

# Nature-Inspired Alternatives to PEG for Next-Generation Long-Circulating Nanocarriers

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**Abstract:** Polyethylene glycol (PEG) has long been considered as the gold standard for imparting stealth properties to nanocarriers. However, the recent emergence of anti-PEG antibodies has spurred innovation toward nature-inspired alternatives. By mimicking the structural and functional architectures of biological systems such as cell membranes and protein corona, nanocarriers can be engineered to achieve prolonged circulation, superior biocompatibility, and active targeting capabilities. This perspective presents nature-inspired alternatives to PEG, including cell membranes and the protein corona, for extending the circulation time of nanocarriers. It also highlights current challenges associated with these nature-inspired alternatives and outlines future research directions to overcome these hurdles in designing next-generation long-circulating nanocarriers.

**Keywords:** long circulation, ABC phenomenon, cell membranes, protein corona

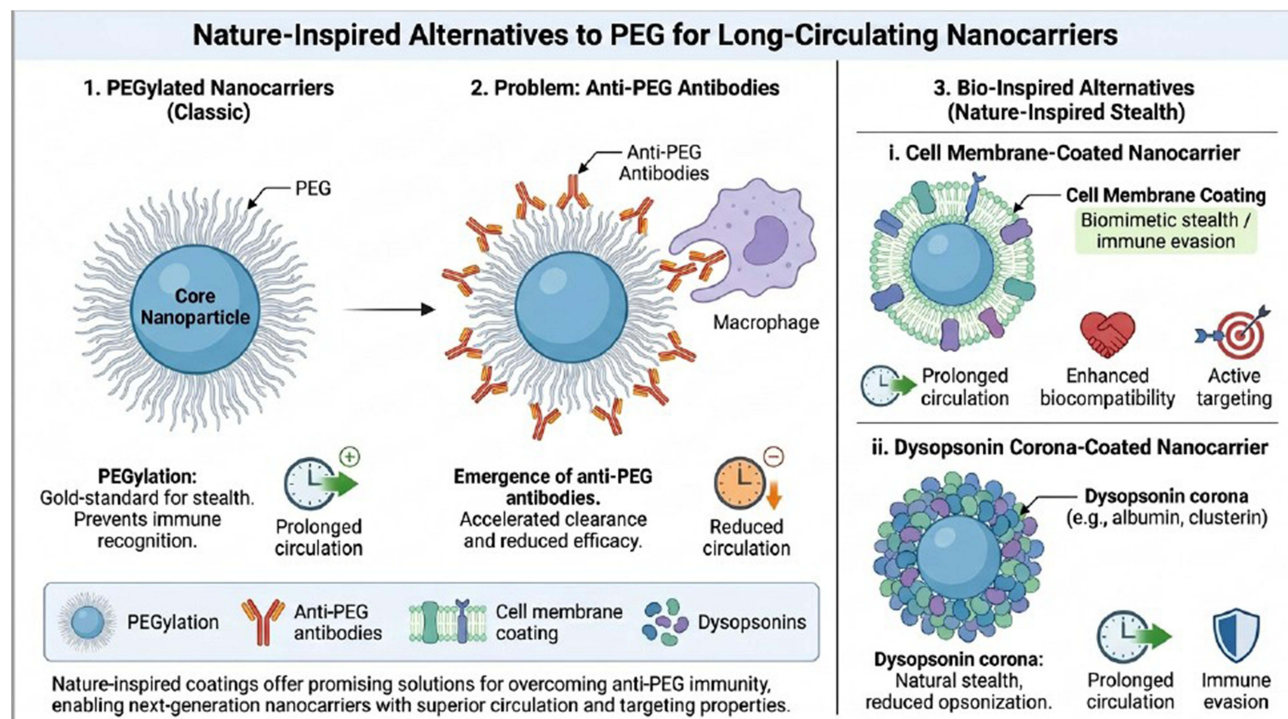
## Introduction

### The PEG Paradigm and Its Pitfalls

PEGylation, the covalent attachment of polyethylene glycol (PEG) to therapeutic agents, is a well-established and clinically approved drug delivery method that has been used for decades to extend drug circulation time and reduce immunogenicity, with minimal side effects.<sup>1</sup> The use of PEG has been approved by the U.S. Food and Drug Administration (FDA) as a base or vehicle in cosmetics, foods, and pharmaceuticals, including oral, topical, injectable, nasal, and rectal formulations. It is slightly toxic and is easily eliminated from the body via feces or kidneys.<sup>2</sup> PEGylation technology has emerged as a widely recognized approach for prolonging the blood residence time of various therapeutics, including small molecules and proteins, leading to significant advancements in the development of drug-loaded nanoparticles and biologics. The hydrophilic PEG chains form a hydration layer around the nanocarriers, which prevents the recognition and binding of nanocarriers by opsonins through spatial repulsion. Consequently, PEGylation is considered to decrease the phagocytosis and clearance of nanocarriers from the systemic circulation by the mononuclear phagocyte system (MPS).<sup>3</sup> The impact of PEGylation on the pharmaceutical industry is evident from the multibillion-dollar market value of PEGylated drugs, as over 30 PEGylated products are currently used in clinics, with many more undergoing clinical trials. For further information, please refer to work published by Gao et al<sup>4</sup> Table 1 summarizes some FDA-approved PEGylated nanocarriers.

Despite the success of PEGylated therapeutics, recent studies have revealed that PEG is not as biologically inert as previously believed. Repeated administration can induce the production of anti-PEG antibodies, resulting in the accelerated blood clearance (ABC) phenomenon and reduced therapeutic efficacy.<sup>5,6</sup> In this phenomenon, the second dose of PEGylated nanocarriers is rapidly cleared from the bloodstream when injected within a certain time interval from the first dose, due to their accelerated accumulation in the liver. This phenomenon alters the biodistribution of the encapsulated drug, leading to decreased therapeutic efficacy and potentially causing adverse effects.<sup>7</sup> In preclinical animal models, the initial administration of PEGylated nanocarriers induces the production of anti-PEG antibodies. These antibodies specifically recognize and bind to

## Graphical Abstract



the surface of subsequently administered PEGylated nanocarriers, triggering activation of the complement system. This immune response significantly accelerates the *in vivo* clearance of nanocarriers.<sup>8</sup> Similarly, clinical studies in humans have frequently reported elevated titers of anti-PEG IgM and IgG antibodies in patients treated with PEGylated biotherapeutics. The presence of these antibodies is associated with reduced therapeutic efficacy, increased toxicity, and a higher incidence of adverse effects. Collectively, these findings challenge the widely held assumption that PEG is nonimmunogenic. Instead, PEGylated nanocarriers commonly provoke an immune response, wherein the induced anti-PEG antibodies contribute to

**Table 1** FDA Approved PEGylated Nanocarriers

Identifier (Year)	Generic Name	Parent Drug	Mode of Action of PEG	Indication	Approval Holder
NDA 050718 (1995)	Doxorubicin HCl liposomes	Doxorubicin in liposomes	Reduction in protein adsorption and phagocytic clearance	Multiple myeloma, Ovarian cancer, AIDS-related Kaposi's Sarcoma	Schering
NDA 207793 (2015)	Irinotecan liposomes	Irinotecan in liposomes	Reduction in protein adsorption and phagocytic clearance	Metastatic adenocarcinoma	Merrimack Pharmaceuticals
NDA 210922 (2018)	Patisiran	siRNA in LNPs	Reduction in protein adsorption and phagocytic clearance	Polyneuropathy of hereditary transthyretin-mediated amyloidosis	Alnylam Pharmaceuticals
BLA 125742 (2021)	COVID-19 mRNA vaccine	mRNA in LNPs	Reduction in protein adsorption and phagocytic clearance	COVID-19	BioNTech/Pfizer
BLA 125752 (2022)	COVID-19 mRNA vaccine	mRNA in LNPs	Reduction in protein adsorption and phagocytic clearance	COVID-19	Moderna

diminished therapeutic outcomes by mediating the ABC phenomenon.<sup>9</sup> Therefore, drug delivery scientists are actively seeking for alternative solutions to PEG to enhance the circulation time and efficacy of therapeutics.

Recently, biologically inspired materials, such as cell membrane-coated nanoparticles and endogenous dysopsonin coronas, have been employed in drug delivery applications. Unlike synthetic polymer-coated stealth nanoparticles, which primarily rely on hydration coronas for their function, these alternative nanoparticles incorporate active biological components to achieve anti-phagocytic effects *in vivo*.<sup>10</sup> Specifically, cell membrane constituents are extracted from healthy cells and subsequently coated onto the surfaces of nanocarriers, effectively masking them as native cells. This “cell membrane camouflage” strategy reduces immune system recognition and prolongs circulation time. Consequently, it facilitates immune evasion and promotes targeted interactions with specific cell types, thereby enhancing the specificity and efficacy of drug delivery systems.<sup>11</sup> The protein corona contains dysopsonins, such as albumin, histidine-rich glycoprotein, clusterin, Apo A4, and Apo C3, which extend the blood circulation time of nanoparticles.<sup>12–14</sup> Albumin, the most abundant serum protein, is particularly associated with dysopsonin-mediated immune evasion, thereby prolonging nanoparticles circulation time.<sup>15</sup>

This perspective introduces nature-inspired alternatives to PEG, such as cell membranes and protein coronas, to overcome the ABC phenomenon and prolong the circulation time of nanocarriers.

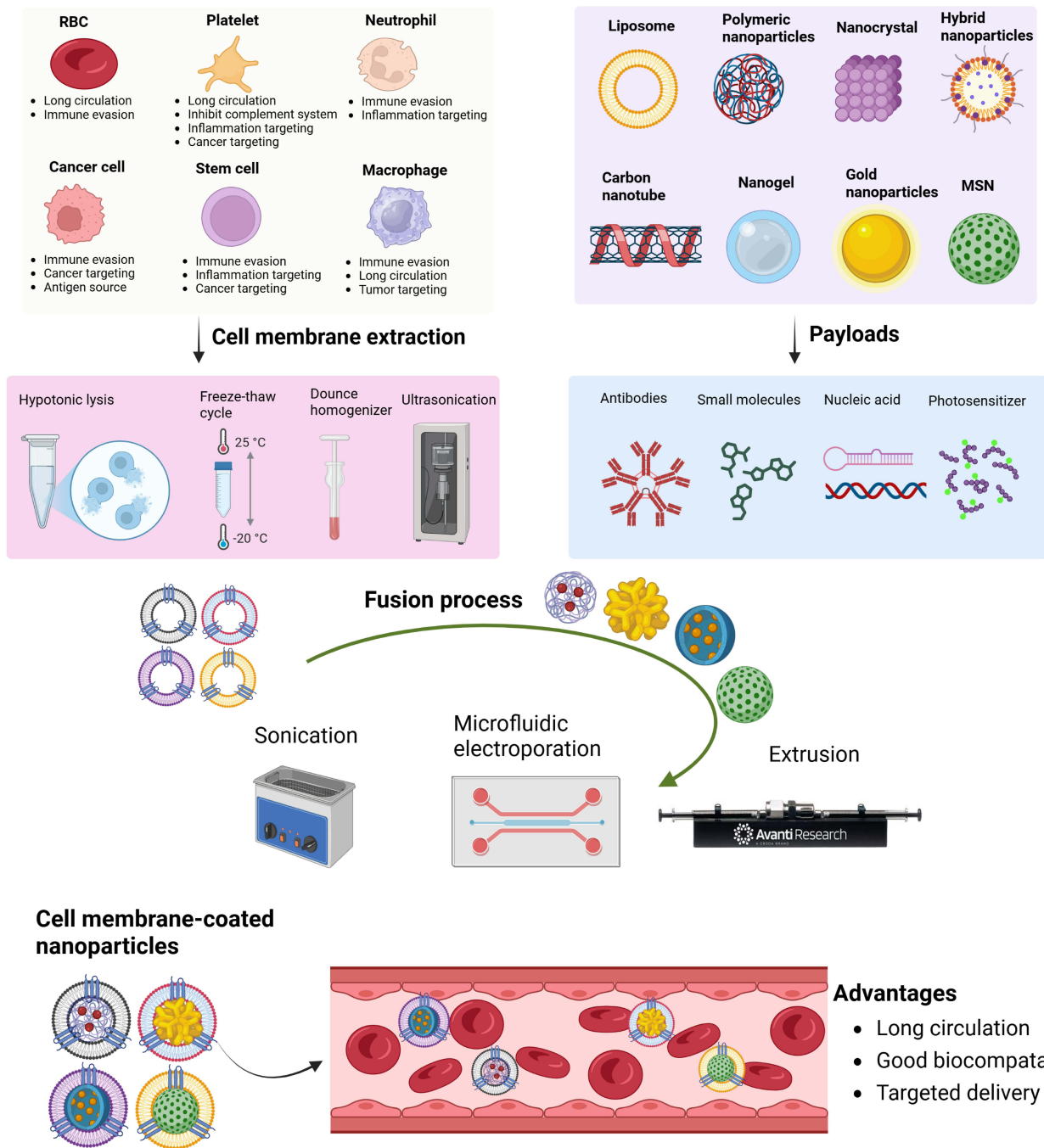
## Natural Architectures for Next-Generation Long-Circulating Nanocarriers

### Cell Membranes

Cells, the fundamental units of the body, perform a wide range of functions, including the ability to interface and interact with the surrounding environment. Rather than synthetically replicating these functions, researchers are increasingly leveraging naturally isolated cell membranes to enhance the biointerfacing capabilities of nanoparticles.<sup>16</sup> Cell membrane coating involves isolating cell membranes from various source cells and applying these membranes onto nanoparticles. The cell membrane is isolated from source cells using various techniques, including hypotonic lysis, dounce homogenization, ultrasonication, and freeze-thaw cycles. Careful attention must be paid to preserve the integrity and functionality of the cell membrane. The isolated cell membranes are then coated onto nanoparticle cores. Both organic (eg., liposomes, PLGA) and inorganic (eg. metal-based) nanoparticle cores are used, each offering distinct advantages in terms of therapeutic efficacy, drug loading, and stability.<sup>17</sup> The coating of membrane onto nanoparticles is typically achieved through techniques such as sonication, extrusion, and electroporation. Sonication uses ultrasonic waves to coat membrane vesicles onto nanoparticles. Ultrasonic parameters should be optimized to enhance fusion efficiency while minimizing protein denaturation and drug leakage. In the extrusion process, nanoparticle cores and membrane vesicles are passed through polycarbonate membranes with varying pore sizes to fuse the membrane with the nanoparticles. Although this process is effective and yields stable results, it is not suitable for large-scale production. In electroporation, an electric pulse creates transient pores in the cell membrane, allowing nanoparticles to enter the cell membrane. This process significantly preserves the membrane proteins and integrity.<sup>18</sup> The resulting cell membrane-coated nanoparticles have inherent properties, such as prolonged circulation, immune evasion, biocompatibility, and homotypic targeting<sup>19</sup> (Figure 1). Zhang’s lab was the pioneer in reporting cell membrane-coated nanotechnology as a long-circulating biomimetic nanosystem in 2011. The researchers isolated cell membranes from red blood cells (RBCs) and coated them onto PLGA nanoparticles. The resulting RBC membrane-coated nanoparticles conferred stealth properties to polymeric nanoparticles. These RBC membrane-coated nanoparticles exhibited a circulation half-life significantly longer than that of their PEGylated counterparts.<sup>20</sup> Subsequent research has explored coating nanoparticles with membranes derived from platelets,<sup>21</sup> cancer cells,<sup>22</sup> leukocytes,<sup>23</sup> and stem cell.<sup>24</sup>

### RBC Membrane

RBCs, commonly known as erythrocytes, are abundant in the human body and play crucial roles in oxygen transport. The lipid bilayer of RBC exhibits distinct asymmetry, with phosphatidylethanolamine and phosphatidylserine predominantly located on the inner leaflet, while sphingomyelin and phosphatidylcholine are primarily found on the outer leaflet. This arrangement helps maintain membrane fluidity and prevents unwanted cell aggregation. Additionally, negatively charged sialylated glycoproteins on the surface reduce nonspecific protein binding and inhibit activation of the complement system.



**Figure 1** Schematic illustration of method of preparation and inherent properties of cell membrane-coated nanoparticles. (<https://www.BioRender.com>).

Key surface proteins such as CD47, CD59, and CD55 protect RBCs from phagocytosis and complement-mediated destruction. Furthermore, the absence of mitochondria and nuclei decreases the cells' metabolic activity and reduces their potential to elicit immune responses.<sup>25</sup> The high density of CD47 proteins expressed on their surfaces signals immune cells to inhibit immune attacks, allowing RBCs to circulate without being targeted by the host immune system. This immune-evasive property of RBC membranes makes them particularly advantageous as a coating material for nanoparticles, as they enhance circulation longevity and improve biocompatibility.<sup>26,27</sup> Building on this concept, Rao et al functionalized Fe<sub>3</sub>O<sub>4</sub> nanoparticles with RBC membranes. In vitro macrophage uptake and in vivo pharmacokinetic studies demonstrated that due to the presence of CD47, Fe<sub>3</sub>O<sub>4</sub> nanoparticles evaded immune clearance via the CD47/SIRP- $\alpha$  signaling pathway. Upon repeated

administration of the RBC membrane-coated Fe<sub>3</sub>O<sub>4</sub> nanoparticles, no ABC phenomenon was observed. Therefore, the researchers concluded that RBC membranes are a superior alternative to PEG for prolonging the systemic circulation time of nanoparticles.<sup>28</sup> Similarly, Piao et al found that RBC membranes serve as alternative coating materials to PEG to extend the blood residence time of gold nanocages used in photothermal therapy.<sup>29</sup>

### Platelet Membrane

Platelet membrane coating endows nanoparticles with properties such as prolonged circulation time, immune evasion, and enhanced targeting of inflammation, tumors, and other pathological sites. The prolonged circulation is attributed partly to their “marker-of-self” receptor, CD47, and sialylated glycans, which prevents macrophage-mediated phagocytosis of platelet membrane-coated nanoparticles. In addition to CD47, platelet membranes also contain P-selectins, glycoprotein (GP) Ib, and integrins such as  $\alpha$ IIb $\beta$ 3 and  $\alpha$ 5 $\beta$ 1.<sup>30</sup> P-selectins mediate interactions with inflamed or damaged tissues, improving targeting efficiency in cardiovascular diseases.<sup>31</sup> They can also bind to overexpressed CD44 on tumors, facilitating dynamics and complex tumor-platelet cross-talk critical for tumor growth and metastasis. GPIb binds to exposed collagen in damaged vasculature to initiate tissue repair. With the help of GPIb, platelets can also bind directly to pathogenic bacteria, aiding in their removal from the body. Integrins such as  $\alpha$ IIb $\beta$ 3 and  $\alpha$ 5 $\beta$ 1 binds to the extracellular matrix in the tumor milieu, optimizing therapeutic cargo delivery and enhancing treatment outcomes.<sup>32</sup> Immunomodulatory proteins like CD40L and CD62P are also expressed on platelets membranes, making platelet membrane-coated nanoparticles highly applicable in immunotherapy.<sup>31</sup> With such broad and dynamic biointerfacing capabilities, platelet membrane-coated nanoparticles have become attractive drug carriers for long-circulation and targeted delivery applications.

### WBC Membrane

Leukocytes, or white blood cells (WBCs), are immune cells responsible for protecting the body against infections, repairing tissue injuries, engulfing foreign invaders, and resisting pathogens or diseases. Leukocytes, such as neutrophils, macrophages, NK cells, and T cells, play essential roles in many important diseases, including infections, cancers, and inflammatory disorders. Their functional diversity have inspired the development of WBC membrane-coated nanoparticles that inherit entire source cell antigens. WBC membrane-coated nanoparticles act as source cell decoys and simulate their broad biointerfacing properties, with intriguing therapeutic potentials.<sup>33</sup> Proteins expressed on the cell membranes of immune cells confer a diverse array of functionalities to nanoparticles, including extended circulation time in the bloodstream, enhanced antigen recognition for improved targeting, optimized cellular interactions, controlled drug release profiles, and reduced in vivo toxicity.<sup>34</sup>

### Cancer Cell Membrane

Cancer cells utilize various complex immune evasion mechanisms that enable them to grow uncontrollably. The ability of cancer cells to escape immune surveillance involves a complex interplay between tumor cells, the tumor microenvironment, and immune cells. Cancer cells employ several strategies to evade the immune system, including creating an immunosuppressive microenvironment, altering antigen presentation, and inhibiting immune cell functions. These strategies enable cancer cells to persist and proliferate despite immune surveillance.<sup>35</sup> For homotypic targeting, galectin-3, T antigen (Thomsen-Friedenreich glycoantigen), and epithelial cell adhesion molecule (EPCAM) on cancer cell membranes facilitate homotypic adhesion among cancer cells. Moreover, antigens present on cancer cell membranes can be effectively utilized in cancer immunotherapy. Therefore, coating nanoparticles with cancer cell membranes retains tumor-specific antigens and homotypic targeting capabilities, enriching drug delivery approaches for cancer immunotherapy.<sup>36</sup>

### Stem Cell Membrane

The unique properties of stem cells primarily arise from the diverse array of receptors on their membranes, including chemokine, cytokine, cell-matrix, growth factor, and cell-cell communication receptors. Chemokines play a crucial role in stem cell migration, adhesion, and homing to tumors or injured sites. Growth factor receptors are the second most abundant type of stem cell membrane receptor and are associated with stem cell differentiation and migration. Cytokine receptors guide stem cells toward injured areas. Cell-matrix receptors such as CD44 are involved in cell homing, adhesion, and migration. Notch, a transmembrane receptor, mediates signaling between the cells and the nucleus. Therefore, coating nanoparticles with mesenchymal stem cell membranes is an effective method for selective targeting, enabling entry into specific cells.<sup>37</sup>

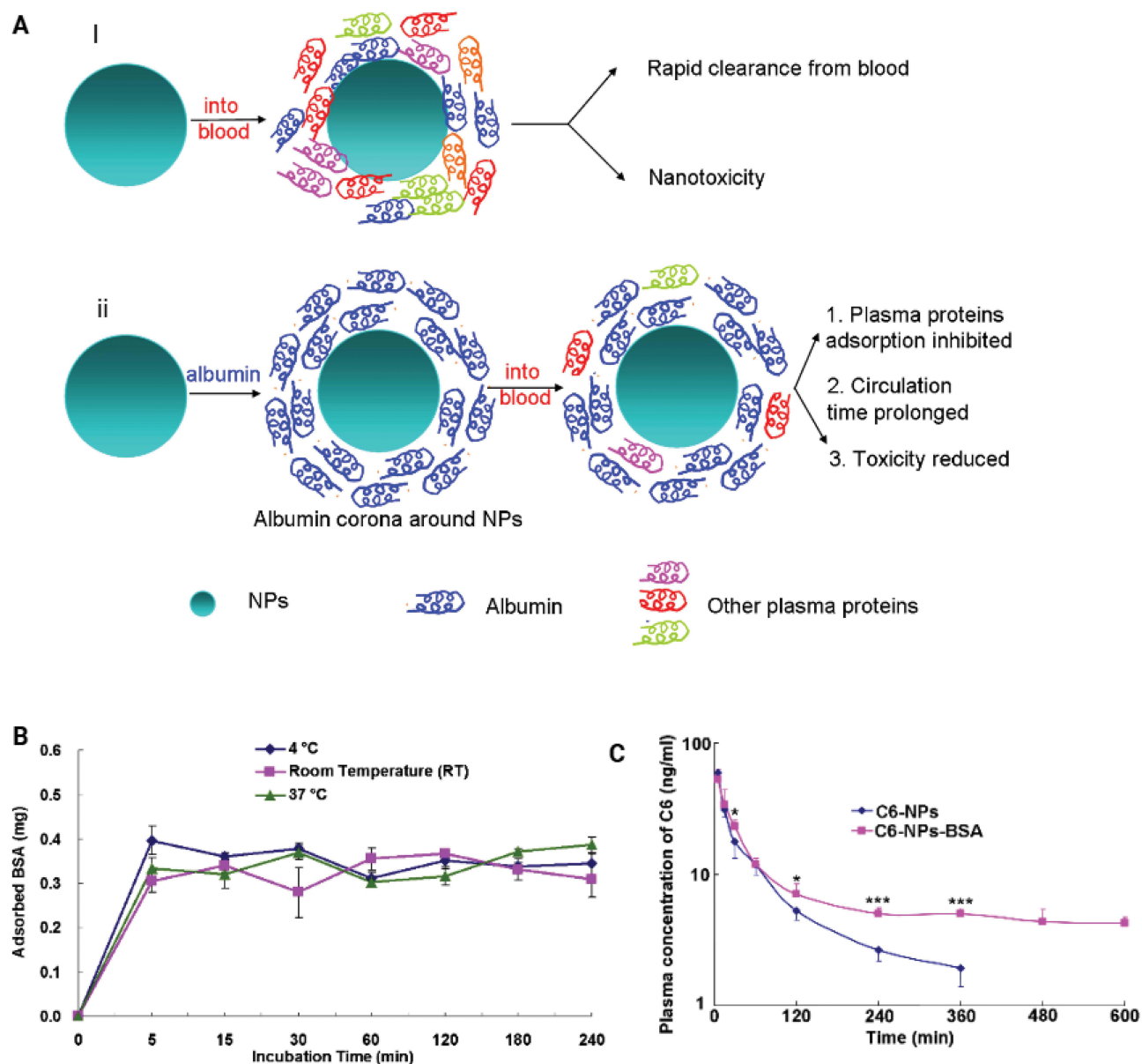
## Protein Corona

After systemic administration, nanoparticles are exposed to several thousands of proteins in the blood. These proteins are adsorbed on the surface of nanoparticles and form a layer around the nanoparticles called a protein corona. The protein corona changes the physicochemical characteristics of nanoparticles, such as size, surface charge, functionality, and surface composition, thus providing a new biological identity to nanoparticles. This nanoparticle–protein complex determines various biological responses, such as circulation time, cellular uptake, bioavailability, and even toxicity.<sup>38</sup> Historically, the formation of a protein corona has been associated with adverse delivery outcomes due to opsonization. Opsonins are proteins that bind to the surface of exogenous particles, including synthetic nanomaterials in the bloodstream, thereby marking them for recognition, sequestration, and subsequent degradation by MPS.<sup>39</sup> However, there is also a silver lining. The protein corona contains dysopsonins, such as albumin, histidine-rich glycoprotein, clusterin, Apo A4, and Apo C3, which prolong the blood circulation time of nanoparticles.<sup>12–14</sup> Albumin is the most abundant serum protein and is associated with dysopsonin-mediated immune evasion, prolonging the circulation time of nanoparticles.<sup>15</sup> Albumin is the predominant protein in blood plasma, constituting approximately 60% of the total blood protein content. As a highly water-soluble globular protein, albumin exhibits biodegradability, biocompatibility, non-immunogenicity, and well-established clinical safety. Its distinctive pocket-like structural features, defined by specific chemical configurations and conformations, enable interactions with a wide range of pharmaceutical agents, potentially protecting these compounds from metabolic degradation and elimination *in vivo*. With a half-life of approximately 19 days and the ability to evade renal clearance, albumin effectively prolongs the systemic circulation time of nanomedicines. The internalization of albumin by tumor cells primarily occurs through receptor-mediated transcytosis involving gp60 receptors and the secreted protein acidic and rich in cysteine (SPARC) pathway, facilitating active tumor targeting without the need for external ligand modification.<sup>40</sup> Due to these advantages, the preformed albumin corona provides a protective coating to the polymeric nanoparticles. The albumin-nanoparticle nexus inhibits plasma protein adsorption and decreases complement activation, which ultimately prolongs the circulation time and reduces the toxicity of polymeric nanoparticles (Figure 2).<sup>41</sup> Similarly, *in situ* albumin corona protected maleimide-decorated nanoparticles from phagocytosis in the systemic circulation, prevented the ABC phenomenon after subsequent dose administration, and facilitated nanoparticle accumulation at tumor sites.<sup>42</sup> Albumin corona has enabled the targeted delivery of drug nanocarriers to the liver,<sup>43</sup> kidney,<sup>44</sup> and heart,<sup>45</sup> thus regulating their biodistribution. Clusterin (also known as apolipoprotein-J) is a major protein of the corona that is attached to the surface of polymer-modified nanoparticles. The incorporation of polymer-modified nanoparticles with clusterin reduced macrophage uptake, providing a dysopsonin-mediated immune evasion function of clusterin.<sup>12</sup> Aoyama et al also reported that clusterin provides a stealth effect to non-PEGylated silver and silica nanoparticles. Binding of clusterin to both nanoparticles suppressed the cellular uptake of nanoparticles in human macrophage-like cells (THP-1 cells).<sup>46</sup> Histidine-rich glycoprotein is the most abundant protein in the hard corona of SiO<sub>2</sub> nanoparticles. Histidine-rich glycoproteins compete and bind with high affinity to the nanoparticle surface, forming a stable and homogenous corona that inhibits the binding and uptake of nanoparticles by macrophages.<sup>14</sup> CD47 is a “marker of the self.” Building on this understanding, multiple research groups have engineered vectors, including nanoparticles and lentiviruses, functionalized with CD47 to evade immune cell detection.<sup>47–49</sup> In 2013, the laboratory of D. Discher introduced simplified variants of CD47, termed “minimal self-peptides,”<sup>50</sup> which have demonstrated significant efficacy in preventing macrophage-mediated clearance of various nanomedicines such as albumin-based nanocarriers,<sup>51</sup> silica nanoparticles,<sup>52</sup> and lipid nanoparticles.<sup>53</sup> Recently, Ponton et al reported the cloaking of albumin and CD47 peptides on mesoporous silica nanoparticles for enhanced immune evasion and synergistic combination therapy. The results showed that albumin and CD47 peptide provided long circulation times to mesoporous silica nanoparticles and mitigated macrophage phagocytosis by up to 3.5-folds.<sup>54</sup> These findings suggest that dysopsonins in the protein corona can be utilized as substitutes for PEG to provide stealth ability to the nanocarriers.

Table 2 summarizes several representative studies of biomimetic nanosystems as nature-inspired alternatives to PEG, highlighting their surface proteins, improvements in circulation half-life, and key features.

## Current Challenges and Future Prospects

Despite the considerable advantages of cell membrane-coated nanoparticles—such as prolonged blood circulation, biocompatibility, immune evasion, and targeted efficiency—this technology is still in its infancy. From bench to bedside,



**Figure 2** (A) Schematic illustration of the biological responses to nanoparticles in the absence and presence of albumin Corona. (i) Upon entry into the bloodstream, various plasma proteins adsorbed onto the bare nanoparticles, leading to accelerated clearance and toxicity. (ii) The presence of preformed albumin corona on the surface of NPs effectively inhibits the adsorption of plasma proteins, thereby extending circulation time and mitigating the associated toxicity of the nanoparticles. (B) Adsorption kinetics of both soft and hard BSA corona. (C) Pharmacokinetic profiles of coumarin-6 in nanoparticles and nanoparticles albumin corona after I.V. administration into the healthy male SD rats. Adopted from<sup>41</sup> with permission. Copyright Elsevier, 2013.

several theoretical challenges and technical barriers need to be overcome. Currently, only a few defined membrane proteins are responsible for immune evasion and targeting properties; however, numerous other proteins may target different organs and potentially trigger immune responses. Therefore, a three-dimensional microenvironment should be recreated to facilitate cell-cell and cell-extracellular matrix interactions, enabling differentiation between functional proteins and those that may provoke immune responses.<sup>56</sup>

The large-scale production of cell membrane-coated nanoparticles remains a significant challenge to their widespread application. Current cell membrane coating techniques primarily rely on membrane extrusion and sonication, each with distinct advantages and disadvantages. Specifically, sonication provides high production efficiency but results in low uniformity, whereas membrane extrusion achieves high uniformity at the cost of production efficiency. These limitations

**Table 2** Summary of Biomimetic Nanosystems as Nature-Inspired Alternatives to PEG, Highlighting Their Surface Proteins, Improvements in Circulation Half-Life, and Key Features

Biomimetic Nanosystems	Surface Proteins/Biomarkers	Circulation Half-Life Improvements	Key Features	Ref.
RBC membrane-coated Fe <sub>3</sub> O <sub>4</sub> nanoparticles (Fe <sub>3</sub> O <sub>4</sub> @RBC NPs)	CD47	After 24 h, the blood retention of RBC membrane-coated Fe <sub>3</sub> O <sub>4</sub> nanoparticles was 14.2% of injected dose per gram	<ol style="list-style-type: none"> <li>1. Extended circulation time and no ABC phenomenon</li> <li>2. Administration of Fe<sub>3</sub>O<sub>4</sub>@RBC NPs does not elicit immune responses neither at cellular level nor the humoral level</li> <li>3. Biocompatible</li> </ol>	[28]
Platelet membrane-coated PLGA nanoparticles (PNPs)	CD47, CD59, CD55, integrin components (α2, α1b, α5, α6, β1, and β3) and other transmembrane Proteins (CLEC-2, GPIIb, GPIV, GPV, GPIIb, and GPIX)	Prolonged circulation time	<ol style="list-style-type: none"> <li>1. Reduced cellular uptake by macrophage-like cells and lack particle-induced complement activation</li> <li>2. Selective adhesion to damage human and rodent vasculatures as well as enhanced binding to platelet-adhering pathogens</li> </ol>	[21]
Nanoporous silicon particles functionalized with leukocyte membranes (leukolike vectors)	LFA-1, CD3z, CD45, Lck	Enhanced particle circulation time	<ol style="list-style-type: none"> <li>1. The leukolike vectors showed cell-like functions</li> <li>2. Enhanced circulation time and improved accumulation in a tumor</li> </ol>	[23]
Mesenchymal stem cell membrane-coated gelatin nanogels	—	Decreased clearance by RES	<ol style="list-style-type: none"> <li>1. Biocompatible drug delivery system</li> <li>2. High tumor targeting</li> </ol>	[24]
Albumin-coated PLGA nanoparticles (PLGA@BSA NPs)	Albumin	Longer blood circulation time	<ol style="list-style-type: none"> <li>1. In vitro, PLGA@BSA NPs exhibited higher cytotoxicity, stability, cell internalization, and spheroids penetration</li> <li>2. Longer blood circulation time in vivo</li> </ol>	[55]

could be overcome by employing advanced fabrication methods such as microfluidic technologies, three-dimensional printing, and particle replication in non-wetting templates.<sup>26</sup>

Preclinical data on cell membrane-coated nanoparticles face challenges in the reproducibility of experimental results and safety assessments. Significant heterogeneity exists in the sources of cell membranes. Variations in cell lines, culture conditions, passage numbers, and extraction methods lead to differences in membrane structure, composition, and protein expression. Similarly, preparation techniques, particle size ranges, extrusion cycles, and coating ratios, and other parameters of nanoparticles lacks standardized protocols. Therefore, future research should shift from individual laboratory practices toward standardized, verifiable, reproducible, and scalable protocols to establish a robust data foundation for subsequent clinical translation. Regarding safety assessments, the ultrasonic disruption and membrane isolation steps are prone to contamination if sterile conditions are not strictly maintained. Moreover, traditional sterilization methods can damage membrane structure and function due to the sensitivity of cell membranes to high temperatures and disinfectants. Consequently, a comprehensive safety evaluation system should be established to conduct systemic toxicological studies involving multiple doses, large-animal models, and long-term assessments to clarify the safety of cell membrane-coated nanoparticles.<sup>57</sup>

## Conclusion

In the post-PEG era, this perspective highlights the paradigm shift in the design of long-circulating nanocarriers by adopting nature-inspired architectures. While PEG has served as an indispensable benchmark for decades, the challenges posed by the ABC phenomenon and anti-PEG antibodies have catalyzed the exploration of more sophisticated biomimetic strategies. As detailed in this perspective, the direct utilization of cell membranes, from erythrocytes to immune cells, offers a remarkable degree of biological authenticity, effectively translating the innate “self-recognition” mechanisms of parental cells to synthetic cores. Concurrently, rational exploitation of the protein corona, either through pre-

coating or by engineering surfaces that recruit specific dysopsonins, represents a complementary approach that works in harmony with the biological processes of the body. Collectively, these nature-inspired platforms not only address the immunological shortcomings of PEG, but also introduce multifunctionality, such as enhanced biocompatibility and the potential for active targeting without complex chemical modifications. However, transitioning these biomimetic systems from the laboratory to the clinic requires addressing significant challenges, including standardization of manufacturing, scale-up reproducibility, and comprehensive immunogenicity profiling. Future research will likely focus on advanced membrane coatings or precisely engineered corona-forming moieties to create next-generation nanocarriers that are not merely invisible to the immune system, but also active participants in the biological milieu. Ultimately, by learning from and harnessing nature's own architecture, we are poised to develop more intelligent, safer, and more effective therapeutic vehicles for a new era of nanomedicine.

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## Disclosure

The authors declare no conflict of interest.

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