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Interaction of Nanoparticles with Blood Components and Associated Pathophysiological Effects

Gerardo González De La Cruz,
Patricia Rodríguez-Fragoso, Jorge Reyes-Esparza,
Anahí Rodríguez-López, Rocío Gómez-Cansino and
Lourdes Rodriguez-Fragoso

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Abstract

Nanotechnology currently plays a pivotal role in several fields and has enabled substantial advances in a relatively short time. In biomedicine, nanomaterials can be potentially employed as a tool for early diagnosis and an innovative mode of drug delivery. Novel nanomaterials are currently widely manipulated without a full assessment of their potential health risks. It is commonly thought that nanomaterials' first contact with the organism is through the different components of the immune system. However, if the entry route is intravenous, the first contact will be with the blood's components (erythrocytes, platelets, white cells, plasma and complement proteins). The presence of nanomaterials within a dynamic environment such as the bloodstream can produce potential harmful effects following interaction with several blood components. The design of innovative strategies leading to the development of more hemocompatible nanomaterials is also necessary.

Keywords: nanotechnology, blood, complement, protein corona

1. Introduction

Current nanotechnology plays a pivotal role in a variety of fields and has enabled substantial advances in a relatively short time. In biomedicine, nanomaterials can be potentially employed as a tool for early diagnosis and an innovative mode of drug delivery [1–3]. As nanomaterial research grows, increased occupational exposure and very likely environmental pollution occur due to a lack of handling regulations.

The studies about the nanomaterials started fifteen years ago, and knowledge regarding their toxic potential is still limited and without appropriate regulatory measures in place [4–6]. Toxicologists, epidemiologists, and sociologists have particularly debated the future implications of nanotechnology as well as concerns regarding their toxicity and potential environmental impact. Nanomaterial application has expanded across a variety of fields, and the lack of attention involving their regulation is worrisome [7]. Novel nanomaterials are currently widely manipulated without a full assessment of their potential health risks, while nanomaterials that are already commercially available have no Safety Data Sheets. There is an urgent need for studies that will help identify, understand, and predict the cellular or tissue responses that nanomaterials can trigger in humans: it is important to understand how safe they are and establish respective protective measures.

The potential medical applications of nanomaterials are spreading to the fields of imaging, therapy, and nanodiagnostics [8, 9]. Regardless of the medical use they are given, nanomaterials come into contact with human tissues and cells which can trigger reactions that might include nanomaterial-blood interactions, damage, acute inflammation, and chronic inflammation.

Human beings have developed evolutionary defense mechanisms against the microorganisms and foreign particles with which they might potentially interact. When effective, these mechanisms provide immunity, that is, resistance to the invasive agents. Their failure results in illness. The human immune system modulates many important biological protective processes [10–12]. It coordinates responses involving a variety of cells and molecules to protect us from invading pathogens, as well as cancer cells and foreign agents [13, 14]. It is commonly thought that nanomaterials' first contact with the organism is via the different components of the immune system. However, if the entry route is intravenous, the first contact will be with the blood's components (erythrocytes, platelets, white cells, plasma and complement proteins). This interaction can lead to different associated pathophysiological processes, as will be enunciated below (**Figure 1**). Knowing what happens when nanomaterials interact with blood components is an essential step when evaluating health risks.

Until now, all biomaterials meant for use in humans trigger a tissue response when they come in contact with either healthy or sick tissue [15–17]. However, this response is triggered by physical contact between the tissue and the biomaterial which is implanted in an organ or tissue. When we talk about nanomaterials, it should be considered that due to their size, effects will take place at a nanolevel, that is, at the cellular or molecular levels. The response they trigger will not be necessarily the same as the one occurring after the implantation of a biomaterial. Additionally, since the projected applications of nanomaterials in nanomedicine involve diagnosis (imaging) and treatment (nanotransporters)—mostly for cancer—host contact with nanomaterials will be of an intravascular nature. Nanomaterial-blood interactions have been linked to inflammatory responses; early response to this damage mainly involves the blood and the vascular endothelium. Once nanomaterials enter the bloodstream, they come into contact with blood cells (red cells, white cells, and platelets), complement proteins, and plasma proteins. It is important to understand how they interact with those elements to assess their effective toxic potential, in both the blood and remote sites.

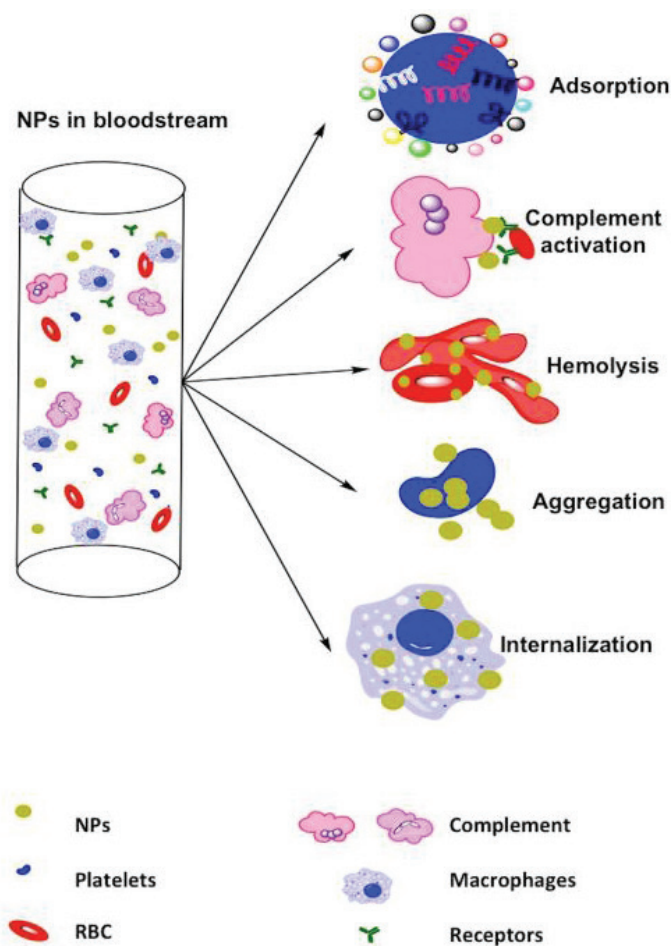


Figure 1. Interaction of nanoparticles (NPs) with bloodstream components and physiological effects.

1.1. Interaction of nanomaterials with red cells

Erythrocytes or red blood cells are exposed to attacks throughout their life span which results in constant biochemical and morphological changes. These cells' contact with nonbiological objects may significantly affect their functions [18, 19]. Nanomaterial interaction with these cells has different effects depending on their intrinsic characteristics. Venkatesan et al. [20] and Choimet et al. [21] recently reported the high hemocompatibility of chitosan nanoparticles loaded with siRNA-Npr3 and nanoparticles formed with colloidal apatite; however, chitosan nanoparticles dissolved with tripolyphosphate (TPP) to acid pH produce hemolysis [22]. Kim et al. [23] carried out rheological measurements and showed that, at concentrations of 12.5 $\mu\text{g/mL}$, silica nanomaterials caused hemolysis, deformation, and aggregation of erythrocytes. It is well known that negatively charged silver nanoagents (AgNPs) strongly interact with organic cations of the erythrocyte membrane and stimulate hemolysis [24]. Wang et al. [25] found that red blood cells and hemoglobin concentrations increased in rats treated with graphene quantum dots (5 mg/kg). The reason why erythrocytes do not show immediate damage when exposed to toxic substances is because they have a system of antioxidant defense that includes nonenzymatic antioxidants such as glutathione and antioxidant enzymes such

as catalase and peroxiredoxin-2 [26, 27]. The presence of this defense system could explain their resistance to the damage induced by nanoparticles, indicating that these cells are not as sensitive to the toxic effects of nanoparticles. However, one of the factors that can influence whether a nanoparticle leads to hemolysis or not is the presence of surfactants [28] and [29] coatings. Surfactants confer different properties to nanomaterials, altering charge, interfacial tension, and becoming an amphiphilic molecule, which reduces the nanomaterial coalescence. Coatings add different chemical groups to the surface of nanoparticles confer different chemical behaviors. However, hemocompatibility will be different for each type of nanoparticle, making it impossible to anticipate if one nanoparticle will be toxic when surfactants or coatings are added.

Recent studies have shown the usefulness of erythrocytes as nanoparticle carriers: they assist their adherence to the vascular endothelium [30] and serve as a platform to bypass the immune system [31, 32]. The physical and chemical properties of erythrocytes are ideal for drug delivery. According to data regarding cell-based therapies, those using erythrocytes have proved to be the most stable, versatile, safe, and easy to manufacture. This strategy is based on temporarily opening pores in the membrane of erythrocytes, easily transporting drugs and ensuring that the latter can stay within these cells once the pores have closed [33]. One of the main uses for this system is the delivery of contrast agents contained within superparamagnetic iron oxide (SPIO) nanoparticles, ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles, very small superparamagnetic iron oxide (VSPIO) nanoparticles, and monocrySTALLINE iron oxide nanocompound (MION) particles, which are already registered and approved for use in the United States and Europe [34]. These have been successfully employed for magnetic particle inspection (MPI) techniques involving the imaging of vessels or structures filled with blood, both during interventions and when monitoring long-term cardiovascular diseases [35]. There is no doubt regarding the hemolytic potential of nanomaterials, and since the presence of hemolysis for long periods can have fatal health effects, an assessment of each nanomaterial's hemolytic potential is quite important.

1.2. Interaction of nanomaterials with platelets

As they go through the blood, nanoparticles can also interact with platelets. When these blood cells come into contact with any material, they adhere to its surface and begin a cascade of signals that eventually leads to fibrin cross-linking and clot formation. While platelet binding is the main process that maintains hemostasis and prevents hemorrhages, it can also lead to the appearance of potentially deadly thrombi that can cause strokes or cerebrovascular accidents [36]. Thrombus formation involves a series of cellular events that entail the participation of molecular components, mainly proteins. If a nanomaterial has the capacity to induce platelet aggregation and alter the normal process of coagulation, it could lead to bleeding or thrombosis. Hence, it is important to know the thrombogenic capacity of each type of nanomaterial, especially when considering their potential nanobiomedical applications.

There are few reports regarding the interaction between nanoparticles and platelets. Unfortunately, most of them show evidence of the procoagulant effects of employed nanomaterials, along with their potential health risks if the exposed person is going through pathological

processes such as cardiovascular disease or metabolic syndrome. Nanoparticle-platelet interaction and endothelial injury may result in the activation of the coagulation cascade, the formation of blood clots, and the partial or total occlusion of blood vessels by thrombi. These effects will depend not only on the size, charge, hydrophobicity, or type of cover but also on the intrinsic characteristics of the nanoparticles (**Figure 2**).

Nanoparticle size seems to be an important factor for platelet activation. It has been observed that the smaller the nanoparticles are, the more likely it is that these cells will be activated. It was already demonstrated that platelet response increases with the size reduction of gold nanoparticles (AuNPs) [37]. On the other hand, SiO₂ nanoparticles have been shown to produce more severe effects when they are about 50–70 nm in size. Concordantly, another work suggests that the effect of 200 nm SiO₂ particles was more intense than that caused by 50 nm ones [38]. Nanoparticles' capacity to induce platelet activation has been amply reported. Examples include gold (AuNP) and silver (AgNP) nanoparticles, as well as CdTe and CdSe quantum dots [39–41]. As far as coating is concerned, carboxyl, amino, phosphate, or hydroxyls are all known to lead to platelet activation [42]. On the other hand, negatively charged surfaces can more easily initiate thrombotic events because, in physiological coagulation, platelet contact with anionic surface starts the coagulation cascade [43]. It was recently reported that, at low concentrations (50 ng/mL), TiO₂ nanoparticles could trigger the activation of the contact system, leading to inflammation-induced thrombosis in a complete blood in vitro model [44].

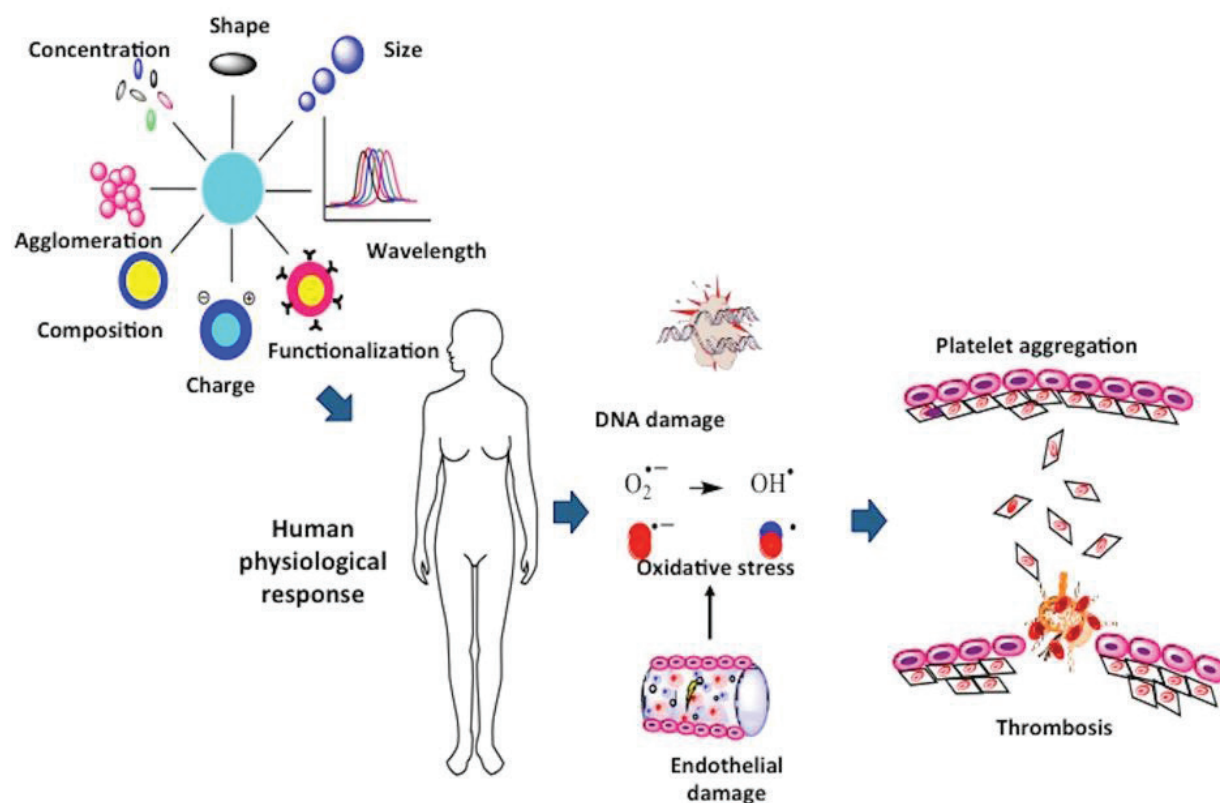


Figure 2. Effect of nanoparticles properties on human physiological response.

Simple and multiwalled carbon nanotubes (SWCNTs and MWCNTs), iron nanoparticles (Fe_2O_3 and Fe_3O_4 NPs), silicon oxide nanoparticles (SiO_2 NPs), pegylated nanoparticles (PEGylated), titanium oxide nanoparticles (TiO_2 NPs), and zinc oxide nanoparticles (ZnONP) are known not to induce platelet activation [45]. This makes them ideal for theranostics. Interestingly, just like several types of nanoparticles that can induce platelet activation, certain nanomaterials are being used for diagnosis in thrombotic disease since thrombogenic proteins range from nanometers to micrometers in size. High-resolution imaging is required to observe these proteins in real time, and this is being achieved via the use of nanotransporters. For example, liposomes contain thrombin inhibitors for acute thrombosis, perfluorocarbon nanoparticles with thrombin inhibitors, polymer nanotransporters with antithrombotic activity, magnetic nanoparticles conjugated with thrombolytic activity urokinase, and Fe_2O_3 nanoparticles conjugated with plasminogen activator for thrombosis [46]. Identifying the prothrombotic or nanotransporting potential of a nanomaterial is important given its potential medical implications.

1.3. Interaction of nanomaterials with peripheral mononuclear cells

Peripheral blood mononuclear cells (PBMC) are another important element in the bloodstream. While there are many studies on lymphocyte cell lines, the use of PBMC cells allows for the simultaneous analysis of nanoparticle effects on several important immune cells such as B-cells, T-cells, monocytes, and natural killer (NK) cells. Studying nanomaterials with these types of cells are crucial since these will interact with nanoparticles once the latter are introduced into the blood torrent. The peripheral blood mononuclear cells (lymphocytes and monocytes) represent a host defense system that is capable of releasing various inflammatory mediators after its activation. The physicochemical properties of nanomaterials can act as intrinsic signals that aid immunity.

Immune cells need to communicate to exercise their function. One way is via the production and release of exosomes, nanovesicles that are naturally present in and are released by the majority of cells in the body. These exosomes can act as a means of communication for transferring functional proteins, mRNA and microRNA. Studies conducted by Andersson-Willman et al. [47] show that in subtoxic concentrations, TiO_2 and ZnO nanoparticles do not interfere with the traffic and release of these exosomes in PBMC cell populations. Adhesion molecules such as integrins and selectins also play an important role in immune response. ZnO NPs alter the expression of several integrins, L-selectin and chemokine receptor CXCR4, important molecules for key cellular functions such as adhesion, migration, and cell proliferation [48]. Immune cells also have other functions, such as inducing the proliferation of other cells, phagocytizing, or killing. It has been pointed out that peripheral blood immune cells (lymphocytes, NK cells, granulocytes, and monocytes) have a different sensitivity to the effect of polylactic-glycolic acid (PLGA-PEO) nanoparticles. These particles suppressed the proliferative function of lymphocytes and the killing activity of NK cells, but stimulated phagocytic activity of granulocytes and monocytes, as well as the respiratory burst of phagocytes [49].

Nanoparticles have different toxic effects in human PBMC. Lankoff et al. [50] used silica nanoparticles and observed no significant cytotoxic and genotoxic effects in peripheral blood

lymphocytes. However, cell proliferation was affected in a concentration-dependent manner. Those same authors found that surface charge and zeta potential are important for the binding and uptake of nanoparticles into cells. Peripheral blood lymphocytes died after exposure to nanoparticles containing silicon and carbon nanotubes, an effect that was dependent on the concentration of the nanoparticles employed [51, 52]. TiO_2 , ZrO_2 , and Al_2O_3 nanoparticles did not damage these cells' DNA at concentrations of 1, 10, and 100 $\mu\text{g/mL}$ [53]. Nanoparticle size seems to influence toxicity. Studies involving peripheral blood lymphocytes treated with SiO_2 nanoparticles of different sizes (6, 20, and 50 nm) induced size-dependent cytotoxic, genotoxic, and mutagenic effects [54].

Nanoparticle coating also seems to influence the toxicity induced in peripheral blood mononuclear cells. Oleate F_3O_4 nanoparticles produce cytotoxic and genotoxic effects. Oleate seems to confer a different load and agglomeration potential, favoring cell uptake and, therefore, cytotoxicity [55]. Recently, Farace et al. studied the effect of nanocapsules (PCs, 170–300 nm) coated with chitosan and pluronic PEG on peripheral blood mononuclear cells and subpopulations of T lymphocytes and monocytes which were taken as representative of the innate immune response [56]. They observed that different types of NCs produce different effects on immune cells. For example, the PEG NCs were completely inert, while Pluro NCs and Chito NCs had immunomodulatory effects. Pluro nanoparticles induced an immune response through CD69 up-modulation in monocytes and increased the release of IL-6, IL-10, IL-12, and $\text{TNF}\alpha$. On the other hand, Chito nanoparticles produced apoptosis in monocytes and T-cells, as an increase in the secretion of pro-inflammatory cytokines ($\text{TNF}\alpha$ and IL-12) [57]. Interestingly, Chito NCs induced the secretion of IL-4 and IL-13 cytokines. Normally, the T effector (Th_2) helper cells produce a cytokine profile that includes IL-4, IL-6, IL-10, and IL-13. These cytokines signal B-cells to proliferate and differentiate in antibody-producing plasma cells. The possible activation of Th_2 cells mediated by Chito NCs might be responsible for the induction of allergy in humans.

1.4. Interaction of nanomaterials with complement proteins

The complement system is part of innate immunity and is one of the oldest defense systems. Any absence or abnormalities in this system or any of its components can cause serious and even deadly disease. The complement system has three known modes of activation: the classical, alternative, and lectin pathways, which differ both in their activation mechanisms and initial components. The main biological functions of this system include (a) opsonization, (b) chemotaxis, (c) cellular and bacterial lysis, (d) anaphylatoxin function, and (e) participation in the elimination of immune complexes [58]. The system is composed of several components (C1, C2 to C9) and factors (B, D, Hf, and P) and gets its name from the fact that it complements the immune response mediated by antibodies [59].

It is not known why certain nanoparticles cause the activation of the complement system, but it is of knowledge that the surface charge plays an important role. It has been noted that charged nanoparticles do more to activate the complement than neutral counterparts (e.g., polypropylene sulfur nanoparticles, lipid nanocapsules, polycation-based nanoparticles containing cyclodextrin and polystyrene nanospheres [60–63]). Also, polymer coatings made of

polyethylene glycol (PEG) and poloxamine-908 partially neutralize the surface charge and reduce the activation of the complement system [64, 65]. However, similar studies using dextran and chitosan showed that the size and shape of the polymer influenced the degree of complement activation, which was not determined by the effects of the load [66]. The presence of thiol groups in the nanoparticle's surface also increases the activation of the complement [67].

We know that hydrophobic surfaces are more powerful activators than hydrophilic ones and that the inclusion of NH_2 , $-\text{OH}$, or $-\text{COOH}$ groups influences the activation of the complement [68]. Nanotubes functionalized with psychosine activate the complement via the classical pathway [69]. Several studies have shown that the activation of the complement can be dependent on size, polydispersity index, zeta potential, and surface ligand density [70–72].

The activation of the complement system leads to an inflammatory response via the release of anaphylatoxins (e.g., C3a and C5a), C3b and C5b–C9 lytic complex, since this response originates uncontrolled activation, which can lead to organism collapse [73]. One of the diseases that has been directly associated to the activation of the complement system is C activation-related pseudoallergy (CARPA), which entails reactions of hypersensitivity. Such situations demand security evaluations and the development of technologies that consider complement activation and nanomaterials' potential to induce CARPA [74]. Complement activation has also been associated with the development and growth of tumors [75]. The generation of C5a in a tumor environment increases tumor growth by promoting the recruitment of suppressor cells derived from myeloid in malignant tumors and the deregulation or suppression of CD8 cytotoxic cells. This is therefore another important consideration when evaluating new nanomaterials.

It is clear that nanomaterials can have different effects on the components of the immune system in peripheral blood and at the tissue level. It is also evident that the physical, chemical, and optical properties of nanomaterials are critical for this interaction. That is in fact what has led to the design of tools that can be employed in the field of immunology. Nanomaterials are being used in the development of vaccines and immunotherapy and even therapeutic methods that seek to inhibit the complement system in cancer treatment [76]. There is an urgent need to understand the exact mechanisms of nanoparticle/immune interaction so as to have a more complete picture of what could actually happen in humans, thus ensuring more effective and secure applications.

1.5. Interaction of nanomaterials with plasma proteins

So far, there is no evidence that just by entering the bloodstream, nanoparticles can interact with associated cells and molecules and trigger a variety of potentially adverse effects. As nanoparticles go through the systemic circulation, they will also interact with plasma proteins. Protein adsorption in biological medium is an important issue when measuring biological response to nanoparticles [77–79]. Binding of plasma components and the formation of nanoparticle-protein interactions largely determines nanoparticle fate in the systemic circulation and should influence functionality as much as the plasma protein binding of drugs [80].

Knowledge regarding nanoparticle-protein interaction mechanisms has evolved over the past few years. Initially, several authors had indicated that protein adsorption decreased subsequent to the functionalization of the nanomaterial since the hydrophobicity of the nanoparticle's surface was also reduced [81]. However, nanoparticle-protein interaction is very complex and that the scenario will depend on whether this interaction occurs in the blood, interstitial liquid, or some other biological liquid, as well as the specific surface properties of particular nanoparticles (size, shape, load, composition, and surface functionalization) [82].

It has been recently noted that once a nanoparticle enters the biological environment, it becomes coated in proteins, the so-called protein corona that will influence the fate of the nanoparticle inside the organism (i.e., the time spent in the bloodstream, biodistribution, cellular uptake, and intracellular localization) (**Figure 3**). This will also depend on the biological environment and on whether the biological environment is physiologically ill or healthy [83]. In addition to the above, it must be considered that the ultimate goal in nanomedicine is to

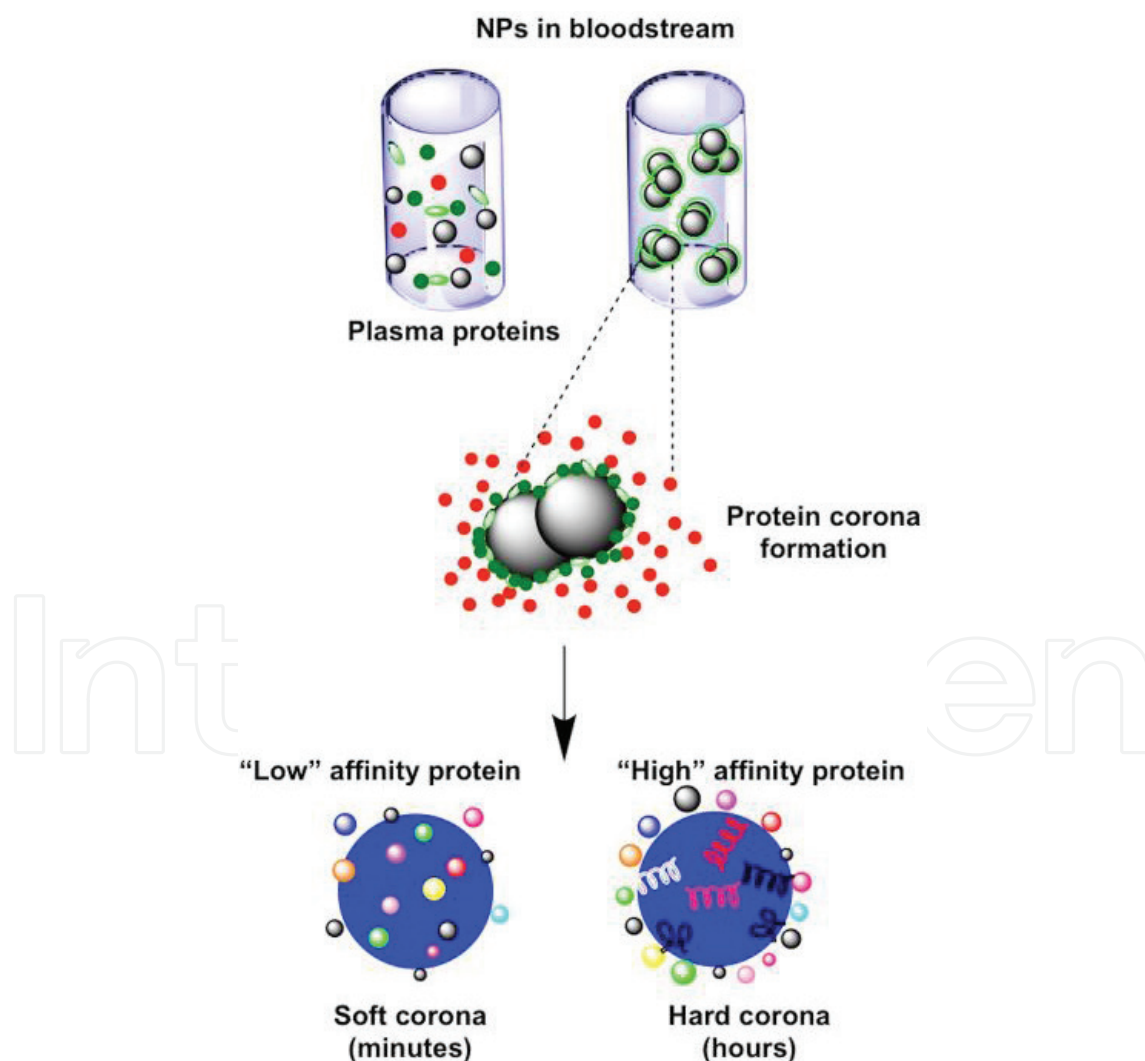


Figure 3. Nanoparticles (NPs) in bloodstream and corona protein formation.

use nanoparticles as transporters or a contrast medium for imaging. For theranostic purposes, nanoparticles must be functionalized with peptides, proteins, antibodies, oligonucleotides, or drugs, which means that the proteins that make up the corona will probably vary depending on the molecule with which the nanoparticle is conjugated and will provide the nanomaterial not only with a new biological identity but also with new physicochemical properties, changing shape, size, load, surface composition, and state of aggregation. This will also allow conformational changes [84, 85].

The binding of nanoparticles to plasma proteins such as albumin can increase biological properties that reduce the activation of the complement system, increasing blood circulation time and reducing toxicity [86]. In this regard, it would seem that the adsorption of circulating proteins might confer safety, facilitate interactions mediated by receptors, and improve the pharmacokinetic profile, i.e., these are potential theranostic advantages. However, the proteins that are involved in relevant physiological and toxicological processes in the bloodstream, such as the complement and coagulation factors, have also been identified forming the protein corona. The formation of the latter may additionally reduce target cellular interactions by making the ligands inaccessible to their surfaces [87]. For these reasons, the formation of the protein corona could be disadvantageous for theranostic purposes.

Another subject of study in this regard is that of the “hard or soft corona.” The term “hard corona” describes a long life and low complexity balance, while “soft corona” consists of the formation of layers of highly complex biomolecules that exchange quickly. That said, this concept is not widely used by researchers, and studies on ligand-receptor interaction with nanoparticles do not specify if the interaction is with a hard or soft corona [88].

When does the protein corona form and how quickly? Studies by Tenzer et al. [89] showed almost instant formation upon nanoparticle contact with the blood (<30 s). This group studied positively and negatively charged polystyrene nanoparticles (nPsNPs and pPsNPs, respectively) and silica nanoparticles of various sizes ($\varnothing \approx 35, 120$, and 140 nm), loads, and surface modifications (unmodified amine and carboxylate), exposing them to human plasma for different periods of time. They quantified the formation of 166 different protein coronas every 30 s for PsNPs and silica nanoparticles (35 nm). When modified the surfaces were able to quantify the formation of 300 different protein coronas.

Some authors have pointed out that the protein corona can increase the useful drug load capacity of nanoparticles. The very small size of the nanoparticles facilitates their travel down the bloodstream, their incorporation into cells, and their interaction with the cellular compartments with different molecules, including DNA. A way in which the protein corona can improve not only nanoparticles' drug transporting capacities but also their pharmacokinetic properties is by increasing payload capability through the use of porous materials (e.g., porous silicon) that can be packaged with the drug, as well as through the volume increase of liposomes. However, most current methods, unaware of the formation of the protein corona, typically load the drugs over the nanoparticles surface via chemical conjugation or adsorption. In these cases, the maximum amount that can be charged is restricted to a single layer [90]. Nanoparticles functionalized with polyethylene glycol (PEG) have been recently

developed. PEG provides colloidal stability even under conditions of physiological salinity caused by interparticle repulsion. However, even complex pegylation is unable to completely prevent the formation of the protein corona, even though the degree of protein adsorption is clearly reduced [91].

The adsorption of serum proteins and the formation of a corona are part of the immune response. Expanding the circulation time of the nanoparticles means more contact with the blood proteins, a higher probability of thrombogenicity, and the activation of the complement system [92]. Since the corona depends on the characteristics of the nanoparticle (chemical surface, size, shape, and charge), these properties could be adjusted in such a way for the proteins that make it up to mitigate the immune response. Tuning the properties of affinity toward the corona could optimize the biocompatibility of the nanoparticles and reduce their toxicity. However, this process is not easy, and few researchers designing nanomaterials take corona formation into consideration. Ideally, nanoparticle development should encompass studies that provide data regarding nanoparticle-protein interactions, as is customary during the development of a new drug. There are few reports on this subject, and limited knowledge in this field may be a reason for the lack of successful clinical treatments.

1.6. Interaction of nanomaterials with the vascular endothelium

Oftentimes, the study of nanomaterial-blood interactions focuses on blood cells and proteins. However, the vascular endothelium where these elements are contained must also be taken into consideration and plays an important role because these cells and proteins interact with it triggering severe pathophysiological processes. In addition to the multiple direct physical interactions between nanoparticles and endothelial cells, nanoparticles enter and circulate in the blood vessel. Among other important functions, the endothelium maintains the vascular tone, vascular cell growth regulation, leukocyte and platelet adhesion regulation, thrombosis and fibrinolysis regulation, and inflammation mediation. The normal endothelium may detect hemodynamics (e.g., pressure and friction forces) and hormonal changes (e.g., vasoactive substances as well as mediators that occur in blood cells and platelets). As a consequence, endothelial cells synthesize and release biologically active substances that maintain vascular homeostasis. Endothelial damage accompanied by endothelial dysfunction plays a crucial role and is associated with a prothrombotic state. Several reports associate nanomaterial exposure to endothelial damage [93–95] because blood is the main route for nanoparticle transportation during distribution [96]. Some of the most important findings regarding nanoparticles and endothelial cell interaction are described below.

There are several reports in the literature regarding nanomaterials that affect cell viability and proliferation. Among them are gallium nitride nanoparticles (GaN NPs) [97], cerium dioxide nanoparticles (CeO₂ NPs) [98], gold nanospheres [99, 100], silica NPs [101–103], CdTe [104], and silver nanoparticles [105] to quote some examples. Silver nanoparticles have received much attention as of late due to the biological effects they produce in endothelial cells, e.g., decreased cell viability, induced apoptosis, increased ROS production, increased production of IL-6 and IL-8 interleukins, and increased expression of adhesion proteins, which can

promote inflammation [106–108]. Sun et al. have shown that the interaction of silver nanoparticles with the cell membrane of endothelial cells is the main factor behind endothelial dysfunction and may be associated with thromboembolic problems [109]. It has also been found that silicon nanoparticles induce oxidative stress, inflammation, alteration of the oxide nitric (NO) balance, and endothelial dysfunction via the activation of MAPK/Nrf2. They can also induce inflammation and cytotoxicity in endothelial cells through the activation of potassium channels [103]. Moreover, it has been suggested that nanoparticles can regulate the barrier function of tight junction (occludins, claudins, and ZO proteins) because they interact with key kinases, altering not only the oxidative status around the junction between endothelial cells but also altering the blood flow into the vessel [110]. These data indicate that nanoparticle/endothelial cell interaction can modify the function of the blood vessel, whether in the site of injection at the moment of intravenous administration, during the distribution process, or when directed toward specific targets.

Nanomaterials are being used to direct and deliver drugs toward the endothelium and improve treatments for oncological, cardiovascular, pulmonary, neurologic, and ophthalmic diseases; they also have nanodiagnostic potential [111–121]. One of the problems in cancer is the formation of new blood vessels that irrigate the tumor (angiogenesis). Targeting nanoparticles toward the tumor and allowing these to exert their harmful effects on the endothelial wall could reduce the size of the tumor due to lack of nutrients. Some of the nanomaterials used for this purpose are liposomes (Ala-Pro-Arg-Pro-Gly (APRPG) liposomes). These can successfully target tumor microvessels via functionalization with Ala-Pro-Arg-Pro-Gly (APRPG) peptide, which binds the blood vessels through the VEGF receptor-1 [122]. Another application involves the treatment of corneal endothelial dystrophy to improve and integrate cell therapy through superparamagnetic nanoparticles that facilitate the delivery of human corneal endothelial cells (HCECs) [123].

2. Conclusion

To summarize, the presence of nanomaterials within a dynamic environment such as the bloodstream can produce potentially harmful effects following interaction with several blood components. As reported in the literature, results have not been wholly encouraging because the said interaction can lead to different associated physiopathological processes linked to hemocompatibility. There is no doubt that nanomaterials might have theranostic potential for different clinical specialties and that their features improve upon traditional strategies: they are small and have physicochemical and optical properties that help direct molecules toward specific sites to control specific processes on a vascular level. However, the properties behind these advantages also create limitations, since most nanomaterials can cause important nano-level interactions. The hemocompatibility of nanomaterials is essential when we consider that, regardless of the route of entry, the blood will transport them at any given time. Further in-depth studies are needed to understand, predict, and counteract the conduct of nanomaterials within the cellular and molecular microenvironments. The design of innovative strategies leading to the development of more hemocompatible nanomaterials is also necessary.

Author details

Gerardo González De La Cruz¹, Patricia Rodríguez-Fragoso¹, Jorge Reyes-Esparza², Anahí Rodríguez-López², Rocío Gómez-Cansino² and Lourdes Rodríguez-Fragoso^{2*}

*Address all correspondence to: mrodriguez@uaem.mx

¹ Departamento de Física, CINVESTAV – I.P.N, Mexico, D.F., Mexico

² Facultad de Farmacia, Universidad Autónoma del Estado de Morelos, Cuernavaca, Mexico

References

- [1] Singh PK, Jairath G, Ahlawat SS. Nanotechnology: A future tool to improve quality and safety in meat industry. *Journal of Food Science and Technology*. 2016;**53**:1739-1749. DOI: 10.1007/s13197-015-2090-y
- [2] Kour H, Malik AA, Ahmad N, Wani TA, Kaul RK, Bhat A. Nanotechnology—New life-line for food industry. *Critical Reviews in Food Science and Nutrition*. 2015;**5**. DOI: 10.1080/10408398.2013.802662
- [3] Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: A review of FDA-approved materials and clinical trials to date. *Pharmaceutical Research*. 2016;**33**:2373-2387. DOI: 10.1007/s11095-016-1958-5
- [4] Fard JK, Jafari S, Eghbal MA. A review of molecular mechanisms involved in toxicity of nanoparticles. *Advanced Pharmaceutical Bulletin*. 2015;**5**:447-454. DOI: 10.15171/apb.2015.061
- [5] Haase A, Tentschert J, Luch A. Nanomaterials: A challenge for toxicological risk assessment?. *EXS*. 2012;**101**:219-250. DOI: 10.1007/978-3-7643-8340-4-8
- [6] Hulla JE, Sahu SC, Hayes AW. Nanotechnology: History and future. *Human & Experimental Toxicology*. 2015;**34**:1318-1321. DOI: 10.1177/0960327115603588
- [7] Mühlebach S, Borchard G, Yildiz S. Regulatory challenges and approaches to characterize nanomedicines and their follow-on similars. *Nanomedicine (London, England)*. 2015;**10**:659-674. DOI: 10.2217/nnm.14.189
- [8] Keles E, Song Y, Du D, Dong WJ, Lin Y. Recent progress in nanomaterials for gene delivery applications. *Biomaterials Science*. 2016;**4**:1291-1309. DOI: 10.1039/c6bm00441e
- [9] Padmanabhan P, Kumar A, Kumar S, Chaudhary RK, Gulyás B. Nanoparticles in practice for molecular-imaging applications: An overview. *Acta Biomaterialia*. 2016;**41**:1-16. DOI: 10.1016/j.actbio.2016.06.003
- [10] Walls J, Sinclair L, Finlay D. Nutrient sensing, signal transduction and immune responses. *Seminars in Immunology*. 2016;**28**:396-407. DOI: 10.1016/j.smim.2016.09.001

- [11] Kulkarni OP, Lichtnekert J, Anders HJ, Mulay SR. The immune system in tissue environments regaining homeostasis after injury: Is "Inflammation" always inflammation?. *Mediators of Inflammation*. 2016;**2016**:2856213. DOI: 10.1155/2016/2856213
- [12] Weidenbusch M, Anders HJ. Tissue microenvironments define and get reinforced by macrophage phenotypes in homeostasis or during inflammation, repair and fibrosis. *Journal of Innate Immunity*. 2012;**4**:463-477. DOI: 10.1159/000336717
- [13] Plitas G, Rudensky AY. Regulatory T cells: Differentiation and function. *Cancer Immunology Research*. 2016 Sep 2;**4**:721-725. DOI: 10.1158/2326-6066
- [14] Guillerey C, Huntington ND, Smyth MJ. Targeting natural killer cells in cancer immunotherapy. *Nature Immunology*. 2016;**17**:1025-1036. DOI: 10.1038/ni.3518
- [15] Anderson JM. Biological responses to materials. *Annual Review of Materials Research*. 2001;**31**:81-110. DOI: 10.1146/annurev.matsci.31.1.81
- [16] Gardner AB, Lee SKC, Woods EC, and Acharya AP. Biomaterials-based modulation of the immune system. *BioMed Research International*. 2013;**2013**:732182. DOI: 10.1155/2013/732182
- [17] Christo SN, Diener KR, Bachhuka A, Vasilev K, Hayball JD. Innate immunity and biomaterials at the nexus: Friends or foes. *BioMed Research International*. 2015;**2015**:342304. DOI: 10.1155/2015/342304
- [18] Mendonça R, Silveira AA, Conran N. Red cell DAMPs and inflammation. *Inflammation Research*. 2016;**65**:665-678. DOI: 10.1007/s00011-016-0955-9
- [19] Manaargadoo-Catin M, Ali-Cherif A, Pougny JL, Perrin C. Hemolysis by surfactants—A review. *Advance in Colloid and Interface Science*. 2016;**228**:1-16. DOI: 10.1016/j.cis.2015.10.011
- [20] Venkatesan B, Tumala A, Subramanian V, Vellaichamy E. Data on synthesis and characterization of chitosan nanoparticles for in vivo delivery of siRNA-Npr3: Targeting NPR-C expression in the heart. *Data in Brief*. 2016;**8**:441-447. DOI: 10.1016/j.dib.2016.05.074
- [21] Choimet M, Hyoung-Mi K, Jae-Min O, Turrette A, Drouet C. Nanomedicine: Interaction of biomimetic apatite colloidal nanoparticles with human blood components. *Colloids and Surfaces B: Biointerfaces*. 2016;**145**:87-94. DOI: 10.1016/j.colsurfb.2016.04.038
- [22] de Lima JM, Sarmiento RR, de Souza JR, Brayner FA, Feitosa AP, Padilha R, Alves LC, Porto IJ, Batista RF, de Oliveira JE, de Medeiros ES, Bonan PR, Castellano LR. Evaluation of hemagglutination activity of chitosan nanoparticles using human erythrocytes. *BioMed Research International*. 2015;**2015**:247965. DOI: 10.1155/2015/247965
- [23] Kim J, Heo YJ, Shin S. Haemocompatibility evaluation of silica nanomaterials using hemorheological measurements. *Clinical Hemorheology and Microcirculation*. 2016;**62**:99-107. DOI: 10.3233/CH-151953
- [24] Chen LQ, Fang L, Ling J, Ding CZ, Kang B, Huang CZ. Nanotoxicity of silver nanoparticles to red blood cells: Size dependent adsorption, uptake, and hemolytic activity. *Chemical Research in Toxicology*. 2015;**28**:501-509. DOI: 10.1021/tx500479m

- [25] Wang K, Gao Z, Gao G, Wo Y, Wang Y, Shen G, Cui D. Systematic safety evaluation on photoluminescent carbon dots. *Nanoscale Research Letters*. 2013;**8**:122. DOI: 10.1186/1556-276X-8-122
- [26] Lee T, Kim S, Yu S, Kim S, Park D, Moon H. Peroxiredoxin II is essential for sustaining life span of erythrocytes in mice. *Blood*. 2003;**101**:5033-5038. DOI: 10.1182/blood-2002-08-2548
- [27] Gonzalez R, Auclair C, Voisin E, Gautero H, Dhermy D, and Boivin P. Superoxide dismutase, catalase, and glutathione peroxidase in red blood cells from patients with malignant disease. *Cancer Research*. 1984;**44**:4137-4139
- [28] Thasneem YM, Sajeesh S, Sharma CP. Effect of thiol functionalization on the hemocompatibility of PLGA nanoparticles. *Journal of Biomedical Materials Research. Part A*. 2011;**99**:607-617. DOI: 10.1002/jbm.a.33220
- [29] Barshtein G, Livshits L, Shvartsman LD, Shlomai NO, Yedgar S, Arbell D. Polystyrene nanoparticles activate erythrocyte aggregation and adhesion to endothelial cells. *Cell Biochemistry and Biophysics*. 2016;**74**:19-27. DOI: 10.1007/s12013-015-0705-6
- [30] Villa CH, Pan DC, Zaitsev S, Cines DB, Siegel DL, Muzykantov VR. Delivery of drugs bound to erythrocytes: New avenues for an old intravascular carrier. *Therapeutic Delivery*. 2015;**6**:795-826. DOI: 10.4155/tde.15.34
- [31] Villa CH, Anselmo AC, Mitragotri S, Muzykantov V. Red blood cells: Supercarriers for drugs, biologicals, and nanoparticles and inspiration for advanced delivery systems. *Advanced Drug Delivery Reviews*. 2016;**106**:88-103. DOI: 10.1016/j.addr.2016.02.007
- [32] Zhang H. Erythrocytes in nanomedicine: An optimal blend of natural and synthetic materials. *Biomaterials Science*. 2016;**4**:1024-1031. DOI: 10.1039/c6bm00072j
- [33] Rossi L, Pierigè F, Antonelli A, Bigini N, Gabucci C, Peiretti E, Magnani M. Engineering erythrocytes for the modulation of drugs' and contrasting agents' pharmacokinetics and biodistribution. *Advanced Drug Delivery Reviews*. 2016;**106**:73-87. DOI: 10.1016/j.addr.2016.05.008
- [34] Takeuchi Y, Suzuki H, Sasahara H, Ueda J, Yabata I, Itagaki K, Saito S, Murase K. Encapsulation of iron oxide nanoparticles into red blood cells as a potential contrast agent for magnetic particle imaging. *Advanced Biomedical Engineering*. 2014;**3**:3743. DOI: 10.14326/abe.3.37
- [35] Ekstrand-Hammarström B, Hong J, Davoodpour P, Sandholm K, Ekdahl KN, Bucht A, Nilsson B. TiO₂ nanoparticles tested in a novel screening whole human blood model of toxicity trigger adverse activation of the kallikrein system at low concentrations. *Biomaterials*. 2015;**51**:58-68. DOI: 10.1016/j.biomaterials.2015.01.031
- [36] Laloy J, Minet V, Alpan L, Mullier F, Beken S, Toussaint O, Lucas S, Dogné J. Impact of silver nanoparticles on haemolysis, platelet function and coagulation. *Nanobiomedicine*. 2014;**4**:1-9. DOI: 10.5772/59346
- [37] Deb S, Patra HK, Lahiri P, Dasgupta AK, Chakrabarti K, Chaudhuri U. Multistability in platelets and their response to gold nanoparticles. *Nanomedicine*. 2011;**7**:376-384

- [38] Nemmar A, Albarwani S, Beegam S, Yuvaraju P, Yasin J, Attoub S, Ali BH. Amorphous silica nanoparticles impair vascular homeostasis and induce systemic inflammation. *International Journal of Nanomedicine*. 2014;**9**:2779-2789. DOI: 10.2147/IJN.S52818
- [39] Aseychev AV, Azizova OA, Beckman EM, Dudnik LB, Sergienko VI. Effect of gold nanoparticles coated with plasma components on ADP-induced platelet aggregation. *Bulletin of Experimental Biology and Medicine*. 2013;**155**:685-688
- [40] Samuel SP, Santos-Martinez MJ, Medina C, Jain N, Radomski MW, Prina-Mello A, Volkov Y. CdTe quantum dots induce activation of human platelets: Implications for nanoparticle hemocompatibility. *International Journal of Nanomedicine*. 2015;**10**:2723-2734. DOI: 10.2147/IJN.S78281
- [41] Dunpall R, Nejo AA, Pullabhotla VS, Opoku AR, Revaprasadu N, Shonhai A. An in vitro assessment of the interaction of cadmium selenide quantum dots with DNA, iron, and blood platelets. *IUBMB Life*. 2012;**64**:995-1002. DOI: 10.1002/iub.1100
- [42] Fröhlich E. Action of Nanoparticles on platelet activation and plasmatic coagulation. *Current Medicinal Chemistry*. 2016;**23**:408-430
- [43] Ilinskaya AN, Dobrovolskaia MA. Nanoparticles and the blood coagulation system. Part I: Benefits of nanotechnology. *Nanomedicine (London, England)*. 2013;**8**:773-784. DOI: 10.2217/nnm.13.48
- [44] Nemmar A, Melghit K, Ali BH. The acute proinflammatory and prothrombotic effects of pulmonary exposure to rutile TiO₂ nanorods in rats. *Experimental Biology and Medicine* (Maywood, NJ). 2008;**233**:610-619. DOI: 10.3181/0706-RM-165
- [45] Karagkiozaki V, Pappa F, Arvaniti D, Moumkas A, Konstantinou D, Logothetidis S. The melding of nanomedicine in thrombosis imaging and treatment: A review. *Future Science OA*. 2016;**2**:FSO113. DOI: 10.4155/fso.16.3
- [46] Varna M, Juenet M, Bayles R, Mazighi M, Chauvierre C, Letourneau D. Nanomedicine as a strategy to fight thrombotic diseases. *Future Science OA*. 2015;**1**:4. DOI: 10.4155/fso.15.46
- [47] Andersson-Willman B, Gehrmann U, Cansu Z, Buerki-Thurnherr T, Krug HF, Gabrielsson S, Scheynius A. Effects of subtoxic concentrations of TiO₂ and ZnO nanoparticles on human lymphocytes, dendritic cells and exosome production. *Toxicology and Applied Pharmacology*. 2011;**264**:94-103. DOI: 10.1016/j.taap.2012.07.021
- [48] Lozano-Fernández T, Ballester-Antxordoki L, Pérez-Temprano N, Rojas E, Sanz D, Iglesias-Gaspar M, Moya S, González-Fernández Á, Rey M. Potential impact of metal oxide nanoparticles on the immune system: The role of integrins, L-selectin and the chemokine receptor CXCR4. *Nanomedicine*. 2014;**10**:1301-1310. DOI: 10.1016/j.nano.2014.03.007
- [49] Tulinska J, Kazimirova A, Kuricova M, Barancokova M, Liskova A, Neubauerova E, Drlickova M, Ciampor F, Vavra I, Bilanicova D, Pojana G, Staruchova M, Horvathova M, Jahnova E, Volkovova K, Bartusova M, Cagalinec M, Dusinska M. Immunotoxicity

and genotoxicity testing of PLGA-PEO nanoparticles in human blood cell model. *Nanotoxicology*. 2015;**9**:1:33-43. DOI: 10.3109/17435390.2013.816798

- [50] Lankoff A, Arabski M, Wegierek-Ciuk A, Kruszewski M, Lisowska H, Banasik-Nowak A, Rozga-Wijas K, Wojewodzka M, Slomkowski S. Effect of surface modification of silica nanoparticles on toxicity and cellular uptake by human peripheral blood lymphocytes in vitro. *Nanotoxicology*. 2013;**7**:235-250. DOI: 10.3109/17435390.2011.649796
- [51] Andreeva ER, Rudimov EG, Gornostaeva AN, Beklemyshev VI, Makhonin II, Maugeri UO, Buravkova LB. In vitro study of interactions between silicon-containing nanoparticles and human peripheral blood leukocytes. *Bulletin of Experimental Biology and Medicine*. 2013;**155**:396-398
- [52] Kim JS, Song KS, Yu IJ. Multiwall carbon nanotube-induced DNA damage and cytotoxicity in male human peripheral blood lymphocytes. *International Journal of Toxicology*. 2016 Jan-Feb;**35**(1):27-37. DOI: 10.1177/1091581815598749
- [53] Demir E, Burgucu D, Turna F, Aksakal S, Kaya B. Determination of TiO₂, ZrO₂, and Al₂O₃ nanoparticles on genotoxic responses in human peripheral blood lymphocytes and cultured embryonic kidney cells. *Journal of Toxicology and Environmental Health A*. 2013;**76**:990-1002. DOI: 10.1080/15287394.2013.830584
- [54] Battal D, Çelik A, Güler G, Aktaş A, Yildirimcan S, Ocakoglu K, Çömelekoğlu Ü. SiO₂ Nanoparticle-induced size-dependent genotoxicity – An in vitro study using sister chromatid exchange, micronucleus and comet assay. *Drugs and Chemical Toxicology*. 2015;**38**:196-204. DOI: 10.3109/01480545.2014.928721
- [55] Magdolenova Z, Drlickova M, Henjum K, Rundén-Pran E, Tulinska J, Bilanicova D, Pojana G, Kazimirova A, Barancokova M, Kuricova M, Liskova A, Staruchova M, Ciampor F, Vavra I, Lorenzo Y, Collins A, Rinna A, Fjellsbø L, Volkovova K, Marcomini A, Amiry-Moghaddam M, Dusinska M. Coating-dependent induction of cytotoxicity and genotoxicity of iron oxide nanoparticles. *Nanotoxicology*. 2015;**9**:1:44-56. DOI: 10.3109/17435390.2013.847505
- [56] Farace C, Sánchez-Moreno P, Orecchioni M, Manetti R, Sgarrella F, Asara Y, Peula-García JM, Marchal JA, Madeddu R, Delogu LG. Immune cell impact of three differently coated lipid nanocapsules: Pluronic, chitosan and polyethylene glycol. *Scientific Reports*. 2016;**6**:18423. DOI: 10.1038/srep18423
- [57] Khon X, Hellerman GR, Zhang W, Jena P, Kumar M, Behera A, Behera S, Lockey R, Mohapatra SS. Chitosan interferon- γ nanogene therapy for lung disease: Modulation of t-cell and dendritic cell immune responses. *Allergy, Asthma & Clinical Immunology*. 2008;**4**:95. DOI: 10.1186/1710-1492-4-95
- [58] Pham CT, Mitchell LM, Huang JL, Lubniewski CM, Schall OF, Killgore JK, Pan D, Wickline SA, Lanza GM, Hourcade DE. Variable antibody-dependent activation of complement by functionalized phospholipid nanoparticle surfaces. *Journal of Biological Chemistry*. 2011;**286**:123-130. DOI: 10.1074/jbc.M110.180760

- [59] Knopf PM, Rivera DS, Hai SH, McMurry J, Martin W, De Groot AS. Novel function of complement C3d as an autologous helper T-cell target. *Immunology & Cell Biology*. 2008;**86**:221-225
- [60] Reddy ST, van der Vlies AJ, Simeoni E, Angeli V, Randolph GJ, O'Neil CP, Lee LK, Swartz MA, Hubbell JA. Exploiting lymphatic transport and complement activation in nanoparticle vaccines. *Nature Biotechnology*. 2007;**25**:1159-1164. DOI: 10.1038/nbt1332
- [61] Vonarbourg A, Passirani C, Saulnier P, Simard P, Leroux JC, Benoit JP. Evaluation of pegylated lipid nanocapsules versus complement system activation and macrophage uptake. *Journal of Biomedical Materials Research. Part A*. 2006;**78**:620-628. DOI: 10.1002/jbm.a.30711
- [62] Bartlett DW, Davis ME. Physicochemical and biological characterization of targeted, nucleic acid-containing nanoparticles. *Bioconjugate Chemistry*. 2007;**18**:456-468. DOI: 10.1021/bc0603539
- [63] Nagayama S, Ogawara K, Fukuoka Y, Higaki K, Kimura T. Time-dependent changes in opsonin amount associated on nanoparticles alter their hepatic uptake characteristics. *International Journal of Pharmaceutics*. 2007;**342**:215-221
- [64] Al-Hanbali O, Rutt KJ, Sarker DK, Hunter AC, Moghimi SM. Concentration dependent structural ordering of poloxamine 908 on polystyrene nanoparticles and their modulatory role on complement consumption. *Journal of Nanoscience and Nanotechnology*. 2006;**6**:3126-3133
- [65] Bertholon I, Vauthier C, Labarre D. Complement activation by core-shell poly(isobutylcyanoacrylate)-polysaccharide nanoparticles: Influences of surface morphology, length, and type of polysaccharide. *Pharmaceutical Research*. 2006;**23**:1313-1323. DOI: 10.1007/s11095-006-0069-0
- [66] Talaei F, Azhdarzadeh M, Hashemi Nasel H, Moosavi M, Foroumadi A, Dinarvand R, Atyabi F. Core shell methyl methacrylate chitosan nanoparticles: In vitro mucoadhesion and complement activation. *Daru*. 2011;**19**:257-265. DOI: 10.1038/srep02814
- [67] Nilsson KN, Ekdahl TE, Mollnes JD. Lambris, The role of complement in biomaterial-induced inflammation. *Molecular Immunology*. 2007;**44**:82-94. DOI: 10.1016/j.molimm.2006.06.020
- [68] Rybak-Smith MJ, Tripisciano C, Borowiak-Palen E, Lamprecht C, Sim RB. Effect of functionalization of carbon nanotubes with psychosine on complement activation and protein adsorption. *Journal of Biomedical Nanotechnology*. 2011;**7**:830-839
- [69] Pacheco PM, LE B, White D, Sulchek T. Tunable complement activation by particles with variable size and Fc density. *Nano Life*. 2013;**3**:1341001. DOI: 10.1142/S1793984413410018
- [70] Yu K, Lai BF, Foley JH, Krisinger MJ, Conway EM, Kizhakkedathu JN. Modulation of complement activation and amplification on nanoparticle surfaces by glycopolymer conformation and chemistry. *ACS Nano*. 2014;**8**:7687-7703. DOI: 10.1021/nn504186b

- [71] Thomas DG, Chikkagoudar S, Heredia-Langer A, Tardiff MF, Xu Z, Hourcade DE, Pham CT, Lanza GM, Weinberger KQ, Baker NA. Physicochemical signatures of nanoparticle-dependent complement activation. *Computational Science & Discovery*. 2014;**7**:015003. DOI: 10.1088/1749-4699/7/1/015003
- [72] Banda NK, Mehta G, Chao Y, Wang G, Inturi S, Fossati-Jimack L, Botto M, Wu L, Moghimi SM, Simberg D. Mechanisms of complement activation by dextran-coated superparamagnetic iron oxide (SPIO) nanoworms in mouse versus human serum. *Particle and Fibre Toxicology*. 2014;**11**:64. DOI: 10.1186/s12989-014-0064-2
- [73] Cho H. Complement regulation: Physiology and disease relevance. *Korean Journal of Pediatrics*. 2015;**58**:239-244. DOI: 10.3345/kjp.2015.58.7.239
- [74] Szebeni J, Storm G. Complement activation as a bioequivalence issue relevant to the development of generic liposomes and other nanoparticulate drugs. *Biochemical and Biophysical Research Communications*. 2015;**468**:490-497. DOI: 10.1016/j.bbrc.2015.06.177
- [75] Moghimi SM. Cancer nanomedicine and the complement system activation paradigm: Anaphylaxis and tumour growth. *Journal of Controlled Release*. 2014;**190**:556-562. DOI: 10.1016/j.jconrel.2014.03.051
- [76] Hotaling NA, Tang L, Irvine DJ, Babensee JE. Biomaterial strategies for immunomodulation. *Annual Review of Biomedical Engineering*. 2015;**17**:317-349. DOI: 10.1146/annurev-bioeng-071813-104814
- [77] Cedervall T, Lynch I, Lindman S, Berggård T, Thulin E, Nilsson H, Dawson KA, Linse S. Understanding the nanoparticle-protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. *Proceedings of the National Academy of Sciences of the United States of America*. 2007;**104**:2050-2055. DOI: 10.1073/pnas.0608582104
- [78] Chen K, Rana S, Moyano DF, Xu Y, Guo X, Rotello VM. Optimizing the selective recognition of protein isoforms through tuning of nanoparticle hydrophobicity. *Nanoscale*. 2014;**6**:6492-6495. DOI: 10.1039/c4nr01085j
- [79] Lundqvist M, Sethson I, Jonsson BH. Protein adsorption onto silica nanoparticles: Conformational changes depend on the particles' curvature and the protein stability. *Langmuir*. 2004;**20**:10639-10647. DOI: 10.1021/la0484725
- [80] Lynch I, Dawson KA. Protein-nanoparticle interactions. *Nanotoday*. 2008;**3**:40-47. DOI: 10.1016/S1748-0132(08)70014-8
- [81] Saptarshi SR, Duschl A, Lopata AL. Interaction of nanoparticles with proteins: Relation to bio-reactivity of the nanoparticle. *Journal of Nanobiotechnology*. 2013;**11**:26. DOI: 10.1186/1477-3155-11-26
- [82] Treuel L, Brandholt S, Maffre P, Wiegele S, Shang L, Nienhaus GU. Impact of protein modification on the protein corona on nanoparticles and nanoparticle-cell interactions. *ACS Nano*. 2014;**8**:503-513. DOI: 10.1021/nn405019v

- [83] Maffre P, Brandholt S, Nienhaus K, Shang L, Parak WJ, Nienhaus GU. Effects of surface functionalization on the adsorption of human serum albumin onto nanoparticles – A fluorescence correlation spectroscopy study. *Beilstein Journal of Nanotechnology*. 2014;**5**:2036-2047. DOI: 10.3762/bjnano.5.212
- [84] Caracciolo G, Farokhzad OC, Mahmoudi M. Biological identity of nanoparticles in vivo: Clinical implications of the protein corona. *Trends in Biotechnology*. 2016; **S0167-7799**:30149-30154. DOI: 10.1016/j.tibtech.2016.08.011
- [85] Monopoli MP, Aberg C, Salvati A, Dawson KA. Biomolecular coronas provide the biological identity of nanosized materials. *Nature Nanotechnology*. 2012;**7**:779-786. DOI: 10.1038/nnano.2012.207
- [86] Peng Q, Zhang S, Yang Q, Zhang T, Wei XQ, Jiang L, Zhang CL, Chen QM, Zhang ZR, Lin YF. Preformed albumin corona, a protective coating for nanoparticles based drug delivery system. *Biomaterials*. 2013;**34**:8521-8530. DOI: 10.1016/j.biomaterials.2013.07.102
- [87] Pearson RM, Juetter VV, Hong S. Biomolecular corona on nanoparticles: A survey of recent literature and its implications in targeted drug delivery. *Frontiers in Chemistry*. 2014;**2**:108. DOI: 10.3389/fchem.2014.00108
- [88] Sacchetti C, Motamedchaboki K, Magrini A, Palmieri G, Mattei M, Bernardini S, Rosato N, Bottini N, Bottini M. Surface polyethylene glycol conformation influences the protein corona of polyethylene glycol-modified single-walled carbon nanotubes: Potential implications on biological performance. *ACS Nano*. 2013;**7**:1974-1989. DOI: 10.1021/nn400409h
- [89] Tenzer S, Docter D, Kuharev J, Musyanovych A, Fetz V, Hecht R, Schlenk F, Fischer D, Kiouptsi K, Reinhardt C, Landfester K, Schild H, Maskos M, Knauer SK, Stauber RH. Rapid formation of plasma protein corona critically affects nanoparticle pathophysiology. *Nature Nanotechnology*. 2013;**8**:772-781. DOI: 10.1038/nnano.2013.181
- [90] Hamad-Schifferli K. Exploiting the novel properties of protein coronas: Emerging applications in nanomedicine. *Nanomedicine (London, England)*. 2015;**10**:1663-1674. DOI: 10.2217/nnm.15.6
- [91] Docter D, Westmeier D, Markiewicz M, Stolte S, Knauer SK, Stauber RH. The nanoparticle biomolecule corona: Lessons learned - challenge accepted? *Chemical Society Reviews*. 2015;**44**:6094-6121. DOI: 10.1039/c5cs00217f
- [92] Lee YK, Choi EJ, Webster TJ, Kim SH, Khang D. Effect of the protein corona on nanoparticles for modulating cytotoxicity and immunotoxicity. *International Journal of Nanomedicine*. 2014;**10**:97-113. DOI: 10.2147/IJN.S72998
- [93] Montiel-Dávalos A, Ventura-Gallegos JL, Alfaro-Moreno E, Soria-Castro E, García-Latorre E, Cabañas-Moreno JG, del Pilar Ramos-Godinez M, López-Marure R. TiO₂ nanoparticles induce dysfunction and activation of human endothelial cells. *Chemical Research in Toxicology*. 2012;**25**:920-930. DOI: 10.1021/tx200551u
- [94] Liu X, Xue Y, Ding T, Sun J. Enhancement of proinflammatory and procoagulant responses to silica particles by monocyte-endothelial cell interactions. *Particle and Fibre Toxicology*. 2012;**9**:36. DOI: 10.1186/1743-8977-9-36

- [95] Gaillet S, Rouanet JM. Silver nanoparticles: Their potential toxic effects after oral exposure and underlying mechanisms--A review. *Food and Chemical Toxicology*. 2015;**77**:58-63. DOI: 10.1016/j.fct.2014.12.019
- [96] Gromnicova R, Kaya M, Romero IA, Williams P, Satchell S, Sharrack B, Male D. Transport of gold nanoparticles by vascular endothelium from different human tissues. *PLoS One*. 2016;**11**:e0161610. DOI: 10.1371/journal.pone.0161610
- [97] Braniste T, Tiginyanu I, Horvath T, Raevschi S, Cebotari S, Lux M, Haverich A, Beilstein AH. Viability and proliferation of endothelial cells upon exposure to GaN nanoparticles. *Beilstein Journal of Nanotechnology*. 2016;**7**:1330-1337. DOI: 10.3762/bjnano.7.124
- [98] Strobel C, Oehring H, Herrmann R, Förster M, Reller A, Hilger I. Fate of cerium dioxide nanoparticles in endothelial cells: Exocytosis. *Journal of Nanoparticle Research*. 2015;**17**:206. DOI: 10.1007/s11051-015-3007-4
- [99] Freese C, Uboldi C, Gibson MI, Unger RE, Weksler BB, Romero IA, Couraud PO, Kirkpatrick CJ. Uptake and cytotoxicity of citrate-coated gold nanospheres: Comparative studies on human endothelial and epithelial cells. *Particle and Fibre Toxicology*. 2012;**9**:23. DOI: 10.1186/1743-8977-9-23
- [100] Anspach L, Unger RE, Gibson MI, Klok HA, Kirkpatrick CJ, Freese C. Impact of polymer-modified gold nanoparticles on brain endothelial cells: Exclusion of endoplasmic reticulum stress as a potential risk factor. *Nanotoxicology*. 2016;**10**:1341-1350. DOI: 10.1080/17435390.2016.1214761
- [101] Freese C, Schreiner D, Anspach L, Bantz C, Maskos M, Unger RE, Kirkpatrick CJ. In vitro investigation of silica nanoparticle uptake into human endothelial cells under physiological cyclic stretch. *Particle and Fibre Toxicology*. 2014;**11**:68. DOI: 10.1186/s12989-014-0068-y
- [102] Yang L, Yan Q, Zhao J, Li J, Zong X, Yang L, Wang Z. The role of potassium channel in silica nanoparticle-induced inflammatory effect in human vascular endothelial cells in vitro. *Toxicology Letters*. 2013;**223**:16-24. DOI: 10.1016/j.toxlet.2013.08.017
- [103] Guo C, Xia Y, Niu P, Jiang L, Duan J, Yu Y, Zhou X, Li Y, Sun Z. Silica nanoparticles induce oxidative stress, inflammation, and endothelial dysfunction in vitro via activation of the MAPK/Nrf2 pathway and nuclear factor- κ B signaling. *International Journal of Nanomedicine*. 2015;**10**:1463-1477. DOI: 10.2147/IJN.S76114
- [104] Yan M, Zhang Y, Xu K, Fu T, Qin H, Zheng X. An in vitro study of vascular endothelial toxicity of CdTe quantum dots. *Toxicology*. 2011;**282**:94-103. DOI: 10.1016/j.tox.2011.01.015
- [105] Rosas-Hernandez H, Jimenez-Badillo S, Martinez-Cuevas PP, Gracia- Espino E, Terrones H, Terrones M, Hussain SM, Ali SF, Gonzalez C. Effects of 45-nm silver nanoparticles on coronary endothelial cells and isolated rat aortic rings. *Toxicology Letters*. 2009;**191**:305-313. DOI: 10.1016/j.toxlet.2009.09.014

- [106] Shi J, Sun X, Lin Y, Zou X, Li Z, Liao Y, Du M, Zhang H. Endothelial cell injury and dysfunction induced by silver nanoparticles through oxidative stress via IKK/NF- κ B pathways. *Biomaterials*. 2014;**35**:6657-6666. DOI: 10.1016/j.biomaterials.2014.04.093
- [107] Trickler WJ, Lantz SM, Murdock RC, Schrand AM, Robinson BL, Newport GD, Schlager JJ, Oldenburg SJ, Paule MG, Slikker W Jr, Hussain SM, Ali SF. Silver nanoparticle induced blood-brain barrier inflammation and increased permeability in primary rat brain microvessel endothelial cells. *Toxicological Sciences*. 2010;**118**:160-170. DOI: 10.1093/toxsci/kfq244
- [108] Grosse S, Evje L, Syversen T. Silver nanoparticle-induced cytotoxicity in rat brain endothelial cell culture. *Toxicology In Vitro*. 2013;**27**:305-313
- [109] Sun X, Shi J, Zou X, Wang C, Yang Y, Zhang H. Silver nanoparticles interact with the cell membrane and increase endothelial permeability by promoting VE-cadherin internalization. *Journal of Hazardous Materials*. 2016;**317**:570-578. DOI: 10.1016/j.jhazmat.2016.06.023
- [110] Zhang E, Yang WX. Tight junction between endothelial cells: The interaction between nanoparticles and blood vessels. *Beilstein Journal of Nanotechnology*. 2016;**7**:675-684. DOI: 10.3762/bjnano.7.60
- [111] Cheng Y, Morshed R, Auffinger B, Tobias AL, Lesniak MS. Multifunctional nanoparticles for brain tumor imaging and therapy. *Advanced Drug Delivery Reviews*. 2014;**66**:42-57. DOI: 10.1016/j.addr.2013.09.006
- [112] Asai T. Nanoparticle-mediated delivery of anticancer agents to tumor angiogenic vessels. *Biological and Pharmaceutical Bulletin*. 2012;**35**:1855-1861
- [113] Chen X, Fang J, Wang S, Liu H, Du X, Chen J, Li X, Yang Y, Zhang B, Zhang W. A new mosaic pattern in glioma vascularization: Exogenous endothelial progenitor cells integrating into the vessels containing tumor-derived endothelial cells. *Oncotarget*. 2014;**5**:1955-1968. DOI: 10.18632/oncotarget.1885
- [114] Kim YT, Lobatto ME, Kawahara T, Chung BL, Mieszawska AJ, Sanchez-Gaytan BL, Fay F, Senders ML, Calcagno C, Becraft J, Saung MT, Gordon RE, Stroes ESG, Ma M, Farokhzad OC, Fayad ZA, Mulder WJM, Langer R. Probing nanoparticle translocation across the permeable endothelium in experimental atherosclerosis. *Proceedings of the National Academy of Sciences of the United States of America*. 2014;**111**:1078-1083. DOI: 10.1073/pnas.1322725111
- [115] Agyare E, Kandimalla K. Delivery of polymeric nanoparticles to target vascular diseases. *Journal of Biomolecular Research & Therapeutics*. 2014;**3**:S1-S001
- [116] Shuvaev VV, Christofidou-Solomidou M, Scherpereel A, Simone E, Arguiri E, Tliba S, Pick J, Kennel S, Albelda SM, Muzykantov VR. Factors modulating the delivery and effect of enzymatic cargo conjugated with antibodies targeted to the pulmonary endothelium. *Journal of Controlled Release*. 2007;**118**:235-244. DOI: 10.1016/j.jconrel.2006.12.025

- [117] Chen C, Mei H, Shi W, Deng J, Zhang B, Guo T, Wang H, Hu Y. EGFP-EGF1-conjugated PLGA nanoparticles for targeted delivery of siRNA into injured brain microvascular endothelial cells for efficient RNA interference. *PLoS One*. 2013;**8**:e60860. DOI: 10.1371/journal.pone.0060860
- [118] Jumelle C, Mauclair C, Houzet J, Bernard A, He Z, Forest F, Peoc'h M, Acquart S, Gain P, Thuret G. Delivery of molecules into human corneal endothelial cells by carbon nanoparticles activated by femtosecond laser. *PLoS One*. 2015;**10**:e0132023. DOI: 10.1371/journal.pone.0132023
- [119] Ljubimov AV, Saghizadeh M. Progress in corneal wound healing. *Progress in Retinal and Eye Research*. 2015;**49**:17-45. DOI: 10.1016/j.preteyeres.2015.07.002
- [120] Miller-Kleinhenz JM, Bozeman EN, Yang L. Targeted nanoparticles for image-guided treatment of triple negative breast cancer: Clinical significance and technological advances. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*. 2015;**7**:797-816. DOI: 10.1002/wnan.1343
- [121] Kiessling F, Mertens ME, Grimm J, Lammers T. Nanoparticles for imaging: Top or flop? *Radiology*. 2014;**273**:10-28. DOI: 10.1148/radiol.14131520
- [122] Lu ZX, Liu LT, Qi XR. Development of small interfering RNA delivery system using PEI-PEG-APRPG polymer for antiangiogenic vascular endothelial growth factor tumor-targeted therapy. *International Journal of Nanomedicine*. 2011;**6**:1661-1673. DOI: 10.2147/IJN.S22293
- [123] Moysidis SN, Alvarez-Delfin K, Peschansky VJ, Salero E, Weisman AD, Bartakova A, Raffa GA, Merkhofer RM Jr, Kador KE, Kunzevitzky NJ, Goldberg JL. Magnetic field-guided cell delivery with nanoparticle-loaded human corneal endothelial cells. *Nanomedicine*. 2015;**11**:499-509. DOI: 10.1016/j.nano.2014.12.002

