IL)	Enhanced oral drug bioavailability with improved intestinal mucosal tissue permeability	in vitro and in vivo (rats)	[125]
Diagnostics and Theranostics			
Au nanoparticles (IL)	Contrast-enhanced tracers for X-ray dynamic imaging of blood flow	in vitro	[126]
Lanthanide (IL)	Highly sensitive MRI contrast agents	in vivo (mice)	[127]
Iron oxide nanoparticles (IL)	Loading commercial iron oxide nanoparticles for MRI imaging	in vitro	[128]
Iron oxide nanoparticles & Ce6 (SC) and Dox (IL)	Theranostics for image-guided and magnetic field-enhanced combination therapy for cancer	in vitro, in vivo (mice)	[69]
ICG (IL)	Phototheranostic agents for fluorescence imaging and photo-thermal cell destruction	in vitro	[129]
USPIO (IL)	MRI imaging for stem cell therapy	in vitro, in vivo (mice)	[130]

Table 2
Applications of leukocyte-based delivery systems (IL: intracellular drug loading; NIR: near-infrared; SC: surface coupling).

Blood Cells	Cargo	Applications	Studies	Refs
Living blood cells with cargo				
Dendritic cell	Tumor antigen (IL)	Priming T cells to induce tumor suppression	in vitro, ex vivo (mice), in vivo (mice)	[85]
T cell	Interleukin-15,21-loaded nanoparticles (SC)	Promoting T cell expansion and effector function in adoptive T cell therapy for lung and bone marrow metastases	in vitro, in vivo (mice)	[91]
Macrophage	Nanozyme (IL)	Targeted delivery to the affected brain for neuroinflammation and neurodegenerative disorder treatments	in vivo (mice)	[71]
Macrophage	Dox-loaded liposomes (IL)	Targeting deep hypoxic regions within tumors for cancer treatment	in vitro, in vivo (mice)	[87]
Macrophage	Iron oxide nanoparticles (IL)	Imaging tumor regions with MRI	in vitro, in vivo (mice)	[87]
Macrophage	Iron oxide nanoparticles (IL)	Targeting and suppressing tumor growth upon NIR exposure (Photodynamic therapy)	in vitro	[90]
Macrophage	Photodynamic agents (IL)	Delivering cargo to hypoxic regions of tumors	in vitro	[89]
Whole blood	Melanoma TRP-2 mRNA (IL)	Inducing antigen-presenting cells for anti-tumor response	in vivo (mice)	[131]
Living blood cells without cargo				
Dendritic cell	Pulsed with synthetic peptides	Inducing anti-tumor immune response for cancer treatment	in vivo (human, phase II)	[98]
Dendritic cell	Pulsed with deactivated HIV	Inducing immune response for HIV treatment	in vivo (human)	[95]
Macrophage	Transfected with plasmid DNA	Inducing anti-inflammatory and neuroprotective properties in cells for treating neuroinflammation and neurodegenerative disorders	in vitro, in vivo (mice)	[96]
Antigen presenting cell (APC) and T cell	Pulsed with a fusion protein (PA2024)	Sipuleucel-T, the first FDA-approved autologous cellular immunotherapy for advanced prostate cancer treatment	in vivo (human, phase III)	[97,99]

can be found in previously published articles [60–64]. For further information regarding cell-based therapies outside the scope of this review article we would recommend the following: [65].

3.1. Current status of cellular- and subcellular-based targeted drug delivery

An increased interest in blood cell-based delivery systems partly stems from the continuing growth of targeted drug delivery approaches and an unmet need of conventional therapy. Targeted drug delivery's objectives aim to improve therapeutic efficacy, reduce drug toxicity and increase patient safety compliance by utilizing drug carriers. In general, an ideal delivery system must be able to 1) navigate the vasculature while avoiding immune recognition, 2) marginate from dense blood flow and preferentially accumulate at the target site, and 3) localize to subcellular compartments or exocytose for further actions [66].

Table 3
Applications of thrombocyte- and exosome-based delivery systems (Dox: doxorubicin; IL: intracellular drug loading; PTX: paclitaxel; SC: surface coupling; siRNA: short interfering RNA).

Cargo	Applications	Studies	Refs
Thrombocytes			
Dox (IL)	Targeted delivery to circulating tumors	in vitro	[101]
Dox (IL)	Targeted delivery to lymphoma	in vitro, in vivo (mice)	[102,104]
Thrombin-activatable prodrug (SC)	Targeted delivery to new thrombus formation	in vitro, in vivo (mice)	[100]
Exosomes			
Dox (IL)	Targeted delivery to tumor cells	in vitro, in vivo (mice)	[132]
PTX (IL)	Targeted delivery to tumor cells	in vitro, in vivo (mice)	[133]
Cisplatin (IL)	Targeted delivery to tumor cells	in vitro, in vivo (mice)	[134]
Catalase (IL)	Delivery of enzymes to treat Parkinson's disease	in vitro, in vivo (mice)	[135]
siRNA (IL)	Delivery of siRNA against BACE1 mRNA to treat Alzheimer's disease	in vitro, in vivo (mice)	[136]

Blood cells possess features of ideal targeted delivery systems. They have been successfully utilized to carry and deliver diverse endogenous and exogenous cargo and have been successfully engineered to exhibit desired therapeutic functions for various diseases such as cancer, neurodegenerative disorders, and infection (Tables 1–3). Notable features of blood cell-based carriers include protecting cargo from inhibitors and immune clearance, and redistributing cargo such that their exposure to non-target sites can be minimized [67]. For instance, by coupling plasminogen activators to the erythrocyte surface, the therapeutics were redistributed to the center of the vasculature, preventing it from adhering to the vascular wall. This altered functional profile can help prevent bleeding, a common side effect associated with thrombosis treatment [68].

Due to attractive features of blood cell-based delivery systems, research in this field have rapidly and continuously been burgeoning. Most existing works have demonstrated therapeutic utilities of cell-based delivery systems both in vitro and in vivo settings. Although a safety analysis of the carriers remains limited, it seems there is an inverse relationship between the functional richness and safety [69–71]. For example, erythrocytes appear to be the safest carriers but they have limited biological functionality, while leukocytes and thrombocytes are rich in functionality but safety and control can be issues. Although erythrocyte-based carriers are the most established area among other blood components because of their abundance, long lifespan, and claim to being the safest carrier, there can be negative consequences. For example, RBC damage, including hemolysis caused by activation of complement and the RES, vascular occlusion caused by adhesive RBCs, and kidney failure have been reported [72]. Thus, comprehensive analysis of biodistribution, biocompatibility (i.e. resistance to osmotic stress, mechanical and complement insults), pharmacokinetics, pharmacodynamics, trafficking and crosstalk with innate cells of both cell-based delivery systems and cargo deserve more attention [73]. In some applications such as cancer therapy, a long-term study with repeated administration would also need to be evaluated because patients can develop hypersensitivity to therapeutics by producing anti-drug antibodies upon multiple dosages.

3.2. Erythrocytes

Erythrocytes deliver oxygen to tissues via blood flow through the circulatory system. They generally are associated with long circulation times (~3 months) and do not extravasate from circulation until they are removed by degradation via the RES. The innate functions of erythrocytes enable the utility of erythrocyte-based carriers for RES delivery (by using modified carriers), targeting circulating pathological mediators, or targeting entities localized within the bloodstream. Related functionality may include endeavors to control blood fluidity or to manipulate coagulation.

Erythrocytes can carry cargo within their intracellular compartment or coupled to their surface membrane [74–79]. Hypotonic loading and electroporation are primarily the processes used to entrap payload within erythrocytes. These approaches, however, have been reported to be associated with a loss of hemoglobin and compromised membrane integrity [75,80]. These morphological changes could potentially impair erythrocyte biological functionality in oxygen transport, and render them more susceptible to RES clearance. Research has shown that using membrane permeable peptides to aid cargo entrapment or coupling drugs to the erythrocyte surface can bypass the issues related to intracellular loading [81]. Nevertheless, careful considerations must still be taken to minimize RBC disturbance. Improper loading and use of nonspecific cross-linking agents have been shown to cause RBC damage [63]. The Muzykantov group has conducted comprehensive studies on RBC surface coupling techniques. They demonstrated that monovalent affinity fusion proteins could aid the payload capacity to safely attach entities on the surface of circulating erythrocytes in vivo without compromising biocompatibility [70,82]. The in vivo loading is a favorable approach as it eliminates issues associated with ex vivo manipulation, blood transfusion and blood transmission processes.

Erythrocyte-based systems have been shown to leverage innate cellular functions, exhibiting prolonged circulation lifetimes by avoiding immune clearance. The encapsulated agents can be released by slowly diffusing through the cell plasma membrane or eventually released by cell degradation [64]. Cargo coupling to the erythrocyte surface is accessible and easier in terms of controlling the release compared to the encapsulated counterpart. However, it should be reserved for nontoxic drugs that will not cause adverse effects when interacting with other blood cell components. For further enhancement of localizing erythrocytes, modifications of erythrocyte membranes with targeting ligands have been used, in addition to using tissue-penetrating and magnetic fields for cancer treatment [83,84]. Currently, erythrocyte-based carriers have been mainly used for systemic diagnosis, systemic therapy, and cancer treatment (Table 1).

3.3. Leukocytes

3.3.1. Leukocytes with cargo

Leukocytes are generally designated as a delivery system for two main purposes: targeting and immune modulation. Leukocytes can serve as a vehicle to deliver cargo to specific cells [85] or diseased sites [71,86–90] for developing therapeutics for cancer and chronic inflammatory disorders, as leukocytes are implicated in the development of such diseases (Table 2). For example, macrophages were exploited to facilitate protein drugs across the blood brain barrier to increase protein bioavailability within the brain [71,86]. Dendritic cells (DC)s can present the loaded anti-tumor

antigens to endogenous antigen presenting cells and subsequently activate T cells for generating anti-tumor immunity [85]. In the field of cancer immunotherapy, adjuvants loaded on expanded T cells can provide continuous pseudo-autocrine stimulation to enhance the therapeutic impact of the adoptive T cell therapies [91].

Leukocytes may carry cargo via intracellular encapsulation or conjugated/non-conjugated cell-surface coupling (Scheme 1C). The intracellular encapsulation may be accomplished via electroporation in hyperosmotic loading buffers, which causes an influx of water. Generally electroporation is accomplished in an ex vivo context. The resealing of the cell membranes post-electroporation is a passive process. Preparation of cargo hitchhiking can be performed in vivo, thus reducing concerns related to ex vivo manipulation such as limited shelf life and blood-borne infections during the loading and reinfusion processes [92]. Certain pathogens such as *Mycoplasma haemofelis* also employ surface coupling techniques to circulate inside mammals by hitchhiking on erythrocyte surfaces [93]. The design of cargo used for cell surface coupling, particularly for leukocyte hitchhiking, is challenging because it requires precise controls over size, shape and mechanical properties to avoid self-internalization. Regardless of the delivery method, modifying living cells with payloads can cause cellular disruption and cellular malfunctions in some cases [92], possibly causing limitations with cell trafficking, which is one of the premises behind the use of leukocytes. Careful consideration of the cargo loading capacity is also necessary as the nanoparticle concentration on cell membranes has been reported to correlate with cell toxicity [73].

3.3.2. Leukocytes without cargo

Cell-based immunotherapy is an approach that utilizes engineered immune cells, which can be primed *a priori* to defend the body against diseases. Generally, immune cells can be modified ex vivo with immunomodulators such as interleukins and cytokines (Scheme 1C). After transferring into patients, the primed cells can perform as therapeutic cells without cargo to induce patients' endogenous immune systems to exert amplifying or suppressing immune responses against a target disease. Cell-based immunotherapies for cancer and chronic-inflammatory disorders have been explored thoroughly [94–99] (Table 2). Several adaptive immunotherapies are currently underway in clinical trials (see Section 5). Sipuleucel-T has received the first FDA approval as an autologous cellular immunotherapy for treating advanced prostate cancer [97,99].

3.4. Thrombocytes

Comparing to other blood sub-components, using thrombocytes as delivery systems is still an evolving area. Since the primary functions of thrombocytes involves homeostasis and thrombosis, thrombocyte-based delivery systems have potential uses in many conditions associated with damaged vasculature, including: cancer, thrombosis, chronic-inflammatory disorders, and trauma (Table 3). Thrombocytes coupled with thrombin-activatable prodrugs have been demonstrated to selectively lyse new thrombi without disrupting preexisting hemostatic clots [100]. This finding provided a promising avenue for thrombosis treatment with reduced risks of hemorrhage in damaged blood vessels. Likewise, thrombocyte-based carriers are particularly attractive for treatments against metastatic cancer due to recent findings of thrombocyte implications in cancer cell dissemination [101–104].

3.5. Exosomes

Exosomes are of specific interest for their potential applications for diagnosing diseases and drug delivery (Table 3) [217]. Exosomes are known to contain proteins, nucleic acids, lipids, and other cellular components [105,106]. This material provides information about the originating cell as well as the surrounding environment of the cell. Information gained from these vesicles can then be applied towards disease detection and possibly treatment. Recently, research has shown that exosomes are capable of detecting signs of Alzheimer's disease up to 10 years earlier than traditional diagnostic methods [107,108]. Circulating exosomes contained high levels of proteins that are known to accumulate before the onset of Alzheimer's disease. This technology allows opportunity for preventative treatment for high-risk patients that could help prevent the onset of the disease. Research has also found miRNA markers inside exosomes unique to different types of cancer useful for diagnostic purposes [106]. Exosome analysis provides a non-invasive alternative to cancer diagnosis and monitoring. Exosome applications for drug delivery are also being investigated [109]. Exosomes are naturally occurring and therefore relatively biocompatible, have natural specificity for different cells, possess the ability to penetrate tissue, and are stable for relatively long periods. These characteristics provide a strong basis for designing targeted delivery vesicles.

While the potential benefits of exosomes could drastically improve the manner in which diseases are diagnosed and treated, the technology needs greater refinement. Although specific and non-specific cellular uptake of exosomes has been demonstrated [110] in certain cases, differing findings may be a result of inconsistent experimental procedures, as well as indicative of differences in tropism. Additionally, exosome populations exhibit diverse compositions [106]. This leads to difficulty in isolating and characterizing exosomes. Consequently, use of inconsistent delivery vesicles for therapeutics introduces concerns of efficacy and safety. Other complications arise from animal model data which do not translate into humans. For example, exosomes are known to have crossed the blood-brain barrier in a mouse model [111], but these experiments have not translated to humans. Further investigation is needed to determine the therapeutic potential of exosomes.

Exosome-mimetics are currently being investigated as natural exosomes are not easily isolated, depending on the source, and can be costly and time consuming. It has also been theorized that exosome-mimetics can be produced by combining individual subcomponents [112]. Depending on the entity of interest, ensuring the proper directionality of the constituents can be challenging. Furthermore, it is also unknown in some cases which components of cell membranes are required for an intended function of interest. Current methods produce exosome-mimetics directly from cell membranes. Exosome-mimetics derived from monocytes and macrophages have been created by extrusion of cells through a membrane [113] or by slicing cells via blades in microfluidic channels [114]. The cells can be suspended in a solution containing the intended cargo so that the cargo is encapsulated when the membrane fragments reform or they can be loaded with miRNA, siRNA, or plasmid DNA via electroporation.

Due to length restrictions, we would recommend the following articles in regards to nucleic acid delivery via extracellular vesicles for the interested readers: [115–119].

4. Biomimetic-based therapies

4.1. Challenges of synthetic drug carriers

In the last few decades, the utility of synthetic carriers for drug delivery has been flourishing. There have been numerous efforts to develop synthetic delivery systems that can overcome physiological barriers and provide greater therapeutic outcomes compared to conventional systemic delivery, such as intravenous routes.

Examples include studies exploring the interplay among physicochemical properties of delivery systems, hemodynamics and hemorheology, as well as delivery efficacy and safety [137,138]. However, to date, only a handful of these delivery systems have made it to the clinics. The inefficacy of existing delivery systems may be attributed to clearance, poor transportation via blood flow (i.e., solubility issues), and the limited capacity for intracellular trafficking [139]. As navigating the vasculature with sufficient circulation time is the first required process for delivery systems, early work has primarily focused on increasing carrier circulation times. A standard technique of which is to modify the carrier surface with polyethylene glycol (PEG). Due to PEG's capability to generate a stable hydration protective layer that resists protein adsorption and delay carrier clearance [140], several PEGylated therapeutic formulations have been broadly used in the clinics [141]. However, recent findings have revealed that patients who receive repeated delivery of PEGylated medications can develop antibodies against PEG, which could lead to accelerated blood clearance, loss in therapeutic efficacy and ultimately increased undesired adverse events [142–145]. Due to the increasing use of PEG in various consumer products including cosmetic and food additives, about 25% of healthy research participants have also been found to have generated antibodies against PEG, even before the treatment [146]. The pre-existence of anti-PEG immunity has further brought complications to the treatment with PEGylated medications.

To avoid the elicited polymer-specific antibodies, alternative materials capable of forming stealth layers without developing immunity has been adopted. This includes a super-hydrophilic zwitterionic material and CD47, a natural marker of self-ligands, presented on erythrocytes. Drug carriers modified with such components have been shown to reduce macrophage engulfment, avoid clearance significantly better than PEG-counterparts, and more importantly, not trigger the polymer-specific antibodies [147–150]. Although the discovery of PEG-alternatives have demonstrated promising outcomes in the preclinical development stage, the fabrication process in which carriers are synthesized and modified with various ligands (namely the bottom-up process) are commonly associated with non-homogenous surface modifications and expensive production costs [151,152].

To advance the utility of drug delivery systems toward high efficacy and safety, recent efforts have attempted to generate biomimetic carriers, a hybridization of synthetic carriers and cellular-derived membranes prepared from top-down processes. These hybridized carriers simultaneously exploit inherent native biological functions of host cells displayed by cell-derived components and controllability over formulation, storage and utilization associated with synthetic particles. To date, biomimetic carriers derived from various sources [134,153–156] such as blood cells, exosomes, stem cells and bacteria have been gaining considerable attention in biomedical communities. In this section, we will discuss recent applications of biomimetic delivery systems that were derived from erythrocytes, leukocytes, thrombocytes, and exosomes (Table 4).

4.2. Preparation of biomimetic carriers

Biomimetic carriers (Scheme 1D) derived from erythrocyte and leukocyte membranes are generally formulated by integrating the derived cellular membranes extracted by hypotonic lysis solution with the synthetic particles through mechanical extrusion [157–164], as can be seen in Fig. 1. Thrombocyte-derived particles can be prepared by fusing thrombocyte-derived membrane isolated by a repeated freeze-thaw process with synthetic particles using sonication [151,165,166]. A few research endeavors have thoroughly characterized the coated cellular membrane on biomimetic carriers. They found that the carriers typically inherit homogenous coatings of lipid membranes and membrane-associated proteins anchored with the right-side-out conformation (Fig. 2A) [159] and at the density comparable to the cell source [160,167]. The stability of proteins can also be enhanced by modifying the particle surface with carboxylic end groups before the membrane coating process. The interaction of the carboxylic groups and amine groups of proteins can form amide linkages, which further strengthen the protein stability [161]. In addition, the choices of protein components coating the biomimetic carriers can be controlled by isolating proteins using discontinuous sucrose gradient centrifugation processes and selectively integrating the proteins of interest in the particles [161].

4.3. Erythrocyte membrane-derived particles

Erythrocyte membrane-derived particles have been primarily explored for cancer drug delivery and detoxification. Coating synthetic particles with erythrocyte-derived membranes have been shown to circumvent particles from macrophage uptake in vitro [157,158], improve their in vivo residence time compared to PEG polymer (Fig. 2B and C) [159,162], avoid eliciting immune responses, and prevent the accelerated blood clearance phenomenon [148]. The prolonged circulation of erythrocyte-derived particles is likely responsible by CD47 and complement inhibitors (DAF, CD59 and CR1), which play a significant role in complement regulation and the clearance of immune complexes [168].

To facilitate specific tissue targeting, the derived particles can be modified with exogenous ligands. Using a simple lipid insertion technique or linkages such as streptravidin-biotin [70,81,82], cancer-targeting moieties (i.e., folate and AS1411 aptamer, RGD, EpCam, CDX peptide) and protective complement regulatory proteins could be functionalized on the carriers [63,81,169–174]. Incorporating the targeted particles with a photosensitizer can serve as a photodynamic agent for cancer treatment. Similarly, incorporating the targeted particles with oxygen carrying compounds can facilitate oxygen transportation to hypoxic tumors, which has been shown to improve treatment efficiency and increase the survival rate of tumor-bearing mice [175]. Triggered-release can also be achieved by integrating erythrocyte membranes with pH-, ultrasound- or laser-sensitive materials [158,176,177].

Erythrocyte membrane-derived particles can also be utilized as a scavenger decoy, namely a nanosponge, for detoxification treatment. Because of the interaction between erythrocytes with exogenous toxins which can potentially lead to hemolysis, the nanosponges can be used as decoys to preserve endogenous erythrocyte activity by intercepting circulating, broad-spectrum toxins, and other pathological antibodies [178–180]. The movement of nanosponges can be modulated by external sources (e.g. ultrasound [181]) or self-driven (e.g. Janus particles [182]) to increase the toxin neutralization efficiency and decrease adverse events due to hemolysis. Nanosponges can be combined with stimuli-responsive materials carrying therapeutic antibiotics or antivirulence drugs [183,184] or pore-forming toxins for promoting uptake, which can enhance vaccine immunization against bacterial infections [185,186].

Recent work from the Zhang group has advanced such technology further by exploring a facile technique that simultaneously fuses erythrocyte and thrombocyte membranes onto poly(lactic-co-glycolic acid) (PLGA) nanoparticles [187]. These hybridized nanoparticles are expected to have superior functionalities compared to single membrane-coated particles. This study provides an avenue to customize cellular coating components, which can exhibit optimal functionalities suitable for a number of applications.

Table 4
Applications of biomimetic carriers. (Au: gold; Dox: doxorubicin; Ce6: chlorin e6; ICG: indocyanine green; Mg: magnesium; np: nanoparticle; PEG: polyethylene glycol; PFC: perfluorocarbon; PLGA: poly(lactic-co-glycolic acid); PTX: paclitaxel; TTPP: thiamine pyrophosphate; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand; UCST: upper critical solution temperature; x: not applicable).

Material Core	Cargo	Ligands	Applications	Studies	Refs
Erythrocytes					
Cancer Treatment					
PLGA	Gambogic acid	x	Colorectal cancer treatment	in vitro, in vivo (mice)	[192]
PLGA	x	Folate, AS1411	Cancer cell targeting	in vitro	[169]
PLGA	Antigenic peptide, Adjuvant MPLA	Mannose	Cancer immunotherapy	in vitro, in vivo (mice)	[170]
Pluronic F127	Photosentizer	Folate and TPP	Photodynamic therapy	in vitro, in vivo (mice)	[175]
Chitosan	Dox and PTX	DSPE-PEG-RGD	Combination chemotherapy	in vitro, in vivo (mice)	[172]
PLGA	Dox	CDX peptide	Brain cancer-targeted drug delivery	in vitro, in vivo (mice)	[171]
Upconversion nanoparticles	x	DSPE-PEG-Folic acid	Tumor imaging	in vitro, in vivo (mice)	[173]
Au nanocage	PTX	EpCam antibodies	Photothermal and chemical cancer therapy	in vitro	[174]
Polypyrrole np	x	x	Enhanced photothermal therapy for cancer treatment	in vitro, in vivo (mice)	[193]
UCST Micelle	ICG, Dox	x	Chemo-photothermal therapy	in vitro	[194]
PLGA	PFC	x	Relieve tumor hypoxia and enhance radiotherapy	in vivo (mice)	[195]
Albumin	ICG, PFC	x	Photothermal therapy	in vitro, in vivo (mice)	[196]
Liposome	Camptothecin	x	Ultrasound-triggered drug release	in vitro, in vivo (mice)	[158]
PGSC	PTX	x	pH-sensitive carriers for non-small cell lung cancer therapy	in vitro, in vivo (mice)	[176]
Silica	Dox and Ce6	x	Laser-activated theranostics for cancer treatment	in vitro, in vivo (mice)	[177]
Detoxification					
PLGA	x	x	Clearance of antibody-induced anemia disease	in vivo (mice)	[178]
PLGA	x	x	Clearance of pore-forming toxins	in vitro, in vivo (mice)	[185]
PLGA	x	x	Clearance of organophosphate agents	in vivo (mice)	[179]
PLGA + Hydrogel	x	x	Clearance of bacteria pathogens	in vivo (mice)	[180]
PLGA	x	x	Clearance of pore-forming toxins and protect retinas from damage	in vivo (mice)	[197]
Au-Nanowire	x	x	Clearance of toxins via ultrasound-propelled nanomotor	in vitro	[181]
Mg-Janus particle	x	x	Clearance of toxins via water-driven motors	in vitro	[182]
Gelatin	Vancomycin	x	Clearance of bacterial toxins with antibiotic treatment	in vitro	[183]
Hydrogel	Vancomycin	x	Clearance of bacterial toxins with antibiotic treatment	in vitro	[184]
PLGA	Bacterial toxin	x	Toxoid vaccination	in vivo (mice)	[186]
Leukocytes					
Cancer Treatment					
PLGA	Dox	x	Induced cytotoxicity	in vitro	[160]
Silicon	x		Localized cancer therapy	in vitro and in vivo (mice)	[161]
Au-coated silica	x	x	Localized photothermal therapy	in vivo (mice)	[163,164]
Silica	Dox	x	Localized chemotherapy	in vivo (mice)	[163,164]
Detoxification					
PLGA	x	x	Absorb endotoxins and proinflammatory cytokines for sepsis management	in vitro, in vivo (mice)	[198]
Thrombocytes					
Cancer Treatment					
Silica	x	TRAIL	Neutralization of circulating tumor cells and attenuation of metastases	in vitro, in vivo (mice)	[151]
Acid-degradable Nanogel	TRAIL, Dox	x	Localized synergistic anti-tumor therapy	in vivo (mice)	[189]
Detoxification					
PLGA	Vancomycin	x	Treatment of bacterial pathogens	in vitro, ex vivo (human, rats), in vivo (rats, mice)	[165]
PLGA	x	x	Clearance of anti-platelet antibodies for immune thrombocytopenic purpura (ITP) treatment	in vitro, in vivo (mice)	[166]
Erythrocyte & Thrombocytes					
PLGA	x	x	Proof-of-concept to enhance np functionality with hybrid cell membranes	in vitro, in vivo (mice)	[187]
Exosomes					
Monocyte or Macrophage	Cancer drug, RNA/DNA, protein, antigen	x	Treatment of cancer and other diseases	in vitro, in vivo (mice)	[113,114]

4.4. Leukocyte membrane-derived particles

Natural surface moieties present on leukocytes can be used for immune evasion and (sub-)endothelial adhesion which are two primary characteristics required for vascular- and cancer-targeted drug delivery systems. Equipped with active targeting ligands, a study showed that leukocyte membrane-derived particles outperformed the RBC-counterparts in accumulation within

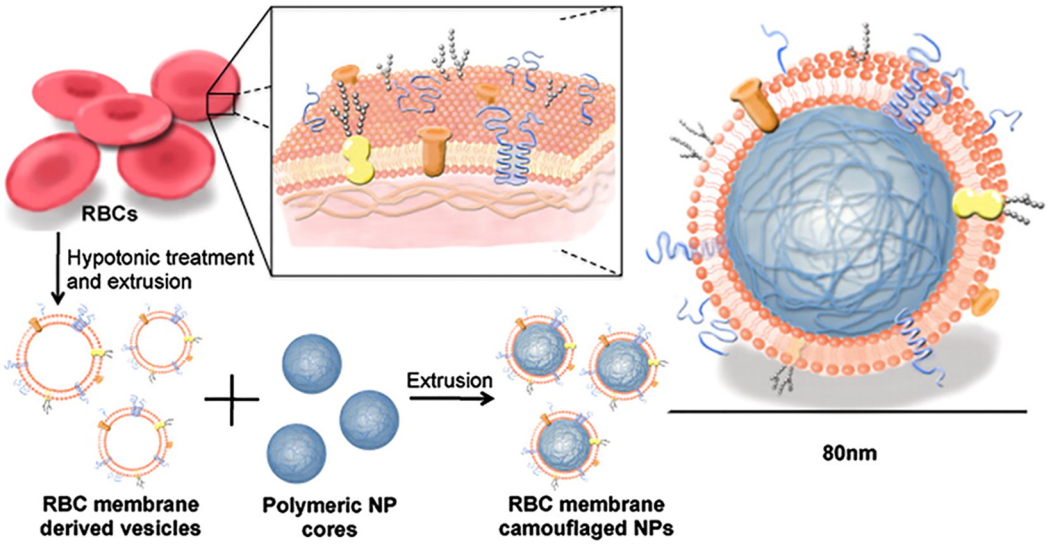


Fig. 1. Preparation of biomimetic carriers. The process for integrating cellular membranes with synthetic particles to form biomimetic carriers. Reprinted [159] with permission from PNAS.

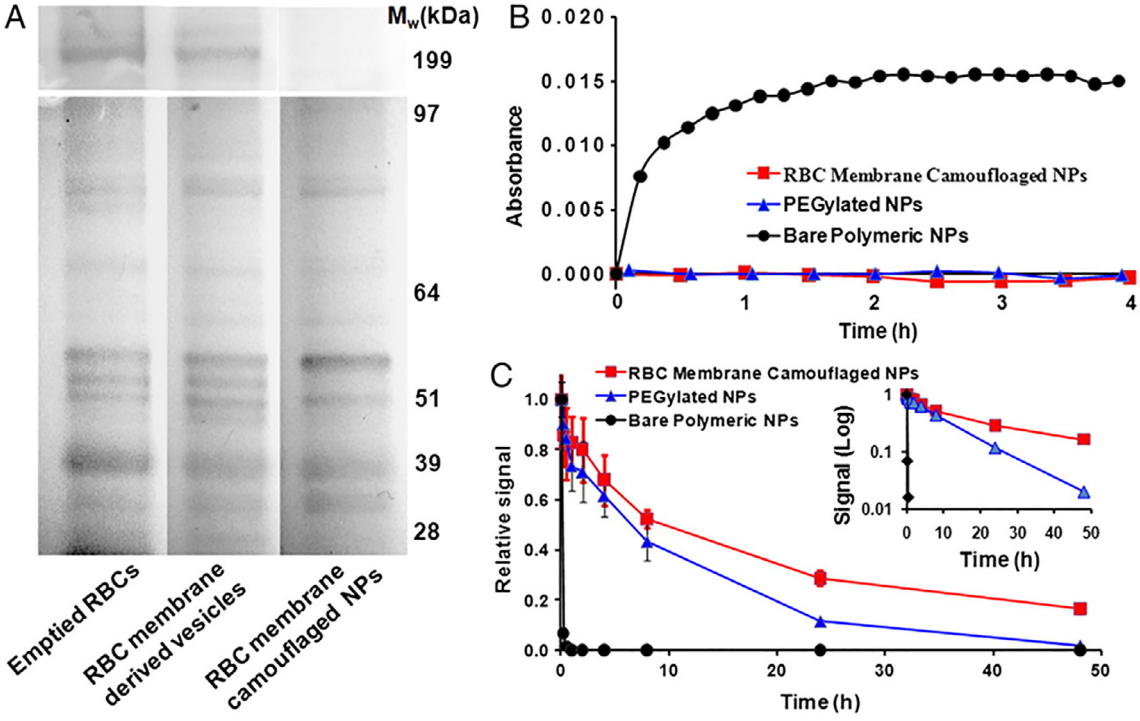


Fig. 2. Characterization of biomimetic carriers. (A) Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was used to identify membrane-associated protein composition of the nanoparticles; (B) Nanoparticle stability in serum was analyzed using absorbance; (C) Fluorescence of blood samples indicated retention of the nanoparticles at various time points. Reprinted [159] with permission from PNAS.

tumors [164]. This is likely because not all tumors possess increased vessel permeability. Thus, long circulating particles derived from erythrocyte membranes alone without additional targeting ligands are likely more ineffective at accumulating within target sites. In addition to preferentially binding inflamed endothelium, leukocyte membrane-derived particles also inherit other functionalities including: avoiding opsonization which would otherwise cause uptake by the mononuclear phagocyte system; transmigrating into sub-endothelial layers; escaping the endolysosomal degradation pathway; and enabling subsequent release of the cargovia hydrolysis or reduction (i.e., via glutathione) [160,161,163]. It is noteworthy that the ability to avoid the RES of a host is generally considered to be limited to autologously-derived particles. For example, mouse leukocyte-derived particles generally cannot avoid particle internalization upon interaction with human macrophages after repetitive interactions [161].

4.5. Thrombocyte membrane-derived particles

Researchers have begun to explore the utility of thrombocyte membrane-derived particles for detoxification and cancer treatment, in light of findings elucidating crucial implications of

thrombocytes with bacteria during infection and between circulating cancer cells during tumor metastasis [103,188]. Thrombocyte membrane-derived particles have been used as a platform to treat immune thrombocytopenic purpura, a thrombocyte disorder causing small blood vessels to clot, which then subsequently causes a low platelet count. The particles were able to preserve circulating platelet activity by delivering antimicrobial drugs to neutralize circulating pathogens and simultaneously acting as a decoy by binding to antiplatelet antibodies to preserve circulating platelet activities [165,166]. In cancer therapy, thrombocyte membrane-derived particles bearing protein inducing apoptosis (TNF-related apoptosis-inducing ligand (TRAIL)) and chemotherapeutic medications have been shown to accumulate within solid tumors and exert an anti-tumor effect on circulating tumors, leading to reduced metastatic potential [151,189].

4.6. Exosome membrane-derived particles

Therapeutic uses of exosomes are fairly new and still being developed. Exosome-mimetics have been shown to exhibit the same membrane components as their cells of origin [113,114]. This is also the case for naturally produced exosomes, which have shown promise in recent studies. Clinical trials have been performed using cancer drugs or antigens loaded in exosomes to combat cancer cells [112,190,191]. In some studies, known negative side-effects were reduced when compared to free drugs [190], and in others the desired therapeutic effect was observed [112,191]. Treatments for Parkinson's disease and Alzheimer's disease have been investigated using exosomes loaded with enzymes [190] and siRNA [112], respectively. Because others have shown successful treatments using exosome-based therapies, there is a growing interest in this field.

5. Potentially clinically impactful technologies

Several notable formulations of the aforementioned blood products are currently being studied in clinical trials, or have become commercial products.

5.1. Blood replacement for oxygen delivery

Considerable efforts in developing blood substitutes have been continuously growing due to current unmet clinical needs associated with natural blood and the great demand in blood transfusion, which is predicted to increase more than 10% in the next decade [199]. Several formulations of RBC substitutes (both hemoglobin-based and PFC-based carriers) were advanced into clinical trials but have been withdrawn primarily due to product safety, concerns for marginal benefits, and the difficulties in storage and preparation [26,200]. PolyHeme®, Hemospan, and pyridoxalated-hemoglobin-polyoxyethylene conjugate (PHP) are examples of hemoglobin-based carriers that had completed phase III clinical trials but were abandoned because of heme-mediated oxidative side reactions [34]. Although currently there is no RBC substitute approved by the FDA for clinical use in humans, Oxyglobin® (glutaraldehyde-polymerized bovine hemoglobin) has been approved for veterinary use in Europe and the U.S. for anemia. Hemopure®, a trade name of Oxyglobin®, is currently used to treat acutely anemic patients during surgery in South Africa. Perftoran (PFC-based RBC substitutes) has also been approved for clinical use in humans in Mexico and Russia, although adverse events such as pulmonary complications continue to be disclosed in certain cases [38]. Efforts to incorporate current technologies to address unmet clinical needs of blood substitutes for patients have been continued. The previously mentioned PRINT technique allows the synthesis of RBC-mimicking particles that resemble a biodistribution similar to natural RBCs [39,40]. These particles can encapsulate oxygen-carrying units along with other molecules such as reducing agents to prevent unwanted, irreversible hemoglobin reactions. Surface properties of these particles can also be facilely tuned to exhibit controllable oxygen release profiles, similar to natural RBCs. Other physical properties and functionalities of the recent generation of RBC substitutes, such as viscosity and deformability, are currently under investigation in preclinical studies to ensure their suitability as an RBC substitution.

5.2. Genetically unmodified therapeutic agents within whole blood

Examples of past or ongoing clinical trials for blood clotting applications using genetically unmodified therapeutic agents derived from whole blood include applications involving: VWF (i.e., Humate-P® (NCT00168090), NCT02472665, and NCT02281500), prothrombin (i.e., NCT02777424, NCT00618098), proaccelerin (i.e., AutoloGel® (NCT00762138)), proconvertin (Factor VII) (i.e., NCT01269138, NCT01779921), antihemophilic factor (i.e., NCT02472665), and the fibrin stabilizing factor (i.e., NCT00883090, NCT00945906, NCT00885742). Examples of past or ongoing clinical trials for extracting blood constituents for therapeutic purposes include applications involving: auto-immunity complications (i.e., NCT00359346, NCT01370200), and hemochromatosis (i.e., NCT00509652, NCT00202436). Examples of past or ongoing clinical trials for delivering blood constituents for orthopedic and arthritis applications involve the following clinical trials: i.e., NCT01926327, NCT02239029, NCT02211521. NCT02370420. An anti-factor XI antisense oligonucleotide (ASO) for the prevention of venous thrombosis was published in the New England Journal of Medicine, demonstrating that their factor XI-ASO therapy had the potential to reduce the rate of postoperative thrombosis. They demonstrated this without increased bleeding which is common with the use of conventional anticoagulants (i.e., NCT01713361) [201]. We recommend interested readers to refer to https://clinicaltrials.gov for further information regarding clinical trials.

5.3. Leukocyte-based carriers

Research exploring blood cells as carriers in targeted drug delivery or as therapeutics themselves (i.e., for immunotherapy) are actively progressing. The approach of using blood-derived living cell entities as drug delivery carriers have been studied for over a decade. However, the strategy of adopting blood cell-based carriers is relatively new and most of these studies are still in the preclinical developmental stage. Considerable efforts have particularly been devoted for cancer immunotherapy, including cancer vaccines (anti-PD-1/PD-L1) and adoptive cell transfer (i.e., Juno Therapeutics' chimeric antigen receptor T cells) where the immune response is programmed to recognize and effectively treat cancer cells. The first clinical study of a cell-based cancer vaccine was conducted by Hsu, et al. in 1996. The developed vaccine, which was prepared ex vivo by pulsing autologous DCs with tumor specific proteins, successfully demonstrated the stimulation of host antitumor immunity and without significant toxicity observed [202].

Following the first clinical trial, DC-based anticancer immunotherapy have entered the clinics but the majority have failed to proceed beyond Phase II studies [203,204]. Notably, Sipuleucel-T (Provenge®) is currently a commercially available vaccine for the treatment of metastatic castration-refractory prostate cancer [97]. Suggested issues responsible for the great failing rate of DC-based products include, but are not limited to, insufficient understanding of the functional heterogeneity of the human DC subset and various barriers that limit T cell proliferation and

eradication capacity, namely immune checkpoints [203–205]. The clinical testing of the first adoptive cell therapy (ACT) was in 1988 [206]. Since then, ACT treatments using naturally isolated T cells or genetically engineered T cells have been intensively explored for inducing complete removal of metastatically spreading cells and chemotherapy-refractory cells. Two outstanding trials involving ACT-based technology with genetically modified lymphocytes took place in 2006; the highest response rate of ACT with naturally derived and isolated T cells subsequently took place in 2011. The former study demonstrated that lymphocytes modified with retroviruses which encoded a T cell receptor successfully mediated cancer regression in metastatic melanoma [207]. The latter study utilized autologous tumor-infiltrating lymphocytes along with a lympho-depleting regimen in patients with refractory metastatic melanoma. To date, this latter study demonstrated the highest response rate for durable and complete cancer regression [208]. Though there are no U.S. FDA-approved ACT treatments to date, the advances in gene therapy have enabled the development of gene-modified T cells programmed to target possibly any tumor antigen and has generated promising results for many malignancies in the clinics [209].

5.4. Erythrocyte-based carriers

RBCs are a candidate for carrying therapeutics, due particularly to their long lifespan in circulation and intracellular enzymatic activities [210]. A commercially available red cell loader (provided by EryDel) is an automatic high-throughput device that encapsulates cargo within human autologous RBCs [211]. Asparaginase-encapsulated erythrocyte, ERYASP, is commercially available for treating acute lymphoblastic leukemia patients. A non-enzymatic use of this technology involves, EryDex, dexamethasone sodium phosphate (DSP)-loaded within autologous erythrocytes which are prepared by the same device. This is an example of RBC-based products for treating ataxia telangiectasia, a rare neurodegenerative disease, which is currently in phase II clinical trials [212].

The significant advances in nanotechnology and molecular biology have enabled the synthetic components that can mimic both mechano- and chemico-biological properties of blood. With current technology, researchers have begun to fabricate artificial red cells (Fig. 3) that can mimic size, shape and deformability (Fig. 4) [213]. Both artificial blood cells and blood cell-camouflaged carriers are now undergoing preclinical development with promising results.

6. Future directions and conclusion

While advances are being made to improve current blood-based technologies, there are challenges to overcome, including but not limited to the host immune response, cargo release, and automated processes. Here we expound upon future directions involving cargo release and automation.

6.1. Challenges of cargo release

One of the technologies being developed to help overcome the obstacle of cargo release from biomimetic carriers focuses on using

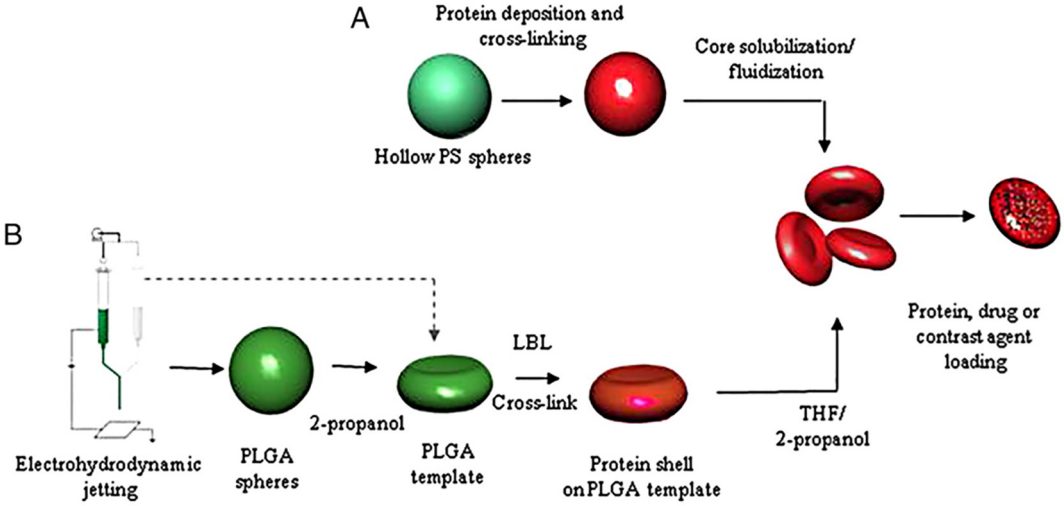


Fig. 3. Fabrication of artificial RBCs. Overview of the two techniques used for fabrication of artificial RBCs. Reprinted [216] with permission from PNAS.

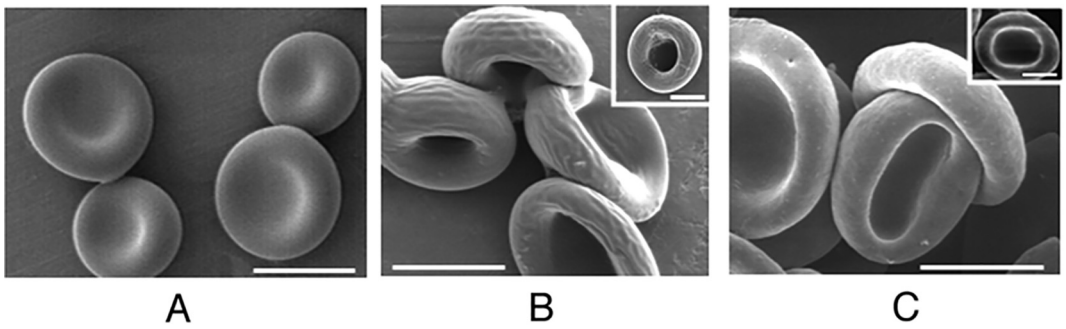


Fig. 4. Imaging of synthetic and natural RBCs. Comparison of synthetic RBCs: PLGA particles using electrohydrodynamic jetting (A); layer-by-layer deposition (polyanion and polycation) with core dissolution (B) and mice RBCs (C); scale bars are 5 μm (inlaid: 2 μm). Reprinted [216] with permission from PNAS.

a photosensitive polymer to release a loaded drug when irradiated with a laser [177,194]. More specifically, a method being investigated involves an upper critical solution temperature (UCST) polymer paired with a photothermal agent that generates heat when a laser is applied. As a result of the generated heat, the polymer expands and releases the loaded drug. The UCST polymer is paired with components of RBC membranes to act as a stealth coating and reduce leakage of the drug while circulating. Another method for controlling cargo release, pairs a polymer with a photosensitizer agent that generates reactive oxygen species when irradiated with a laser. These oxygen species then react with the nanoparticle RBC membrane coating (used to increase circulation time and reduce drug leakage) and cell membranes of nearby tumor cells. Destruction of the nanoparticle membrane releases the loaded drug, which can then further destroy tumor cells. Another technology uses graphene nanosponges as drug carriers [214]. The graphene nanosponge was paired with a photothermal agent and loaded with a tumor drug and PFH. When irradiated with a laser, the photothermal agent heats and vaporizes PFH, which releases the tumor drug to the surrounding area. The use of the graphene nanosponges is of interest because they are able to diffuse into the mass of tumor cells and can carry large amounts of drug because of their sponge-like properties. These three developing technologies have yet to be implemented in clinical trials.

6.2. Challenges of automation

Similar devices to EryDel will help with batch-to-batch consistency and control over the formulations of interest. We foresee the development of similar autonomous devices for other blood cell-based therapies and biomimetic carrier applications, which could be highly valuable for personalized medicine applications. For example, information supplied to automated manufacturing devices could be patient-specific and could have a large library of subcomponents at its disposal which were pre-validated. Such autonomous systems would be expected to collect blood from patients, derive blood vesicles, integrate particles with the vesicles and subsequently introduce the formulation back into the same patient for autologous applications or further enable shelf-storage for allogeneic applications.

With continuous efforts, we envision blood-based therapeutics will be one of the next generations of medicine for numerous medical applications.

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