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Blood components as carriers for small-molecule platinum anticancer drugs

Houzong Yao[a,b] and Guangyu Zhu[b,c]

Abstract: The efficacy of platinum drugs is limited by severe side effects, drug resistance, and poor pharmacokinetic properties. Utilizing long-lasting blood components as drug carriers is a promising strategy to improve the circulation half-lives and tumor accumulation of platinum drugs. Non-immunogenic blood cells such as erythrocytes and blood proteins such as albumins, which have long lifespans, are suitable for the delivery of platinum drugs. In this concept, we briefly summarize the strategies of applying blood components as promising carriers to deliver small-molecule platinum drugs for cancer treatment. Examples of platinum drugs that are encapsulated, non-covalently attached, and covalently bound to erythrocytes and plasma proteins such as albumin and apoferritin are introduced. The potential methods to increase the stability of platinum-based thiol–maleimide conjugates involved in these delivery systems are also discussed. This concept may enlighten researchers with more ideas on the future development of novel platinum drugs that have excellent pharmacokinetic properties and antitumor performance in vivo.

Introduction

After the approval of cisplatin by the US Food and Drug Administration (FDA) for cancer treatment in 1978, two more platinum drugs were internationally approved, and three additional drugs were authorized in some Asian countries.[1] These platinum drugs are now widely used for the treatment of testicular, ovarian, colon, lung, breast, bladder, colorectal, and gastric cancers.[2] The generally accepted action mechanism of platinum drugs to kill cancer cells mainly includes four key steps: cellular uptake through passive diffusion and receptor-mediated active transport; activation by water molecules; covalent binding to the N7 positions of guanines and adenines in the genomic DNA to form intra- and inter-strand crosslinks; and finally, DNA damage that leads to the induction of apoptosis in cancer cells.[3] Despite the great success of platinum drugs in clinics for the treatment of cancer, patients still suffer from severe side effects, and intrinsic or acquired resistance limits the therapeutic efficacy of platinum drugs.[4]

One of the promising strategies to reduce the shortcomings of platinum drugs, i.e., severe side effects and drug resistance, is the development of platinum(IV) prodrugs. Platinum(IV) prodrugs with an octahedral geometry are kinetically more stable than the square-planar platinum(II) drugs. This inertness limits the possibility of premature activation in the blood to damage normal tissues and deactivation by thiol-containing proteins before entering cancer cells.[5] In addition, six-coordinated platinum(IV) prodrugs provide two more axial positions than four-coordinated platinum(II) drugs. Thus, ligands with different properties, such as high lipophilicity, cancer-targeting ability, and other biological activities, can be flexibly anchored to the platinum center to increase cellular accumulation, improve selectivity to cancer cells, and reduce resistance.[6] After entering cancer cells, platinum(IV) prodrugs can be reduced by high-concentration reducing agents in the cancer cells, such as ascorbate and glutathione, and by proteins with reducing abilities to release the conjugated ligands and the active platinum(II) counterparts that can kill cancer cells.[7] Platinum(II) drugs and platinum(IV) prodrugs including those in clinical trials, however, still share a common limitation, which is their insufficient circulation time in vivo. For example, the half-lives of cisplatin and platinum(IV) prodrug intercalated in human plasma are only approximately 0.5 and 1.2 h, respectively.[8] Therefore, the discovery of carriers to enhance the circulation time and subsequently increase tumor accumulation and improve the antitumor effects of platinum drugs is highly appealing.

Blood is a body fluid that contains 45% blood cells and 55% plasma, and it transports oxygen and nutrients to the cells and delivers metabolic wastes away from these cells.[9] Red blood cells (RBCs), i.e., erythrocytes, account for a major portion of blood cells, which have a density of 3.8–5.9 million cells per microliter of blood in an adult.[10] In addition, a small portion of white blood cells and platelets that are responsible for protecting the body from foreign invaders and initiating blood clots, respectively, are present in the blood. Aside from the high proportion of water, plasma contains many other molecules such as albumin, globulins, fibrinogen proteins, nutrients, and ions.[11] Erythrocytes have the properties of long lifespans, flexible transformation, high surface-to-volume ratios, and non-immunogenicity. Based on these advantages, they are regarded as promising drug carriers and widely used for the delivery of antineoplastics, peptides, and enzymes.[12] The non-immunotoxic plasma proteins, such as the most abundant albumin that serves as a taxi to transport hormones, bilirubin, and fatty acids in the blood, have also been used as excellent carriers for various organic drugs.[13] Thus, blood components including erythrocytes and plasma proteins have great potential to be utilized as great carriers for the delivery of platinum drugs.
In this concept, we summarize the recent approaches to utilize erythrocytes and plasma proteins, especially albumin, as carriers for small-molecule platinum drugs in order to increase the circulation time and antitumor activities of platinum drugs. The strategies to improve the stability of thiol–maleimide conjugates are also briefly introduced. This short review highlights the strategies to improve the pharmacokinetic properties and antitumor effects of small-molecule platinum drugs by hitchhiking blood components and may enlighten researchers on the future development of platinum drug candidates that are highly effective in vivo.

**Erythrocytes as carriers for small-molecule platinum drugs**

The most fascinating property of erythrocytes as drug carriers is their long lifespan (approximately 120 days in humans). Moreover, biodegradable erythrocytes have no nucleus and most organelles but have high surface-to-volume ratios. Due to these properties, erythrocytes provide sufficient space for drugs to be encapsulated or loaded on the surface. In addition, biocompatible erythrocytes can protect encapsulated drugs from inactivation in the blood and damage to major organs. Therefore, various anticancer drugs including platinum drugs have been loaded into erythrocytes or attached on the membrane of erythrocytes by different methods to enhance half-lives, avoid rapid clearance, and improve biodistribution. Pores in the erythrocyte membrane can be induced by electroporation or osmosis-based methods including hypotonic hemolysis, which allow drugs to be encapsulated in the erythrocytes. The pores are then resealed to yield drug-loaded erythrocytes. In addition, nanoparticles have been attached to the membrane of erythrocytes via non-covalent interactions such as electrostatic, van der Waals, and hydrophobic interactions. The avidin-biotin bridge method has also been commonly used to conjugate avidin-labeled biopharmaceuticals on the surface of biotinylated erythrocytes.

Carboplatin is the second-generation platinum drug approved by the FDA in 1989 for the treatment of ovarian cancer. When compared to the first-generation platinum drug cisplatin, carboplatin is more stable against hydrolysis and less toxic to normal tissues, especially to the kidney. This higher stability makes carboplatin a good candidate to be loaded into erythrocytes. The encapsulation of carboplatin in human erythrocytes via hypotonic hemolysis was reported by De Flora’s group. Under a hypotonic condition, pores were formed on erythrocytes, which allowed carboplatin to diffuse into the cells. Followed by incubation in an isotonic solution, the pores on erythrocytes were resealed, and the carboplatin-loaded RBCs were formed. The loading amount was up to 5 mg/mL of packed cells, and the cell recovery rate was 70%. After incubation in autologous plasma, carboplatin was slowly released from the loaded erythrocytes at a rate of 12% within 3 h. This slow release of carboplatin indicates that the encapsulation method may lead to a lower clearance rate of carboplatin by the kidney and an increased concentration of carboplatin at the tumor site. This hypo-osmotic method, however, has several limitations. First, the membrane structures, metabolic properties, and GSH concentration in the erythrocytes were significantly disturbed after the encapsulation. Second, carboplatin was rapidly transformed in the erythrocytes into other platinum species including the aquated form, and hemoglobin was found to enhance this transformation. The premature activation of carboplatin limits its bioavailability. Last but not least, the concerns on the erythrocyte source, i.e., limited blood donors, risk of contamination by pathogens, and potential alloimmunization to the erythrocytes of donors, restrict the application of this method in clinical settings.

Auto- binding of platinum drugs onto the surface of intrinsic erythrocytes without damaging the membrane structure is a promising strategy alternative to the hypo-osmotic method. Recently, our group developed an erythrocyte-hitchhiked prodrug strategy to enhance the circulation half-life and tumor accumulation of carboplatin. A carboplatin-based platinum(IV) complex was conjugated with an erythrocyte-auto-binding peptide, ERY1, at the axial position via a thiol-maleimide Michael addition reaction to generate the prodrug ERY1-Pt(IV). The platinum prodrug was stable in a PBS buffer (pH 7.4) after conjugation with the ERY1 peptide, and it could be released from the ERY1-Pt(IV) prodrug by reduction with ascorbate. The prodrug had a high affinity to mouse erythrocytes with an equilibrium dissociation constant (Kd) in the nanomolar range (Kd = 63.3 nM). The efficient binding of ERY1-Pt(IV) to erythrocytes was also confirmed by confocal microscopy and flow cytometry. Subsequently, the prodrug was proved to have a circulatory half-life 18.5 times longer and accumulated tumor level in the tumor 7.7 times higher than the parent drug carboplatin in mice. Collectively, the circulation half-life and tumor accumulation of carboplatin were significantly enhanced by utilizing intrinsic erythrocytes as auto-binding carriers. The application of this strategy in humans, however, needs to be further explored by replacing the ERY1 peptide that can only bind mouse erythrocytes with a human erythrocyte-binding motif.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Strategic illustration of the ERY1-Pt(IV) prodrug for enhanced circulation half-life and tumor accumulation via auto-binding to the intrinsic mouse erythrocytes. Reproduced with permission. Copyright 2022, Wiley Online Library.

**Plasma proteins as carriers for small-molecule platinum drugs**

Human blood albumin (HSA), which accounts for half of the plasma proteins, is made up of 585 amino acids within three domains. The concentration of albumin in the plasma is around 35–50 g/L. The molecular weight of albumin is 67 kDa, and its
half-life is as long as 19 days. HSA mainly maintains oncotic pressure, buffers pH, and transports nutrients including fatty acids, hormones, and other small molecules in the blood. In addition, HSA contains many active binding sites, such as cysteine (Cys34), tryptophan (Trp214), and tyrosine (Tyr411). The protein has a negative charge under physiological conditions (pH 7.4). Furthermore, HSA can preferentially accumulate at the tumor sites via the enhanced permeability and retention (EPR) effect, and it shows an effective accumulation in cancer cells as a source of amino acid. These properties make HSA a great carrier for the delivery of anticancer drugs that can covalently or non-covalently bind to HSA. One example is Abraxane®, which is albumin-bound paclitaxel in nanoparticle formulation. This drug has been approved by the FDA for the treatment of metastatic breast cancer, non-small cell lung cancer, and pancreas adenocarcinoma. There are a number of reports on the delivery of platinum drugs utilizing albumin nanoparticles but they are not the main focus of this concept. Examples of small-molecule platinum drugs that can be delivered by intrinsic HSA are discussed below.

Polynuclear platinum(II) complexes primarily form 1,3- and 1,4-cross-links with DNA, which are quite different from the 1,2-cross-links formed by the approved platinum drugs. These unconventional platinum coordination complexes are among the most promising anticancer complexes to overcome drug resistance. The positively charged polynuclear platinum(II) complexes have a great potential to non-covalently bind to negative HSA and be delivered by the protein in order to optimize the transportation, distribution, and subsequent metabolism of the platinum complexes. Wang and Guo et al. found that a trinuclear platinum(II) complex 1 (Figure 2A) could spontaneously interact with HSA in a reversible and non-covalent manner. The major interaction between the complex and HSA was proved to be hydrophobic binding and π-π stacking, which was determined by ultraviolet-visible (UV-vis), fluorescence, circular dichroism (CD), Fourier transform-infrared (FT-IR) spectroscopies and inductively coupled plasma-mass spectrometry (ICP-MS). Moreover, the major binding site was demonstrated to be the hydrophobic cavity of domain II in HSA (Figure 2B). This reversible and non-covalent interaction makes the HSA-platinum complex a drug reservoir for antitumor purposes. This conclusion can be further solidified by in vivo examinations in the future.

As described above, HSA serves as the transporter of fatty acids. To increase the interaction of platinum drugs with HSA, Lippard et al. developed a platinum(IV) prodrug containing an axial hexaacycl chain that mimics the structure of fatty acids. The resulting platinum(IV) complex 2 (Figure 2C) could be buried under the surface of HSA and bind to HSA at a 1:1 ratio, likely at the Sudlow’s site I (Figure 2D). The binding was non-covalent and reversible, as the lipophilic platinum(IV) complex could be extracted from the aqueous solution of the platinum-HSA conjugate by nonpolar octanol. In addition, the binding to HSA improved the water solubility of the platinum(IV) complex, protected the prodrug from being reduced by reducing agents during circulation, and subsequently increased the stability of the platinum(IV) complex. The half-life of the platinum(IV) complex in the whole blood was 6.8 h, which is 18.9-fold longer than that of cisplatin (t1/2 = 21.6 min). This strategy of conjugating a long hydrophobic chain at the axial position of a platinum(IV) prodrug to improve the binding with HSA was also applied to carry indoleamine-2,3-dioxygenase (IDO) inhibitors (complex 3, Figure 2E) or glycoside ligands (complex 4, Figure 2F). The premature reduction of these small-molecule platinum(IV) prodrugs in the blood during circulation was prohibited by non-covalent binding to HSA. The half-lives of complexes 3 and 4 in the blood were 2.2 h and 20 h, respectively, which are significantly longer than the 21.6 min of cisplatin. The HSA-binding ability and the cancer-targeting property of glucose endow complex 4 a tumor accumulation level 2.2-time higher than the platinum(IV) control satraplatin and a comparable antitumor effect but lower toxicity than oxaliplatin.

Carboplatin was cleared quickly by the kidney; 65% of the injected dose was excreted within 12 h. To avoid fast renal clearance and prolong the retention time of carboplatin in the body, one of the most promising strategies is the binding of carboplatin to the plasma protein HSA. Kratz et al. developed a carboplatin analogue containing a maleimide group that reacts with the Cys34 of endogenous HSA (Figure 3A). In a capillary electrophoresis assay, 50% of the complex 5 bound to HSA within 1 min, proving the fast binding of this maleimide-containing platinum(II) complex to albumin. In addition, the introduction of maleimide group did not influence the ability of carboplatin to form adducts with dAMP and dGMP, such as [(NH₄)₂Pt(dAMP)]₂⁺, [(NH₄)₂Pt(dGMP)]₂⁺, and [(NH₄)₂Pt(dAMP)(dGMP)]. Compared with carboplatin, complex 5 showed an increased antitumor effect in a MaTu (human breast carcinoma) xenograft mice model. The HSA-binding maleimide ligand was also conjugated to a platinum(II)-acridine hybrid via a triazole ligand (complex 6, Figure 3B). 85–90% of the Cys34 in HSA bound to complex 6 after incubation for 3 h in an Ellman’s
test, and the addition of complex 6 to HSA did not disturb the conformation of HSA, indicating that the selective delivery of the platinum(II)-acridine hybrid into tumor tissues by HSA would not be affected.

As discussed above, platinum(IV) complexes bearing hydrophobic unbranched aliphatic chains and platinum(II)-maleimide conjugates bound to HSA non-covalently and covalently, respectively. The platinum(IV) complexes with hydrophobic chains, however, have low solubilities in water, and the platinum(II)-maleimide conjugates are easily hydrolyzed to react with chlorides and sulfides during long-time circulation. Thus, Heffeter and Kowol et al. developed a platinum(IV) complex 7 containing two maleimide ligands at the axial positions (Figure 3C). The complex was soluble in water and more inert than the platinum(II)-maleimide complexes during circulation. Complex 7 could rapidly bind to albumin at the Cys34 position with a binding half-life of approximately 1 h; 80% of complex 7 bound to albumin after incubation for 4 h. After injection into mice via tail veins, complex 7 formed stable adducts with albumin that acted as a carrier, and the circulation half-life of complex 7 was 1.7 times higher than that of oxaliplatin. By using a Pt(IV) form, the premature release of Pt(II) drug was prevented, as supported by the measurement of blood samples using size exclusion chromatography-inductively coupled plasma-mass spectrometry (SEC-ICP-MS). In addition, complex 7 was proved to efficiently accumulate in the tumor tissues with a Pt level 14-fold higher than that of oxaliplatin. The complex entered cancer cells via clathrin- and caveolin-mediated endocytosis. The binding ratio of the platinum(IV) complex 7, which contains two maleimide ligands, to albumin was proved to be 1:1, indicating that only one maleimide ligand reacted with albumin. The remained free maleimide ligand at the opposite axial position may react with other thiol-containing proteins or small molecules, which may lead to undesired pharmacological behaviors. To solve this potential issue, platinum(IV) complexes containing a single maleimide were developed. Complex 8 showed a fast binding rate to albumin in serum (Figure 3D), a higher accumulation level in the tumor than in the liver and kidney, a 4-fold higher Pt level in the tumor than oxaliplatin, and significant tumor shrinkage and/or regression effects. The antitumor performance of the oxaliplatin-based maleimide-containing platinum(IV) complex 8 was improved when compared with the cisplatin-based counterpart; the latter is easily reduced by ascorbate, demonstrating the importance of chemical inertness during circulation. Moreover, maleimide ligands were conjugated to platinum(IV) prodrugs bearing indoleamine 2,3-dioxygenase (IDO) inhibitors or glutamate-cysteine ligase inhibitors (complexes 9 and 10 in Figures 3E and 3F, respectively) to facilitate the binding to albumins. As a consequence, these prodrugs have improved selectivity to malignant tissues and increased antitumor activities in vivo compared to oxaliplatin.

Besides albumin, which is the most abundant protein in the blood, other blood proteins such as apoferritin (AFT) have also been used as carriers to deliver platinum drugs. Apoferritin is the demineralized ferritin that can be internalized through endocytosis by cancer cells expressing ferritin receptors. This property makes apoferritin a prospective vehicle for platinum drugs to relieve drug resistance by enhancing cellular accumulation. Guo and co-authors developed a method to entrap cisplatin, carboplatin, and oxaliplatin into the cavity of apoferritin. At pH 2.0, the protein was dissociated into subunits, and the platinum drugs in their saturated solutions were diffused into the protein cavity. Subsequent to the unfolding process, at pH 7.4, apoferritin was reformed, and the platinum drugs were encapsulated in apoferritin to yield apoferritin-platinum complexes AFT-CDDP, AFT-CBDDCA, and AFT-LOHP (Figure 4). The structural integrity of apoferritin after the encapsulation of platinum drugs was confirmed via UV-vis, CD, dynamic light scattering (DLS) spectroscopies, and Zeta potential measurement. The results indicate that the binding affinity of apoferritin to the target receptors was not changed after encapsulation with the platinum drugs. In addition, the loading amount of platinum in apoferritin was very high, with molar ratios of platinum to apoferritin ranging from 17 to 45. These apoferritin-platinum complexes showed cytotoxicities inferior to the parent platinum(II) drugs in rat pheochromocytoma PC12 cells, presumably due to the slow and controlled release of the platinum drugs from the complexes. The cellular accumulation of AFT-CDDP was found to be 4.5-fold higher than that of cisplatin, confirming the ability of apoferritin to facilitate the cellular uptake of cargoes in cancer cells. However,
CONCEPT

further in vivo experiments are needed to verify the release mechanism of the platinum drugs and the pharmacological performance of these AFI-Pt complexes. In addition, the AFI-Pt complexes were prepared under a non-physiological condition (pH 2.0), which may promote the hydrolysis of platinum drugs. [40]

![Figure 4](image-url)  
**Figure 4.** Schematic illustration of the pH-mediated encapsulation of cisplatin (CDDP), carboplatin (CBDCA), or oxaliplatin (LOHP) by apoferritin (AFt) via an unfolding–refolding process. Reproduced with permission. [20] Copyright 2009, Elsevier

**Strategies to increase the stability of platinum-based thiol-maleimide conjugates**

Like many antibody-drug conjugates (ADCs), platinum-based thiol-maleimide conjugates that can be delivered by erythrocytes or albumins also suffer from stability issues. After a Michael addition reaction between a maleimide in the platinum moiety and a thiol in protein or peptide, the resulting thiosuccinimide may undergo two competing reactions in the plasma: a retro-Michael reaction and a hydrolysis reaction (Figure 5A). The retro-Michael reaction results in the reformation of platinitated maleimide and original thiol, and the former may react with other plasma thiols, leading to reduced delivery efficiency and potential side effects. The second pathway is hydrolysis, where the platinum is still present in the stable ring-open products, which are resistant to thiol exchange and retro-Michael addition. [20] Thus, to reduce the elimination via retro-Michael addition and increase the stability of platinum-based thiol-maleimide conjugates, one potential strategy is the promotion of the hydrolysis of thiosuccinimide ring. Another strategy that is related to hydrolysis is to utilize Michael-transcyclization reaction to open the thiosuccinimide ring and form another stable structure, which has been utilized to stabilize platinum-based thiol-maleimide conjugates. For instance, a free amino group was anchored at the β-position of the sulfur in thiosuccinimide to facilitate the automatic formation of a stable six-membered thiomorpholinone ring via the Michael-transcyclization reaction (Figure 5B). [41] Several strategies to promote the hydrolysis of thiosuccinimide ring have been applied to increase the stability of organic thiol-maleimide conjugates, [42] and these methods have great potential to be utilized for the preparation of stable platinum-maleimide conjugates that can be delivered by blood components to the targeted tumor sites.

![Figure 5](image-url)  
**Figure 5.** A. Michael addition of the platinum-based maleimides to the thiols results in maleimide–thiol conjugates that can undergo further reactions through two pathways: a retro-Michael pathway and a hydrolysis pathway. B. Automatically locking the thioether with a β-amine via a transcyclization reaction.

**Conclusion and perspective**

Although platinum drugs are widely used in the clinic and platinum(IV) prodrugs have been extensively studied in clinical trials, their therapeutic outcomes are still limited by poor pharmacokinetic properties, severe side effects, and drug resistance. To improve the circulation half-lives and increase the biodistribution properties of platinum drugs at the tumor sites, blood components such as erythrocytes, albumins, and apoferritins have been exploited as drug carriers. Erythrocytes do not contain nuclei and most organelles, making them suitable for platinum drugs to be encapsulated. Their membrane structures, however, are disrupted after encapsulation, which may decrease the delivery efficiency. Thus, platinum(IV) prodrugs that can automatically attach to the intrinsic erythrocytes without damaging the membrane structure were recently developed. As the most abundant blood protein, albumin was also used to deliver polynuclear, long alkyl chain-containing, and maleimide-conjugated platinum complexes, and these complexes can be loaded non-covalently or covalently. In addition, the cancer-targeting blood protein apoferritin was applied to deliver globally-approved platinum drugs into cancer cells. As platinum-based thiol-maleimide conjugates involved in erythrocyte- and blood protein-based delivery systems suffer from elimination through a retro-Michael addition reaction, strategies that may be helpful for the rational design of novel platinum-based thiol-maleimide conjugates with high stability are discussed.

In the future, the application of human erythrocytes as carriers to enhance the circulation half-lives and tumor accumulation levels of platinum drugs can be explored by conjugating platinum conjugates with peptides that have an auto-binding property to human erythrocytes. In addition, cancer-targeting units and bioactive molecules can be conjugated at the other axial position of platinum(IV) complexes containing erythrocyte auto-binding peptides to endow them with additional selectivity to tumors and remission to drug resistance. Furthermore, other blood components, such as white blood cells, may be utilized as carriers for platinum drugs to treat cancers.

Collectively, we briefly summarized the strategies that utilize blood components as carriers to enhance the circulatory half-lives and tumor accumulation of small-molecule platinum drugs. There is still a large room for the development of platinum anticancer drugs and prodrugs that can utilize blood components as carriers. We hope that this concept will inspire researchers to develop...
rational designs and construct novel platinum drugs that have excellent antitumor performance in vivo.

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Keywords

Anticancer Agents · Platinum Drugs · Drug Delivery · Erythrocyte · Albumin

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Platinum drug · Platinum(IV) prodrug · Drug carriers · Erythrocytes · Thiol-maleimide conjugate
The long-lasting and non-immunogenic blood components are ideal for the delivery of platinum drugs into tumors. In the concept, we summarize the methods that apply blood components such as erythrocytes, albumins, and apoferritins as carriers to prolong circulation half-life, increase tumor accumulation, and improve the antitumor effects of small-molecular platinum drugs.