Received: 19 September 2021 | Revised: 6 December 2021 | Accepted: 3 January 2022

DOI: 10.1002/jbm.a.37359

REVIEW ARTICLE

Immunomodulatory properties of nanostructured systems for cancer therapy

Edson J. Comparetti[1] | Natalia N. Ferreira[1] | Leonardo M. B. Ferreira[1] | Ramon Kaneno[2] | Valtencir Zucolotto[1]

[1]Nanomedicine and Nanotoxicology Group, Physics Institute of São Carlos, University of São Paulo, São Carlos, Brazil

[2]Department of Microbiology and Immunology, Institute of Biosciences of Botucatu, São Paulo State University, Botucatu, Brazil

Correspondence
Valtencir Zucolotto, Nanomedicine and Nanotoxicology Group, Physics Institute of São Carlos, University of São Paulo, São Carlos, Brazil.
Email: zuco@ifsc.usp.br; zucolotto@usp.br

Funding information
Brazilian National Council for Scientific and Technological Development (CNPq), Grant/Award Number: 142285/2017-0; São Paulo Research Foundation (FAPESP), Grant/Award Numbers: 2018/12670-4, 2019/25645-0, 2020/00124-5

Abstract

Based on statistical data reported in 2020, cancer was responsible for approximately 10 million deaths. Furthermore, 17 million new cases were diagnosed worldwide. Nanomedicine and immunotherapy have shown satisfactory clinical results among all scientific and technological alternatives for the treatment of cancer patients. Immunotherapy-based treatments comprise the consideration of new alternatives to hinder neoplastic proliferation and to reduce adverse events in the body, thereby promoting immune destruction of diseased cells. Additionally, nanostructured systems have been proven to elicit specific immune responses that may enhance antitumor activity. A new generation of nanomedicines, based on biomimetic and bioinspired systems, has been proposed to target tumors by providing immunomodulatory features and by enabling recovery of human immune destruction capacity against cancer cells. This review provides an overview of the aspects and the mechanisms by which nanomedicines can be used to enhance clinical procedures using the immune modulatory responses of nanoparticles (NPs) in the host defense system. We initially outline the cancer statistics for conventional and new treatment approaches providing a brief description of the human host defense system and basic principles of NP interactions with monocytes, leukocytes, and dendritic cells for the modulation of antitumor immune responses. A report on different biomimetic and bioinspired systems is also presented here and their particularities in cancer treatments are addressed, highlighting their immunomodulatory properties. Finally, we propose future perspectives regarding this new therapeutic strategy, highlighting the main challenges for future use in clinical practice.

KEYWORDS
cancer therapy, evasion of immune destruction, hallmarks of cancer, immunomodulation, nanomedicine

1 | AN OVERVIEW OF CANCER STATISTICS AND CONVENTIONAL TREATMENTS

Despite the recent advances in clinical treatments, cancer remains one of the leading causes of death globally, representing a major public health issue. Incidence and mortality data are usually available 2–4 years after the corresponding period, considering the time required for data acquisition, compilation, and dissemination.[1] In an attempt to provide an estimate of the contemporary cancer burden, Global Cancer Observatory (GLOBOCAN) reported 9.9 million deaths and 19 million new cases in 2020. These data represent

underestimated numbers due to the absence of high-quality cancer registries, especially in low- and middle-income countries.[2]

In adults, lung cancer is the most commonly reported malignancy. It is responsible for the highest number of casualties in men (14.3%), followed by prostate cancer (14.1%). In contrast, breast and colorectal cancers are the most prevalent types reported in women, representing 24.5% and 9.4% of the cases, respectively.[2] In children, leukemia and brain tumors are responsible for 50% of the diagnoses, with neuroblastoma, kidney, and Hodgkin lymphoma responsible for the remaining cases.[3] In developed countries, early detection helps in the reduction of the number of deaths. The highest rate of mortality was registered in underdeveloped or developing territories due to a lack of availability of medicines and treatment interruption.[2]

Conventional treatments for cancer include different options. Surgical removal is the first recommended procedure for treating considerable and localized malignancies.[4,5] Since its approval over 60 years ago, standard treatment recommendations continue to be based on chemotherapy, which targets rapidly growing and dividing cells, and radiation therapy, which targets all cells within the localized tumor microenvironment (TME), both using well-established protocols.[6]

As an initial or complementary treatment to surgery, conformational radiotherapy approaches, including intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), aid the optimization of the dose delivered to the target tissues and fractionation of the total dose of radiation in therapeutic sessions to minimize DNA damage in normal cells.[7] However, infliction of injuries to healthy tissues and discomfort in the irradiated regions may occur as side effects of subjection to such treatments.[8]

If surgery and radiotherapy are not recommended, patients should be administered with cytotoxic molecules (chemotherapeutics) through local and systemic administration, oral administration, or even alternative routes.[9,10] Conventional drugs used in chemotherapy regimens exhibit different mechanisms of action, and most can be categorized as (a) alkylating agents for the inhibition of DNA transcription[11]; (b) antimetabolites used as an analog of cell compounds for inducing blockade of metabolic pathways in the S phase[12]; (c) microtubule-targeting agents used for the destruction or stabilization of the cytoskeleton in the gap of growth (G) G0/G1 and/or G2/M phases[13]; (d) topoisomerase inhibitors[14]; and (e) anthracyclines.[15] Owing to a lack of specificity, chemotherapy includes the occurrence of common side effects observed during drug administration, which may change according to the period of exposure, the type of drug administered, and the concentration of the therapeutic agent in the body. The destruction of healthy cells results in the occurrence of several side effects, including dermatological, cardiac, pulmonary, neurological, hematological (leukopenia, thrombocytopenia, and anemia), gastrointestinal (nausea, vomiting, mucositis, and diarrhea), metabolic changes, allergic reactions, and anaphylaxis (Figure 1).[16]

As the incidence rate and mortality of cancer have increased markedly, substantial efforts to prolong survival, to reduce local recurrence, and to minimize the side effects of conventional therapies have become increasingly dependent on modern robotic surgery, tumor adjuvant therapy, and other new technologies, among which the application of nanomedicines should be highlighted.[6]

The next generation of cancer treatments is mainly based on the characterization of molecular features and the identification of a plethora of effective targets for therapy.[17] In the present era, the hallmarks of cancer, first reported by Weinberg and Hanahan, which are used to describe and identify remarkable characteristics of malignant tumor cells, provides evidence that the acquisition of knowledge based on such biological aspects has important implications for the realization of successful cancer therapies.[18,19] Among such new strategies, the recognition of tumor cell capacity in the immune system enables the design and development of novel strategies that can effectively guarantee the success of different immunotherapeutic strategies.

2 | HOST DEFENSE SYSTEM AND IMMUNOTHERAPY

The importance of the human immune system in conferring protection against different pathogens is well established. However, whether cancer prevention is a primary function of the host immune system remains debatable.[20] It is well established that the immune system establishes intricate communication with tumor cells over the entire process of disease development and progression to metastasis. This complex crosstalk established between immunity and cancer development can both result in the inhibition and enhancement of tumor growth, a phenomenon that has been outlined as an important hallmark of cancer.[21,22]

Immunocompetent cells establish interaction with tumor cells in a three-phase multistage process referred to as the "3 Es", namely elimination (also referred to as immunosurveillance), equilibrium, and escape.[23,24] The concept of cancer immunosurveillance originally stated that transformed cells frequently develop, but are recognized and eliminated by the immune system before leading to the development of clinically observable diseases.[25] However, frequent cases of cancer are reported even in individuals with a highly functional and robust immune system. Hence, researchers believe that immunosurveillance is only one facet of the interaction established between immunocompetent cells with tumor cells. Indeed, tumors derived from immunocompetent hosts are less immunogenic than those isolated from immunodeficient hosts,[26,27] indicating that few phenotypical features of tumor cells are acquired via the interaction established with the immune system.[23]

The immune system not only performs the recognition of tumor cells, but also helps modulate tumor cell immunogenicity, establishing an equilibrium phase with selected "silent" variants. These selected variants are resistant to immune effectors and retain genes associated with survival, immune evasion, and the ability to escape to pre-metastatic niches.[28,29] Importantly, such niches comprise limited or absent tissue-resident memory cells responsible for immunosurveillance.[30] Therefore, cancer cells, with the ability to invade the basement membrane and to migrate to distant sites, detect a convenient environment for metastasis. Despite the ability of cancer cells to escape immunosurveillance and specific immune responses, several immunocompetent cells, including dendritic cells (DCs), helper and cytotoxic T lymphocytes, tumor-infiltrating

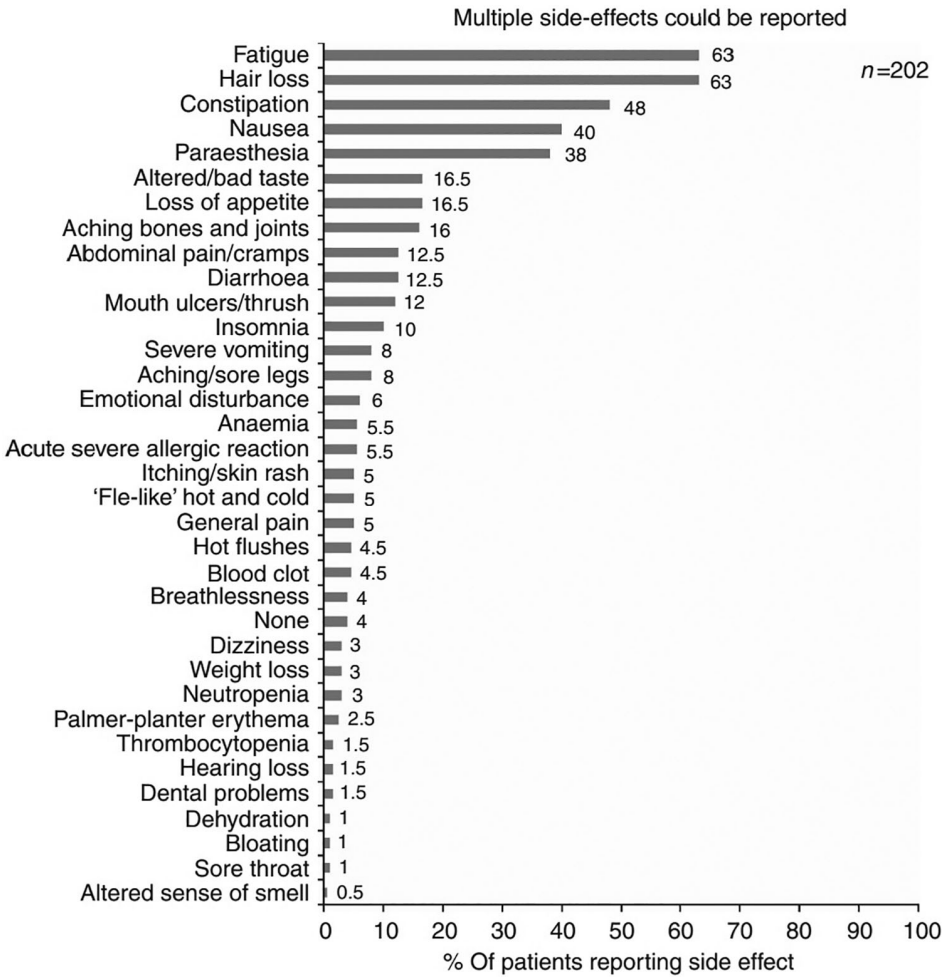

FIGURE 1 Most common side effects of chemotherapeutics reported in patients. Adapted with permission from Ref. 16

macrophages, and natural killer cells, are recruited to mount immune responses against tumor cells.

DCs are the chief antigen-presenting cells (APCs) that perform continuous surveillance and recognition of the microenvironment of tissues and organs where they remain as immature cells (iDCs). iDCs can capture soluble and particulate antigens[31,32] through several surface receptors, such as FcγR,[32] mannose receptor (MR),[33] DC-SIGN,[34] type C lectin receptors (DEC-205),[35] as well as toll-like receptors.[36] These antigens are then processed and disintegrated into peptides that are subsequently presented to T lymphocytes in the context of the major histocompatibility complex (MHC),[32,36] inducing their differentiation into T helper type 1 (Th1), T helper type 2 (Th2), T helper type 17 (Th17), or T helper type 9 (Th9) lymphocytes, which exhibit different roles in the antitumor response.[37]

Conventional DCs are identified by the expression of cluster of differentiation (CD)11c, CD1a, or CD83,[32,36] and are subdivided into $CD1c^+$ (blood DC antigen1^+ cells) and $CD141^+$ (blood DC antigen3^+) subsets.[38,39] Mature DCs express CD80, CD86, CD40, and chemokine (C-C motif) receptor 7 (CCR7).[40] Importantly, during maturation, the co-receptors inducible costimulatory ligand (ICOSL), tumor necrosis factor (TNF) ligand superfamily member 4 (TNFSF4), and TNF ligand superfamily member 8 ((TNFSF8) as well as receptors for interleukin (IL)-2, IL-1, IL12, and IL-18 are also found.[41] It is important to clarify that during maturation, DCs lose the ability to capture and process antigens, but demonstrate increased efficiency at presenting processed peptides to T lymphocytes, thereby triggering a specific immune response against cancer cells.[32,36,42]

In addition to the development of target responses, while $CD4^+$ lymphocytes perform the recognition of tumor antigens processed and presented by professional APCs to initiate a specific immune response, $CD8^+$ lymphocytes demonstrate the ability of direct recognition of tumor antigens expressed on the tumor cell surface, targeting them for cell-mediated cytotoxicity.[37] Therefore, $CD8^+$ cytotoxic T lymphocytes (CTL) are classically considered as the main antitumor effector cells, as they recognize tumor antigens in a restricted manner and exhibit clonal expansion, with their activation and evolution into cytolytic antitumor cells, thereby improving the antitumor status.[43,44]

The presence of cytotoxic lymphocytes at the tumor site has been associated with good clinical outcomes during therapy.[45] Theoretically, an efficient antitumor response driven by the immune system is related to the release of pro-inflammatory cytokines, both by the APCs and the helper T cells generated by the stimulation of $CD4^+$ lymphocytes. However, the ability of the human host immune system to resist or eradicate the formation and progression of incipient neoplasias, late-stage tumors, and metastasis remains an unresolved issue.

Scientific evidence suggests that the immune system may perform functions as a significant barrier to tumor formation and progression, at least in certain types of cancer.[18] In fact, cancer cells that may evade immune destruction by disabling components of the immune system should be recognized, with an aim to eliminate them.[18,20,22,46,47] Understanding these immune inhibitory processes is crucial for predicting the mechanisms by which cancers escape the normal immune system.[47]

Considering the antitumor immunity as a significant barrier to tumor formation and progression, the immunosuppressive cancer cell phenotype is recognized as one of the hallmarks of cancer, which should be addressed to improve novel therapeutic strategies.[21]

As the above-mentioned approaches necessary for an active immune response do not occur in an effective manner for cancer cells, novel therapies are designed with an aim to "re-educate" antitumor responses using cytokine inhibitors. Blockade of the expression of classical biomarkers in regulatory cells has been shown to exhibit excellent results in different cancers, including stomach, neck, kidney, bladder, esophagus, lung, breast, and aggressive malignant melanoma.[48,49] Immunotherapeutic drugs, such as ipilimumab, pembrolizumab, talimogene laherparepvec (T-Vec), and trastuzumab, which are used to block suppressor receptors on lymphocytes (T-linfócito-associada citotóxico 4 - CTLA-4 and Programmed cell death protein 1 – PD1)[48,49] are not indicated for all classes of tumors and do not present the same efficacy in all patients, thereby highlighting the necessity of the standardization of individual protocols, which may substantially increase treatment costs.[50] Despite the use of immunotherapeutic drugs, another promising strategy is to potentiate the naturally occurring immune response of the patient, which can be considered together with nanomedicine strategies in the present era.[20]

3 | NANOMEDICINE IN CLINICAL PROCEDURES

The extensive investigation of effective therapeutic regimens in cancer treatment has been the focus of renowned research groups worldwide. Nanomedicine, which is the application of nanotechnology in diagnosis, prevention, and treatment, represents one of the most advanced technologies for the treatment of different neoplasia types. Nanotechnology has been applied in medical and biomedical practices to improve conventional procedures and to develop novel therapeutic regimens.[51,52] The possibility of modulating the physical and chemical properties of nanosystems according to the desired application, and the ability of nanosystems to cross biological barriers and to accumulate in tumor tissues, contribute to the evident benefits of their utilization as advanced platforms for cancer therapies.[51,52] Therefore, several classes of nanosystems have been extensively studied for anticancer drug delivery, including polymeric nanoparticles (NPs), polymeric micelles, liposomes, nanocapsules, dendrimers, inorganic NPs, nanoemulsions, nanogels, and others, and few have already reached clinical trial stages (Table 1).[51,52] Nanostructured systems loaded with different anticancer agents have shown promising results.[51,52] The possibility of encapsulating different molecules within NPs with controlled surface chemistry, size, shape, and superficial charge allows the targeting of cancer cells to reduce undesired activity in healthy tissues. Herein, we highlight the improvements provided by these nanostructures against cancer cells, emphasizing their immunomodulatory capacity in the TME, blood, and lymphoid organs.

Nanostructured systems overcome the lack of specificity and efficacy associated with the usual clinical techniques, improving therapeutic procedures in primary and metastatic sites.[51] For example, chemotherapeutics adsorbed or covalently bound to nanomaterials can reduce drug withdrawal from the cytoplasm by transporter ABC (ATP-binding cassette).[53] NPs inhibit the main mechanisms of cellular pumps, retaining antineoplastic agents inside cancer cells for extensive periods compared to free drug molecules. Such peculiarity minimizes the low bioavailability of hydrophobic drugs and improves their delivery with low therapeutic resistance.[53,54] Recently, active molecules released from nanostructures were demonstrated to maintain the minimal effective dose for longer periods in the TME.[55–58] In fact, from an immunological perspective, the use of nanocarriers may help stimulate antitumor immunity by promoting the activation of DCs, CTLs, natural killers (NKs) cells, and the depletion of regulatory T cells (Treg) suppression.[59] For example, commercially available nanostructured systems, such as Abraxane® and Doxil®, when administered, are internalized by immune-suppressed macrophages that drive their immune response to an inflammatory profile.[60,61] Daily administration is not necessary for these nanoformulations, as they occur with the use of their free drug molecules, subsequently reducing cytotoxicity in white blood cells (WBCs).[60,61]

Drug delivery nanosystems exhibit fewer side effects, including leucopenia, thrombocytopenia, anemia, fatigue, peripheral neuropathy, and neutropenia,[62] as described for paclitaxel and doxorubicin (DOX). Based on the improvement provided in terms of therapeutic efficacy and its immunological aspects, paclitaxel-loaded nanoparticles (Abraxane®) exhibit not only a slight cytotoxicity in peripheral monocytes in the bloodstream, but also does not induce phenotypic changes.[63,64] Exposure of peripheral blood monocytes to paclitaxel (PTX)-loaded NPs during their in vitro differentiation to DCs did not decrease the expression of CD11c, CD209, and MHC-II.[64] Additionally, NPs-PTX do not interfere with the stimulatory ability of DCs or suppress the capacity to stimulate naive T cells, with no phenotypic and functional changes observed in mature DCs.[64]

4 | NANOMEDICINES FOR THE MODULATION OF HUMAN IMMUNE RESPONSE

The immunomodulatory properties of intravenously administered NPs have been extensively studied for a wide range of clinical applications. Their successful investigation in clinical trials should be based on their immunostimulatory potential, while considering their uptake, presentation of cancer antigens by APCs, and the elicitation of an immune response (Figure 2).[65]

TABLE 1 Nanoparticles (NPs) in clinical use

NP types	Purposes	Approved by FDA and/or EMA	Indication
Lipid	Treatment	Abelcet®	Fungal infections
		Caelyx®	Kaposi's sarcoma, ovary, breast, myeloma
		Doxil®	Ovarian and Breast cancer; myeloma
		Marqibo®	Lymphoblastic leukemia
		MEPACT®	Osteosarcoma
		Myocet®	Breast cancer
		Oncaspar®	Lymphoblastic leukemia
		Onivyde MM-398®	Pancreatic cancer
		Visudyne®	Pathologic myopia, ocular histoplasmosis
		VYXEOS CPX-35®	Myeloid leukemia
	Diagnosis	Definity®	Cardiovascular ultrasound enhancement
		SonoVue®	Contrast agent for liver, spleen, and kidney trauma
Protein-based	Treatment	Abraxane®	Lung, breast, and pancreatic cancer
		Ontak®	T-cell lymphoma
Polymeric	Treatment	Adynovate®	Hemophilia
		Cimzia®	Crohn's disease and rheumatoid arthritis
		Copaxone®	Multiple sclerosis
		Eligard®	Prostate cancer
		Krystexxa®	Chronic gout
		Mircera®	Anemia
		Neulasta®	Neutropenia
		Oncaspar®	Leukemia
		Pegasys®	Hepatitis B, hepatitis C
		Renagel®	Chronic kidney disease
		Welchol®	Type II diabetes
Metallic	Treatment	Feraheme®	Iron deficiency
		Ferinject®	Anemia
		Hensify®	Squamous cell carcinoma
		Injectafer®	Anemia
		Venofer®	Anemia
	Diagnosis	Feridex®	Liver lesions (drug withdrawn from the market)
		Resovist®	Magnetic resonance imaging

The capture of NPs by WBCs may occur via phagocytosis, endocytosis, or adsorption. Among the APCs, DCs play an important role in tumor control via the induction of tumor-specific T-cell responses; therefore, they are an ideal target for the conduction of immunotherapy mediated by nanomedicine usage.[66] As an adjunct therapy, poly(lactic-co-glycolic acid) (PLGA) NPs with different surface modifications can be produced to collect and deliver tumor-derived protein antigens to DCs and macrophages after radiotherapy or chemotherapy.[65] It has also been verified that PLGA NPs may capture damage-associated molecular patterns (DAMPs), which are defined as biomolecules that can help initiate and perpetuate a noninfectious inflammatory response and potentiate immune activity. Particularly, nanostructured systems perform the adsorption of tumor antigenic materials to stimulate DC activation and to enhance antineoplastic immune responses. After capturing nanocarriers loaded with stimulatory drugs or tumor antigens, DCs increase the expression of activation markers to proceed with antigen presentation to naïve lymphocytes. Antigenic materials are degraded by proteases in endosomes and associate with intracellular vesicles carrying MHC class II for further exposure on the cell surface and for establishing interaction with $CD3^+$ T lymphocytes.[67] Cytosolic antigens are processed by proteasomes for association with MHC class I in the endoplasmic reticulum (ER).[67,68] When the peptide–MHC complex is established, MHC-I leaves the ER for localization at the cell surface to recognize $CD8^+$ T cells.[67,69] These processes ensure that fusogenic nanostructures release extracellular proteins into the cytoplasm, inhibiting vesicular degradation and enhancing peptide presentation via MHC class I (Figure 3).[70]

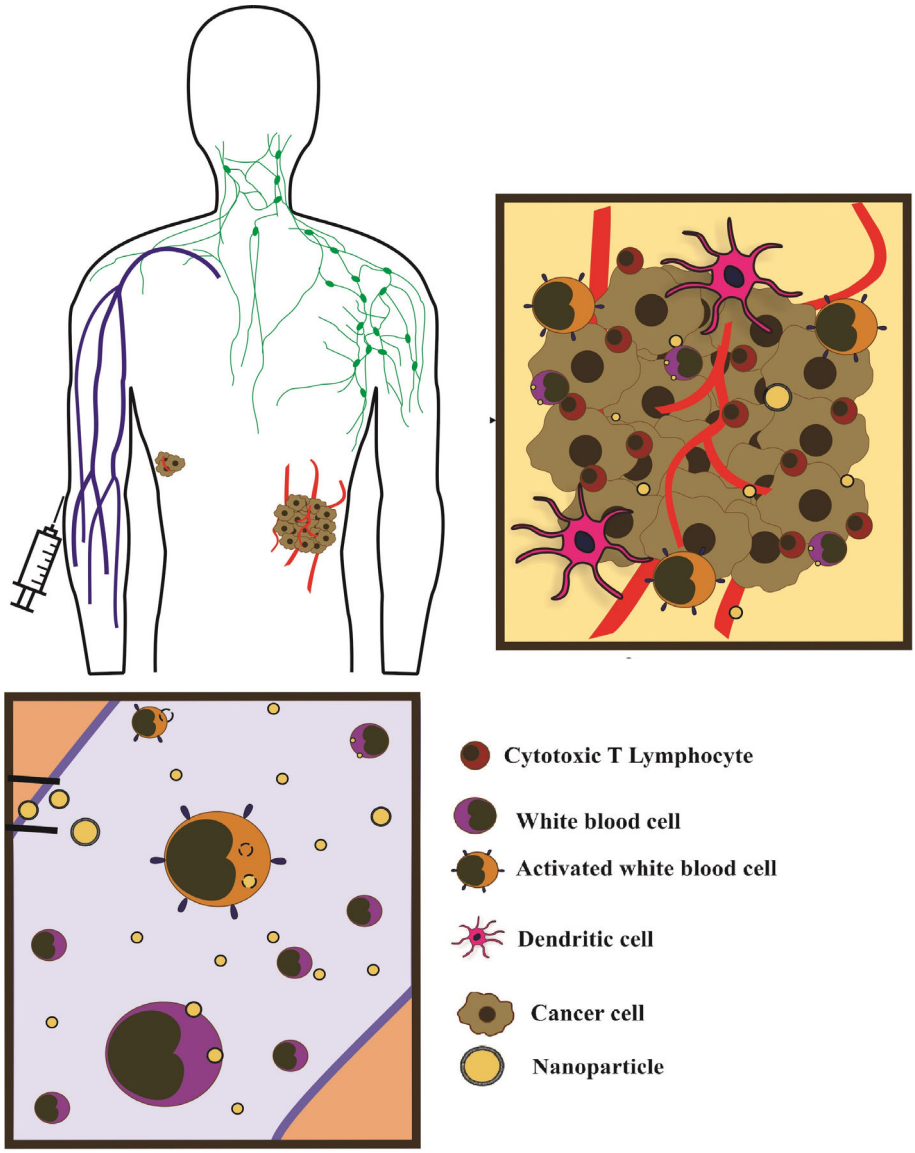

FIGURE 2 New therapeutic strategies using nanoparticles for the activation of phagocytic cells and inhibition of the suppressive profile. The nanoparticles do not need to reach the tumor tissues to produce cytotoxic activity in diseased cells, they can contribute to modulate an individual's immune response in tumor microenvironment. Nanocarriers loaded with antigenic material and adjuvants can induce maturation of B lymphocytes, macrophages, and dendritic cells

With the exhibition of a series of DC subsets, human skin can be an attractive and accessible site for antigen-based immunotherapy. Based on this principle, Boks and co-workers developed a novel therapy using liposomes for the simultaneous delivery of tumor antigens and adjuvants to human skin–resident DCs, exploring their potential for intradermally delivered vaccines. The incorporation of Toll-like receptor 4 (TLR4) monophosphoryl lipid A ligand (MPLA) into liposomes stimulates the skin APCs to instruct tumor-specific $CD8^+$ T cell responses. Interestingly, this was not observed when free MPLA was applied.[66] Once the antigen is captured, peripheral DCs may migrate to lymphoid tissues, triggering the activation of T cells. It is important to highlight that the high levels of the mannose receptor and scavenger receptors on DCs may be more appropriate to target nanostructure capture and to stimulate immune responses.[71]

DC-targeted biomaterials, including hydrogels or other antigen delivery systems, have attracted considerable attention for cancer immunotherapy.[72] Such carriers can help modulate host DC populations by spatiotemporally controlling biochemical molecules, adjuvants, or cytokines. For example, a PEGylated polypeptide hydrogel was designed to encapsulate antigens and a toll-like receptor 3 agonist. The system could stimulate the DC phenotype during activation and in vitro and in vivo maturation, increasing antigen presentation to T lymphocytes and eliciting a response to kill cancer cells.[72]

In addition to the immune system, macrophages and phagocytic cells found in the lung (dust cells), liver (Kupffer cells), kidney (mesangial phagocytes), brain (microglia), bone (osteoclasts), spleen, among others, can undergo activation and differentiation as pro-inflammatory and anti-inflammatory, referring to classic M1 macrophages and alternative M2-type, both derived from immature M0 macrophages.[73] Tumor-associated macrophages (TAMs) usually exhibit the M2 phenotype, providing a favorable environment for cancer progression and producing suppressive signals for the amplification of the Th2 cytokine response.[74,75]

Therefore, new therapeutic strategies that are aimed at re-education of human TAMs and inhibition of their tumor-promoting functions have been proposed.[76] Nanostructures have been proven to disturb biological interactions within tumors by modulating TAM

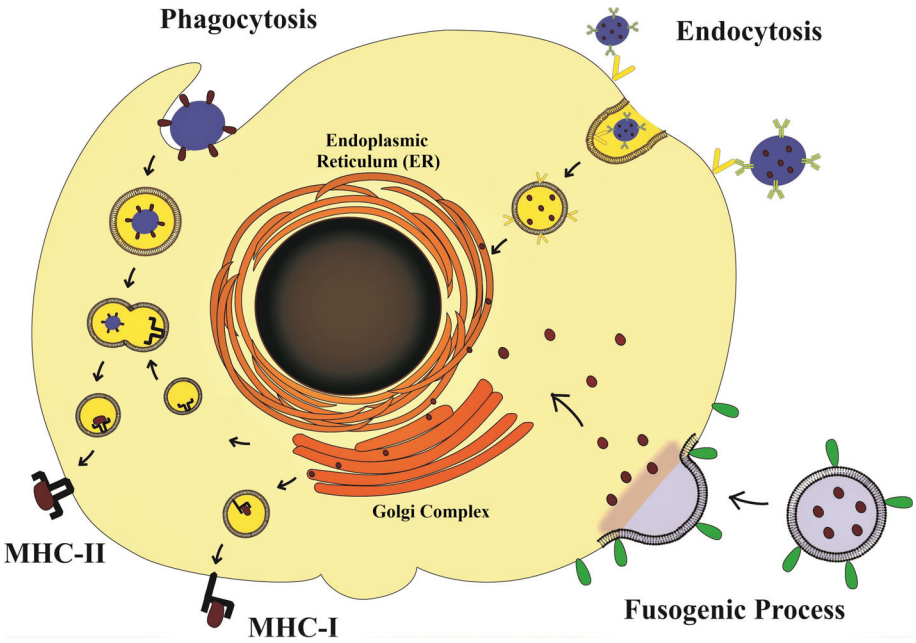

FIGURE 3 The three main routes through which nanoparticles are captured by macrophages and dendritic cells: phagocytosis, endocytosis, and fusion in the plasma membrane. Solid nanoparticles can undergo endocytosis and liposomes can undergo fusion in antigen-presenting cell plasma membranes, delivering tumor antigens into the cytoplasm for future processing in the endoplasmic reticulum and fusion with the major histocompatibility complex in the Golgi apparatus

phenotypes, a process known as polarization.[77] Commercially available clodronate liposomes can be used to efficiently inhibit TAMs and to restore the immune response against liver cancer, colon cancer, and lymphoma.[78–82] Indeed, studies suggest that such NPs increase the M1/M2 cell ratio by reducing the activity of the transcription factor, signal transducer and activator of transcription 3 (STAT3).[78–82]

A series of scientific reports regarding macrophage polarization suggest that while polymeric NPs and liposomes aid the provision of M2-like polarization, inorganic nanostructures must provide M1-like polarization.[77] Particularly, gold nanoparticle (AuNP) uptake by human monocyte-derived macrophages was preferentially driven by the M2-type and alternatively activated cells according to the clear hierarchy M2c > M2 > M2b > M2a > M1.[83] Additionally, AuNPs changed the conformational arrangement (denaturation) of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), inhibiting the production of proangiogenic proteins by cancer-associated fibroblasts (CAFs) in the stroma.[84,85] As VEGF expression is upregulated by cancer and infiltrating cells, cationic AuNPs have been proposed to inhibit their signaling cascade in vitro in a structure-dependent manner.[84,85] Regarding the angiogenic blood vessels, cationic liposomes strongly bound to endothelial cells were internalized, while anionic, neutral, or sterically stabilized neutral liposomes did not demonstrate cellular uptake. This highlights the cationic nanostructures that selectively target angiogenic blood vessels in cancer therapy.[84,85]

In addition to drug carriers for cancer treatment, nanostructures provide additional mechanisms to constitute synthetic elements of immune system, like artificial lymph nodes and antigen presenting cells (aAPCs). In this perspective, NPs boost the immune system activity by delivering cytokines and ligands for T-cell receptor (TCR), CTLA-4, and CD28 to lymphocyte receptors.[86] Usually, these systems are not suppressed by external environment in disease sites and can be used to keep cytotoxic response for longer periods than stimulation by matured APCs (in vitro and in vivo).[87,88]

The first attempts to create aAPCs used virally transfected mouse fibroblasts to express co-stimulatory proteins (CD80, intercellular adhesion molecule 1 [ICAM-1], LFA-3) and peptides of melanoma-associated antigen recognized by T cells (MART-1) via MHC class I for suppressing human leukocyte antigen (HLA) A2.1^{+} cells by osmotic lysis.[87] Similarly, polymeric structures provide cross-presentation in human immature DCs and antigenic peptide fragments to T cells.[88]

To date, magnetic beads are available in clinical treatments after FDA approval to T cell expansion ex vivo. The magnetic resonance imaging (MRI) aids to monitor superparamagnetic and magnetic aAPCs to measure toxic effects until total depletion in vivo.[89] In mice, most of the intravenously injected aAPCs were eliminated through urine or deposited in liver and spleen.[90] The subcutaneous administration stimulate naive lymphocytes in axillary, inguinal, and cervical lymph nodes.[90] Furthermore, oral uptake also delivers NPs through gastrointestinal organs to lymphatic system, crossing mucosa cells in duodenum, jejunum, and ileum to lacteals vessels and mesenteric lymph nodes.[91] Paramagnetic NPs conjugated with anti-HLA-DR and anti-CD28 antibodies, as well with lymphocyte adhesion molecule integrin (anti-lymphocyte function-associated antigen [LAF]-1) increased the CD8^{+} population.[92] After measuring the magnetic moment of these particles, it was possible to observe that conjugation with immunoglobulins distributed them on cell surface, increasing the activity of CTLs and tumor infiltrating lymphocytes (TILs) in the environment of lymphoma.[89] Thus, the latter studies highlight the importance of synthetic biology to replace or make up the lack of biological functions (Table 2).

5 | MAIN CHALLENGES IN THE USE OF NANOPARTICLES IN IMMUNOTHERAPY

Before reaching the targeted cells, NPs can produce side effects in healthy tissues and phenotypic changes in immunocompetent cells,

TABLE 2 Nanoparticles for immunomodulatory cancer therapies

NP types	Cell uptake	Immune response	References
Polymeric antigen-capturing nanoparticles (AC-NPs)	Dendritic cells and macrophages	Expansion of $CD8^+$ T cells, $CD4^+$ T cells.	65
Self-assembled poly(L-valine) hydrogel conjugated with tumor cell lysates	Dendritic cells	Improves antigen delivery in lymph nodes.	72
Melanoma peptides-loaded liposomes	Dendritic cells	Antigen presentation to $CD8^+$ T cells with production of pro-inflammatory cytokines.	66
Fusogenic liposomes	Ovary cell line	Protein cargo released into cellular cytoplasm.	70
Clodronate liposomes	Macrophages	Alters gut microbiota of colon cancer.	79
Gold nanoparticle	Macrophages	Nanoparticle preference capture by M2c > M2 > M2a > M2b > M1.	83
Gold nanoparticle	HUVECs cell line	Inhibits pro-angiogenic proteins expression.	84
Gold nanoparticle	Fibroblasts	Activation of quiescence state in fibroblasts.	85

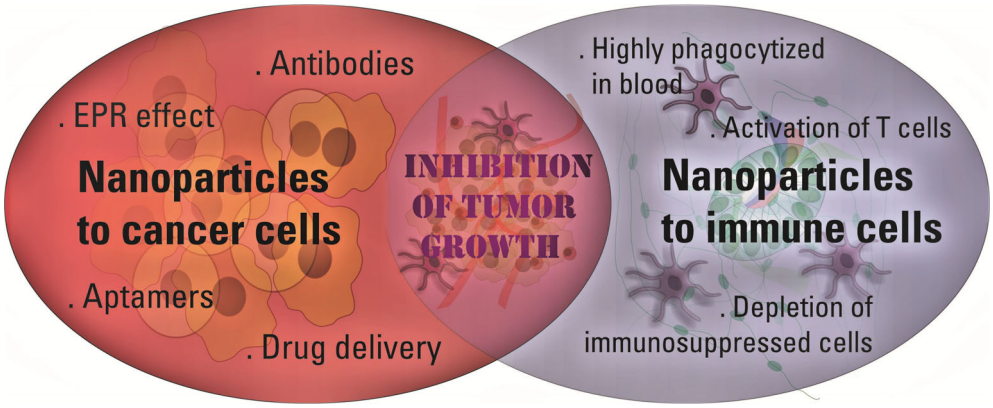

FIGURE 4 Schematic illustration depicting the combination of target therapies and immunomodulatory techniques for retardation of cancer cell growth

which can impair their clinical applications.[93] Therapeutic strategies in nanomedicines consider that both normal and transformed cells internalize NPs through passive and active mechanisms, and promising results may be achieved with the combination of both procedures (Figure 4).

Owing to the process of angiogenesis, the main mechanism responsible for the passive accumulation of macromolecules and nanostructures in the TME is the well-known and so-called permeability and retention effect (EPR), which leads to the accumulation of structures with molecular weights ranging between 10 and 40 kDa.[94] NPs are also retained in hypervascularized tissues, such as the lungs, liver, kidneys, and spleen, ensuring that only a tiny fraction of the administered nanosystems reach the cancer sites.[93] In addition to the aforementioned aspects, several intrinsic factors may influence their efficiency, including pre-existing disease conditions and an individual's genotype.

After administration, WBCs and proteins generated by the humoral response represent the first barriers that must be overcome (or managed) by nanomaterials in the body.[93,95] Under exposition with foreign organisms, APCs perform the activation of innate and adaptive immunological responses that may affect the stability of myelopoiesis and lymphopoiesis.[96] PEGylation or conjugation with biological targeting components is widely known to aid the preservation of NPs in the circulatory system.[97] However, PEGylation may not be efficient at preventing inflammatory stimulus and partial clearance of the NPs before reaching the tumor site.[97] Bio-polymers or biocompatible materials applied at the NP surface result in the reduction of immune cell recognition. Furthermore, the prolonged half-life in the circulatory system increases the deposition of plasma components on the protein corona layer, inducing complement system activation, contact kallikrein reaction, and blood coagulation.[98]

The complement system is activated via three pathways. Notably, all models require the cleavage of plasma Complement (C)3 (C3) protein into C3a and C3b. In the classical model, antibodies (Immunoglobulin G - IgG and Immunoglobulin M - IgM) are deposited on the surface of foreign invaders.[67,99] C1q proteins bind to the Fc region and trigger the cleavage of C4 and C2 proteins into C4a + C4b and C2a + C2b for the formation of C3 convertase (C4bC2a).[67,99]

Alternative activation occurs without the presence of antibodies at the beginning of the process. In blood, the pre-established C3b binds to the carboxylic and amino groups present on the particle surface and results in the generation of the C3 convertase after binding with complement factor B protein.[67,99] Another possibility of activation is dependent on the plasmatic lectin that recognizes mannose fragments on pathogens and triggers C4 and C2 cleavage to generate C3 convertase.[67,99]

After intravenous administration, albumin, immunoglobulin G, and fibrinogen are the first proteins to establish interaction with NPs in blood.[100] Immunoglobulins represent 40% of the proteins in human plasma and are considered the main constituent on the biomaterial surface, stabilizing their dispersion in electrolytes and activating human defense cells after adsorption of immune regulatory proteins.[101–103] Therefore, it is essential to elucidate the activity of blood cascade systems to avoid the occurrence of nonspecific reactions.[104]

Nanomaterials may also induce complement activation-related pseudoallergy (CARPA), a process related to tumor growth in a few patients undergoing nano-therapies.[105] In clinical settings, even after validation through toxicological studies, few patients presented with hypersensitivity and severe allergic reactions (anaphylaxis) following the administration of Doxil (Figure 5).[101,106,107] Continuous activation of the complement system can aggravate the patient's condition.[100] Therefore, monitoring of the hemodynamic and hematological conditions is essential to avoid the occurrence of allergic reactions induced by nanostructures.[108] Importantly, complement activation can aid the recruitment of suppressive immune cells to control the inflammatory response produced by NPs in the cancer microenvironment, inducing tumor cell progression in certain neoplasms.[109,110]

Considering the toxic aspects, several efforts have been engaged to understand NP opsonization by plasma proteins to modulate allergic reactions and to avoid the occurrence of severe side effects during treatment.[104] NP size, shape, surface charge, surface functionalization, and concentration in the blood are known to dictate the complement activity; however, more studies are warranted.[111] Ensuring the control of the complement responses triggered by the amino and hydroxyl groups present on the nanocomposite surface is a major challenge.[112]

When NPs are subjected to conjugation with polymers, different structural conformations may produce distinct complement responses, even for the same surface composition.[109,113] For example, the use of NPs with a diameter of 250 nm conjugated with dextran helped activate the complement cascade, while similar results were not observed for the same NPs with a diameter of 600 nm, indicating the influence of NP size on the recruited response.[114] Polymeric chains may demonstrate thermosensitive and pH-responsive properties and in such cases, when escape from the blood circulatory system is exhibited by NPs to infiltrate in tumors, the reduction in pH results in a conformational change in the polymeric matrix, subsequently exposing or hiding functional groups for protein adsorption.[115]

Few studies have confirmed that complement depletion does not result in the stimulation of the delivery of antigenic materials from NPs to phagocytic cells and consequently inhibits the adaptive immune response against pathogens.[116] Moreover, studies conducted using animal models demonstrated that adsorption of complement proteins on polyhydroxylated-PPS-NPs (25 nm) increased the expression of activation markers, CD80, CD86, and CD40 in immature DCs.[116] Particularly, in the case of nanovesicles, their lipid composition was demonstrated to change the humoral response. The presence of cholesterol molecules modulates the pseudoallergic reaction of liposomes and PEGylated lipid structures, followed by the occurrence of intense leukopenia and thrombocytopenia in mice.[108,117]

Furthermore, the mechanisms by which adsorbed complement proteins on NP contribute to modulating humoral immunity and activation of WBCs warrant further studies to aid the design of versatile nanoplatforms and to improve their application in cancer therapy.

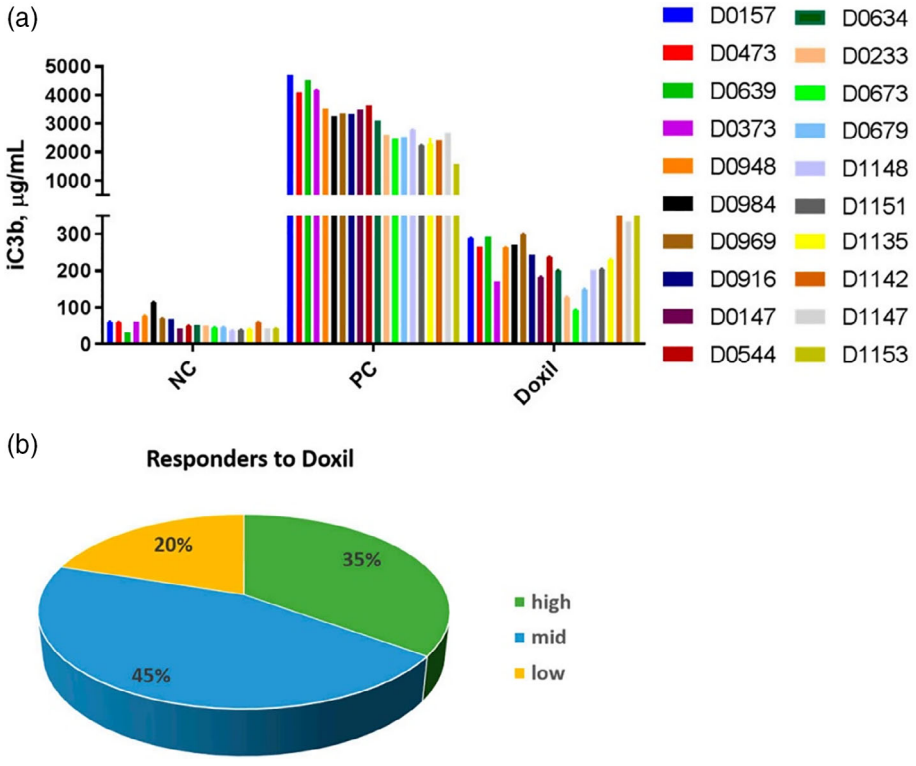

FIGURE 5 A study on the hypersensitivity caused by Doxil. (A) Doxil dispersion was conducted in the plasma of 20 healthy donors (DO) for 30 min, and levels of the complement protein (iC3b) were determined by ELISA ($n = 3$). The results were compared with those obtained from samples without subjection to treatments (negative control [NC]), with cobra venom factor considered as a positive control (PC). (B) The individual variability of complement response was classified with stimulation index (SI) as follows: low (SI ≤2), medium (SI 2–6), and high (SI ≥6). Adapted with permission from Ref. 100

6 | NOVEL STRATEGIES TO BOOST NANOTHERAPEUTIC USE VIA APPLICATION OF BIOINSPIRED AND BIOMIMETIC SYSTEMS

As previously described, despite several benefits regarding the ability of nanostructures to modulate immunological response, these systems require minor improvements before their clinical applications to overcome eventual problems that can undermine their safety.

Recent advances in nanoengineering have proposed the design of bioinspired and biomimetic systems that can ensure NP camouflage, targeting, and accumulation in the tumor microregion via specific functionalization of NPs with biological elements or even with whole natural cell membranes, thus providing higher specificity.[63,118–122] In this process, cellular vesicles are separated from organelles by ultracentrifugation and adsorbed on the NP surface to incorporate biological properties into the nanostructures, thereby increasing biocompatibility, decreasing allergic reaction in vivo, and enhancing their effectiveness against cancer.[123] The resultant nanostructure carries the full array of cancer cell antigens, thereby offering a robust and innovative platform that applies to multiple modalities of anticancer therapy. These engineered biomimetic features are currently under exploration as advanced drug delivery systems in which natural components are used for theragnostic purposes, bypassing macrophage uptake and systemic clearance, improving therapeutic outcomes.[124,125]

In this section, we describe different biomimetic and bioinspired systems engineered through the consideration of different cell structures, covering their immunomodulatory properties concerning cancer therapy.

6.1 | Cellular plasma membrane-derived NPs

Cell membranes may represent the most basic, structural, and functional units of organisms carrying different biomarkers that can assist cell recognition and signal transduction, among other functions.[126] The isolation of extracellular vesicles (exosomes and microvesicles) and their conjugation with therapeutic agents have been addressed in this context.[127] Their reconstruction as nanocarriers can help deliver antineoplastic and immunomodulatory drugs to diseased and healthy cells, replacing synthetic liposomes or polymeric platforms. Plasma membranes isolated from cancer cells, erythrocytes, and leukocytes increase NP functionality in the body, with their immune-stimulatory capacity complementing traditional therapies.[128]

6.1.1 | Cancer cell membrane

The deposition of proteins and lipids from the plasma membrane onto the particle surface aids the development of new nanotherapeutic approaches for the treatment of chronic diseases, such as cancer, subsequently ensuring increased applicability of a wide range of solid NP systems.[126] Based on the excellent results observed with the application of biological vesicles, studies conducted by our group reported the use of cellular membrane-derived nanoparticles (MNPs) to enhance the specificity of external source therapies. PEG-coated gold nanorods incorporated in MNPs derived from lung cancer cell membranes were loaded with the anticancer drug, β-lapachone, and were used to provide a specific multifunctional system combining chemotherapeutic and photothermal cell destruction in a synergic manner.[118] In another study, we reported the use of MNPs for conducting encapsulation of two first-line drugs used in pancreatic cancer treatment.[63] The MNPs were isolated from the pancreatic membrane and incorporated with gemcitabine and paclitaxel to induce apoptosis in PANC-1 cell lines in vitro. Furthermore, the antigenic material carried in the nanovesicles activated human monocytes and DCs in the presence of chemotherapeutic molecules. Such properties can avoid the evasion of cancer cells from the immune system more safely and effectively during treatment.[126]

In fact, biomimetic NPs covered with cancer cell membrane components can be used as vaccines to modulate the immune system.[129–131] Yang and co-workers developed tumor vaccines for cancer prevention and treatment by performing coating of R837-containing poly-(D,L-lactide-co-glycolide) PLGA NPs with mannose-modified tumor cell membranes. The nanovesicles showed enhanced uptake by APCs, such as DCs, which were stimulated to maturation, triggering antitumor immune responses, thereby representing an important potential for clinical translation.[132]

Lipid NPs synthesized with tumor plasma membranes were used to deliver a substantial amount of antigenic material to the APCs. In such cases, macrophages process antigenic proteins and expose them to T lymphocytes via MHC, triggering anti-tumor responses in peripheral lymphoid organs.[129,131] The delivery of antigenic material by lipid NPs stimulates a higher primary and secondary antibody response than that generated after pure antigen administration.[133]

Undoubtedly, the use of cell membrane-coated NP technology provides an excellent nanostructure with immunomodulatory potential. Murine B16-F10 cell-derived NPs exhibited uptake by immature leukocytes, improving WBC activation in draining lymph nodes.[134] After 6 h of subjection to subcutaneous administration, phagocytes demonstrated the expression of maturation markers, CD80/CD86, while Th1 cells secreted a considerable amount of interferon-γ (IFN-γ) and IL-2. The presence of membrane antigens on the NP surface promoted pro-inflammatory activity in TME and adhesion protein expression (such as selectin ligands, integrin, and chemokine receptors) in addition to the targeting of nanocarriers to tumor cells.[135–137]

6.1.2 | Red blood cell membranes (RBCm)

Erythrocytes, or red blood cells, were the first cell type used to establish the lipid and protein isolation protocol to fabricate biomimetic and bioinspired systems. Their abundant "self-markers" such as proteins, glycan, and sialic acid moieties play a critical role in suppressing an immune attack.[138] After hemolysis, erythrocyte lysates are subjected to density gradient centrifugation to obtain membrane

components[139–141] and used to reduce the immune clearance of the NPs (Figure 6).[119–121] Although proteins derived from the RBCm inhibit the capture of nanomaterials by phagocytic cells,[119] do not prevent their retention in the liver, lung, and spleen.[120] To avoid such interactions, antibodies and aptamers can be bound to RBCm to enhance specificity and cell internalization. For example, RBC nanovesicles have been used in fusion with tumor-penetrating peptides for the treatment of metastatic breast cancer, subsequently promoting an increased interaction with tumor tissues.[119] In another study, DOX-containing RBCm-PLGA NPs could cross the microvascular endothelium for glioblastoma treatment. Tumor angiogenesis showed reduction for a few days after its administration to mice.[142] DOX carried by RBCm-NPs has been shown to prevent toxicity in neutrophils, lymphocytes, and monocytes, and to avoid the reduction of plasma compounds, such as albumin, bicarbonate, and creatinine, indicating the absence of organ dysfunction.[143]

Currently, PLGA-based NPs are the most commonly used polymeric structures for designing cell membrane-derived systems. Even when used at high concentrations, PLGA does not interfere with cell phenotype and cell viability.[144–146] More importantly, RBC-covered PLGA NPs have been shown to exhibit increased blood circulation time, showing the importance of both long circulation and tumor penetration for improved therapeutic outcomes.[119]

Also using the RBCm coating technology, a novel antigenic peptide delivery system involving PLGA-NPs was constructed to target carbohydrate receptors present on macrophages and DCs. The addition of mannose was performed to actively target APCs in lymphatic organs. Using in vivo models, the developed nanostructures inhibited tumor growth and suppressed tumor metastasis, in addition to effectively enhancing IFN-γ secretion and $CD8^+$ T cell response. The high accumulation of the nanostructures in the draining lymph nodes increased the expression of CD86 proteins and the production of tumor necrosis factor-α (TNF-α) and IL-12 by phagocytic cells and IFN-γ by Th1 cells.

6.1.3 | White blood cell membranes

Under damaged vasculatures, WBCs migrate from the capillaries to inflamed regions. Neutrophils are professional phagocytic cells that

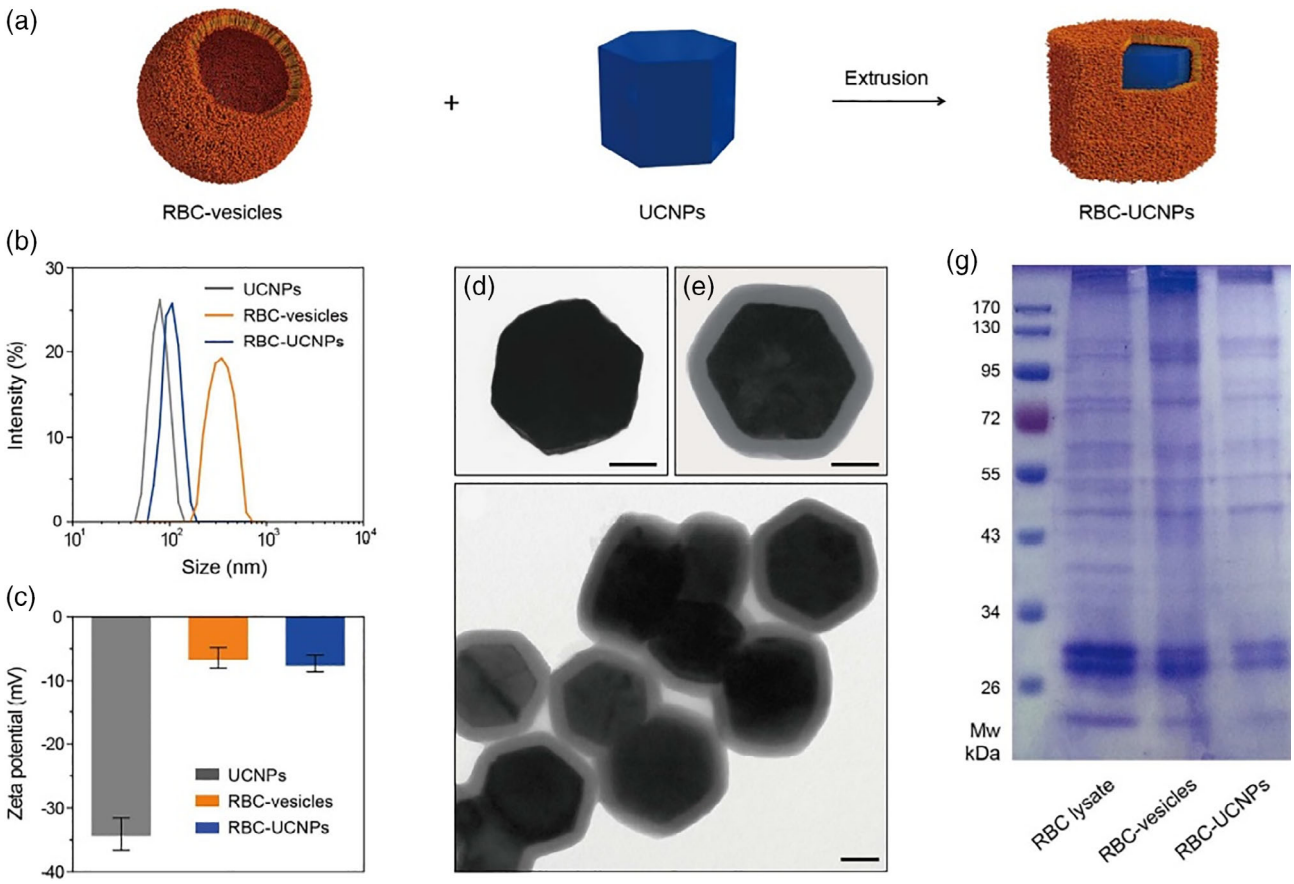

FIGURE 6 (A) Schematic illustration of nanoparticles loaded with erythrocyte plasma membrane. (B) Size and (C) surface zeta potential of upconversion nanoparticles (UCNPs), RBC membrane vesicles and UCNPs fused with the RBC membrane. (D) TEM images of UCNPs, and (E,F) RBC-UCNPs (scale bar = 25 nm) revealed incorporation of the erythrocyte membrane on the nanostructure surface. (G) Polyacrylamide gel electrophoresis conducted for the detection of plasma proteins in the samples of RBCs and RBC-UCNPs. Adapted from Ref. 114; Copyright 2017 American Chemical Society

can cross the endothelial cell barrier to reach the acute inflammation site.[147] Therefore, neutrophil plasma membranes have also been isolated and used to design biomimetic nanovesicles providing NP camouflage for mononuclear phagocyte system clearance, overcoming the vascular barrier, and localization at the target tissue.[148] Gão et al.[149] developed new methodologies based on nitrogen cavitation for the formation of neutrophil plasma membrane nanovesicles rich in integrin-β2. Neutrophil nanovesicles replicate the membrane features of the source cells, which are captured by inflamed microvasculature, a method that can be applied to a wide range of diseases without inflammatory conditions.[149]

Circulating tumor cells (CTCs) comprise organelles that can trigger the early stages of metastasis, rendering them a valuable target for preventing the spread of cancer. Knowledge regarding the occurrence of metastasis also highlights neutrophils as a fundamental cells in the early stages of their formation. Therefore, Kang et al. designed NM-NPs by coating the surface of a PLGA polymer with an inflammatory neutrophil-derived membrane. The biomimetic nanostructure was loaded with carfilzomib (CFZ) to prevent metastasis and inhibit the growth of the already formed cancer sites. Granulocytes were previously co-cultured with LPS to increase inflammatory membrane proteins, preserving L-selectin, CXCR4 (C-X-C chemokine receptor type 4), LFA-1, and β1 integrins to establish interaction with ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), and CD44 molecules on CTC surfaces and inflamed endothelial cells.[135] After binding, nanostructures are selectively endocytosed by clathrin and the caveolae pathway, eliminating cancer cells through the loss of plasma membrane integrity.[135] Furthermore, treatment was found to reduce the expression of inflammatory cytokines and the number of immune-suppressive neutrophils, which promoted cytotoxic effects against inoculated breast cancer cell line (4 T1 cells).[135] As a result, the neutrophil plasma membrane reduced the size and number of metastatic nodules in the lungs, impairing the capability of CTC migration through the circulatory system.[135]

Similar to the procedure adopted for neutrophil membrane nanovesicles, natural membranes derived from macrophages have been applied to coat mesoporous silica nanocapsules loaded with DOX for the treatment of breast cancer. This biomimetic nanostructure effectively integrates tumor-assisted targeting therapy with immunological aspects. In vivo assays have demonstrated effective accumulation in tumors and the inhibition of tumor growth. Additionally, the membrane-coating strategy provided active targeting abilities for recognition of the tumor endothelium.[148]

Proteins derived from the leukocyte plasma membrane were employed as coatings for synthetic phospholipid bilayer NPs, referred to as leukosomes, which could preferentially target inflamed endothelia both in vitro and in vivo.[150] Macrophage membrane-coated liposomes were developed by Cao et al.[58] to improve specific metastasis-targeting capability and to suppress secondary lung tumors resulting from breast cancer metastasis. The emtansine drug was encapsulated into pH-sensitive liposomes and coated with macrophage membranes isolated from a murine monocyte/macrophage cell line (RAW 264.7) with high expression of α4 and β1 integrins. Biomimetic systems were used to effectively enhance cellular uptake and the inhibitory effects on cell viability.[58] The use of macrophage cell membrane coating also inhibited untargeted drug delivery in normal cells and decreased the retention of NPs in the liver, spleen, and lungs.[58,148]

Although the use of bioinspired and biomimetic systems has been described as cellular plasma membrane-derived platforms, we can highlight the use of a series of covering possibilities using different organelles that are currently exploited for their immunomodulatory potential associated with nanosystems for cancer therapy. For example, the extracellular vesicles (EVs), which are important mediators of intercellular communication, have been explored by their immunomodulation ability especially given their capability to transfer bioactive components and to transpose biological barriers.[151]

Considering the above-mentioned DCs capability to induce both primary and secondary immune responses, exosomes from DCs have also been investigated for their immune modulation potential resulting in clinical trials.[152] T lymphocytes elements associated with nanosystems also deserve attention in this regard.[153] The possibilities within this subject are numerous and considering the availability of novel nanomaterials undergoing clinical trials, the biomimetic and bioinspired strategy walks to become the future of nanomaterials.

7 | CONCLUSION AND PERSPECTIVE

Considering increases in the number of individuals affected by cancer and their particularities, there is an urgent need for the discovery of successful therapeutic alternatives. Furthermore, based on the molecular differences noted between patients, the next generation of cancer treatments is likely to be based on molecular features and the identification of effective targets that may constitute personalized medicine in cancer therapy. In this scenario, nanomedicine merits special attention. To improve conventional therapies, new treatments are being developed with aim to abolish the neoplastic ability to evade host defense mechanisms through nanotechnological tools. For instance, NPs may improve cancer immunotherapy results, producing faster innate and adaptive responses compared to conventional treatments. Therefore, to optimize the design of safe formulations, surface-coating biomimetic technologies allow NPs to travel longer distances through vascular networks and enable the establishment of interactions with the immune system without chronic inflammation, providing interesting features. Thus far, these advanced drug delivery systems have been recognized as multifunctional platforms that can trigger immunotherapy responses, thereby emerging as an extremely promising strategy that remains at initial stages of development, which also evidently holds remarkable potential.

As a novel bioinspired and biomimetic platform, advanced drug delivery systems may be effective for delivering multiple tumor antigens to conduct re-education of pro-inflammatory profiles, by exploiting intact and natural organelle functions rather than by replicating these features using synthetic techniques. Although the technique is now widely discussed, few studies have harnessed applied natural organelles as nanovesicles for coordinated delivery to the tumor sites without

evaluating the immunomodulatory aspects provided by these platforms. Owing to these properties, these bioinspired nanostructures are considered excellent candidates as next-generation carriers for suppressing cancer growth and for potentiating the recovery of immunity.

We believe that in the future, the combination of cell biology and nanotechnology may be used to fabricate chimeric nanostructures that can help exploit the intrinsic properties of their origin to exert advanced drug-delivery functions. Nanostructured systems are expected to increase tumor immunogenicity and to modulate autoimmune mechanisms, preventing suppressive effects in the cancer environment. Importantly, the advantages and disadvantages of nanomedicine and immunotherapy are complementary. Furthermore, their combination opens possibilities for the development of new alternative therapeutic strategies that require a multidisciplinary understanding of their properties in the body.

ACKNOWLEDGMENTS

This review was funded by the São Paulo Research Foundation (FAPESP) (project number 2018/12670-4) and the Brazilian National Council for Scientific and Technological Development (CNPq) (project number 142285/2017-0). NNF received fellowships from FAPESP (ref #2019/25645-0).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

All authors contributed to the manuscript substantially and have agreed to the final version.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. CA Cancer. Cancer Statistics, 2012.
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7-30.
4. Akrami M, Arasteh P, Eghbali T, et al. Introducing novel and comprehensive models for predicting recurrence in breast cancer using the group LASSO approach: are estimates of early and late recurrence different? *World J Surg Oncol*. 2018;16(1):185.
5. Hamdy FC, Elliott D, le Conte S, et al. Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. *Health Technol Assess*. 2018;22(52):1.
6. A. Baudino T. Targeted cancer therapy: the next generation of cancer treatment. *Curr Drug Discov Technol*. 2015;12(1):3-20.
7. Baskar R, Lee KA, Yeo R, Yeoh K-W. Cancer and radiation therapy: current advances and future directions. *Int J Med Sci*. 2012;9(3):193.
8. Bentzen SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. *Nat Rev Cancer*. 2006;6(9):702.
9. Ferreira NN, Granja S, Boni FI, et al. Modulating chitosan-PLGA nanoparticle properties to design a co-delivery platform for glioblastoma therapy intended for nose-to-brain route. *Drug Deliv Transl Res*. 2020;10(6):1729-1747.
10. Ferreira NN, Ferreira LM, Miranda-Gonçalves V, et al. Alginate hydrogel improves anti-angiogenic bevacizumab activity in cancer therapy. *Eur J Pharm Biopharm*. 2017;119:271-282.
11. Ralhan R, Kaur J. Alkylating agents and cancer therapy. *Expert Opin Ther Pat*. 2007;17(9):1061-1075.
12. Kaye SB. New antimetabolites in cancer chemotherapy and their clinical impact. *Br J Cancer*. 1998;78(3):1.
13. Yang C-P, Horwitz S. Taxol®: the first microtubule stabilizing agent. *Int J Mol Sci*. 2017;18(8):1733.
14. Hevener K, Verstak TA, Lutat KE, Riggsbee DL, Mooney JW. Recent developments in topoisomerase-targeted cancer chemotherapy. *Acta Pharm Sin B*. 2018;8(6):844-861.
15. Abotaleb M, Kubatka P, Caprnda M, et al. Chemotherapeutic agents for the treatment of metastatic breast cancer: an update. *Biomed Pharmacother*. 2018;101:458-477.
16. Jenkins V, Catt S, Banerjee S, et al. Patients' and oncologists' views on the treatment and care of advanced ovarian cancer in the UK: results from the ADVOCATE study. *Br J Cancer*. 2013;108(11):2264-2271.
17. Wirsching H-G, Galanis E, Weller M. Glioblastoma. *Handbook of Clinical Neurology*. Elsevier; 2016:381-397.
18. Zamarin D, Holmgaard RB, Subudhi SK, et al. Localized oncolytic virotherapy overcomes systemic tumor resistance to immune checkpoint blockade immunotherapy. *Sci Transl Med*. 2014;6(226):226-232.
19. Ferreira NN, Granja S, Boni FI, et al. Modulating chitosan-PLGA nanoparticle properties to design a co-delivery platform for glioblastoma therapy intended for nose-to-brain route. *Drug Deliv Transl Res*. 2020;10:1729-1747.
20. Corthay A. Does the immune system naturally protect against cancer? *Front Immunol*. 2014;5:197.
21. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646-674.
22. Vinay DS, Ryan EP, Pawelec G, et al. Immune evasion in cancer: mechanistic basis and therapeutic strategies. *Semin Cancer Biol*. 2015;35:185-198.
23. Dunn GP, Koebel CM, Schreiber RD. Interferons, immunity and cancer immunoediting. *Nat Rev Immunol*. 2006;6(11):836-848.
24. Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. *Nat Rev Immunol*. 2006;6(10):715-727.
25. Muenst S, Laubli H, Soysal SD, Zippelius A, Tzankov A, Hoeller S. The immune system and cancer evasion strategies: therapeutic concepts. *J Intern Med*. 2016;279(6):541-562.
26. Crowe NY, Smyth MJ, Godfrey DI. A critical role for natural killer T cells in immunosurveillance of methylcholanthrene-induced sarcomas. *J Exp Med*. 2002;196(1):119-127.
27. Shankaran V, Ikeda H, Bruce AT, et al. IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature*. 2001;410(6832):1107-1111.
28. Kaplan RN, Riba RD, Zacharoulis S, et al. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature*. 2005;438(7069):820-827.
29. Peinado H, Zhang H, Matei IR, et al. Pre-metastatic niches: organ-specific homes for metastases. *Nat Rev Cancer*. 2017;17(5):302-317.
30. de Vries NL, van Unen V, Ijsselsteijn ME, et al. High-dimensional cytometric analysis of colorectal cancer reveals novel mediators of antitumour immunity. *Gut*. 2019;69:691-703.
31. Trombetta ES, Mellman I. Cell biology of antigen processing in vitro and in vivo. *Annu Rev Immunol*. 2005;23:975-1028.
32. Banchereau J, Briere F, Caux C, et al. Immunobiology of dendritic cells. *Annu Rev Immunol*. 2000;18:767-811.

33. Syme RM, Spurrell JC, Amankwah EK, Green FH, Mody CH. Primary dendritic cells phagocytose *Cryptococcus neoformans* via mannose receptors and Fcgamma receptor II for presentation to T lymphocytes. *Infect Immun*. 2002;70(11):5972-5981.
34. Cambi A, Gijzen K, Torensma R, et al. The C-type lectin DC-SIGN (CD209) is an antigen-uptake receptor for *Candida albicans* on dendritic cells. *Eur J Immunol*. 2003;33(2):532-538.
35. Mahnke K, Guo M, Lee S, et al. The dendritic cell receptor for endocytosis, DEC-205, can recycle and enhance antigen presentation via major histocompatibility complex class II-positive lysosomal compartments. *J Cell Biol*. 2000;151(3):673-684.
36. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. *Nature*. 1998;392(6673):245-252.
37. De Almeida CV, Kaneno R, Amedei A. Cells in gastrointestinal cancers: role and therapeutic strategies. *Front Anti-Cancer Drug Discov*. 2017;8:1-28.
38. Macri C, Pang ES, Patton T, O'Keeffe M. Dendritic cell subsets. *Semin Cell Dev Biol*. 2017;84:11-21.
39. Dzionek A, Sohma Y, Nagafune J, et al. BDCA-2, a novel plasmacytoid dendritic cell-specific type II C-type lectin, mediates antigen capture and is a potent inhibitor of interferon alpha/beta induction. *J Exp Med*. 2001;194(12):1823-1834.
40. Banchereau J, Palucka AK. Dendritic cells as therapeutic vaccines against cancer. *Nat Rev Immunol*. 2005;5(4):296-306.
41. Nasi A, Bollampalli VP, Sun M, et al. Immunogenicity is preferentially induced in sparse dendritic cell cultures. *Sci Rep*. 2017;7:43989.
42. Mohamadzadeh M, Mohamadzadeh H, Brammer M, Sestak K, Luftig RB. Identification of proteases employed by dendritic cells in the processing of protein purified derivative (PPD). *J Immune Based Ther Vacc*. 2004;2(1):8.
43. Hung K, Hayashi R, Lafond-Walker A, Lowenstein C, Pardoll D, Levitsky H. The central role of CD4+ T cells in the antitumor immune response. *J Exp Med*. 1998;188(12):2357-2368.
44. Carlsson B, Forsberg O, Bengtsson M, Tötterman TH, Essand M. Characterization of human prostate and breast cancer cell lines for experimental T cell-based immunotherapy. *Prostate*. 2007;67(4):389-395.
45. Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science*. 2006;313(5795):1960-1964.
46. Sultan M, Coyle KM, Vidovic D, Thomas ML, Gujar S, Marcato P. Hide-and-seek: the interplay between cancer stem cells and the immune system. *Carcinogenesis*. 2017;38(2):107-118.
47. Messerschmidt JL, Prendergast GC, Messerschmidt GL. How cancers escape immune destruction and mechanisms of action for the new significantly active immune therapies: helping nonimmunologists decipher recent advances. *Oncologist*. 2016;21(2):233.
48. Ascierto PA, Daniele B, Hammers H, Hirsh V, Kim J, Licitra L, Nanda R, Pignata S. Perspectives in immunotherapy: Meeting Report from the "Immunotherapy Bridge", Napoli, November 30, 2016. BioMed Central; 2017.
49. Ascierto PA, Brugarolas J, Buonaguro L, et al. Perspectives in immunotherapy: meeting report from the immunotherapy bridge (29-30 November, 2017, Naples, Italy). *J Immunother Cancer*. 2018;6(1):69.
50. Ventola CL. Cancer immunotherapy, Part 3: challenges and future trends. *P&T*. 2017;42(8):514-521.
51. Anselmo AC, Mitragotri S. Nanoparticles in the clinic. *Bioeng Transl Med*. 2016;1(1):10-29.
52. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: an update. *Bioeng Transl Med*. 2019;4(3):e10143.
53. Robey RW, Massey PR, Amiri-Kordestani L, Bates SE. ABC transporters: unvalidated therapeutic targets in cancer and the CNS. *Anticancer Agents Med Chem*. 2010;10(8):625-633.
54. Yuan Y, Cai T, Xia X, Zhang R, Chiba P, Cai Y. Nanoparticle delivery of anticancer drugs overcomes multidrug resistance in breast cancer. *Drug Deliv*. 2016;23(9):3350-3357.
55. Luan X, Guan Y-Y, Lovell JF, et al. Tumor priming using metronomic chemotherapy with neovasculature-targeted, nanoparticulate paclitaxel. *Biomaterials*. 2016;95:60-73.
56. Amoozgar Z, Wang L, Brandstoetter T, Wallis SS, Wilson EM, Goldberg MS. Dual-layer surface coating of PLGA-based nanoparticles provides slow-release drug delivery to achieve metronomic therapy in a paclitaxel-resistant murine ovarian cancer model. *Biomacromolecules*. 2014;15(11):4187-4194.
57. Tang W, Yang J, Yuan Y, Zhao Z, Lian Z, Liang G. Paclitaxel nanoparticle awakens immune system to fight against cancer. *Nanoscale*. 2017;9(19):6529-6536.
58. Cao H, Dan Z, He X, et al. Liposomes coated with isolated macrophage membrane can target lung metastasis of breast cancer. *ACS Nano*. 2016;10(8):7738-7748.
59. Song Q, Yin Y, Shang L, et al. Tumor microenvironment responsive nanogel for the combinatorial antitumor effect of chemotherapy and immunotherapy. *Nano Lett*. 2017;17(10):6366-6375.
60. Cullis J, Siolas D, Avanzi A, Barui S, Maitra A, Bar-Sagi D. Macropinocytosis of nab-paclitaxel drives macrophage activation in pancreatic cancer. *Cancer Immunol Res*. 2017;5(3):182-190.
61. Mohamed M, Abu Lila AS, Shimizu T, et al. PEGylated liposomes: immunological responses. *Sci Technol Advan Mater*. 2019;20(1):710-724.
62. Dombernowsky P, Gehl J, Boesgaard M, Paaske T, Jensen BV. Doxorubicin and paclitaxel, a highly active combination in the treatment of metastatic breast cancer. 1996, 23–27.
63. Comparetti EJ, Lins PM, Quitiba JV, Zucolotto V. Cancer cell membrane-derived nanoparticles improve the activity of gemcitabine and paclitaxel on pancreatic cancer cells and coordinate immunoregulatory properties on professional antigen-presenting cells. *Mater Adv*. 2020;1(6):1775-1787.
64. Tkach AV, Shurin GV, Shurin MR, et al. Direct effects of carbon nanotubes on dendritic cells induce immune suppression upon pulmonary exposure. *ACS Nano*. 2011;5(7):5755-5762.
65. Min Y, Roche KC, Tian S, et al. Antigen-capturing nanoparticles improve the abscopal effect and cancer immunotherapy. *Nat Nanotechnol*. 2017;12(9):877-882.
66. Boks MA, Bruijns SC, Ambrosini M, et al. In situ delivery of tumor antigen–and adjuvant-loaded liposomes boosts antigen-specific T-cell responses by human dermal dendritic cells. *J Invest Dermatol*. 2015;135(11):2697-2704.
67. Abbas AK, Lichtman AH, Pillai S. *Cellular and Molecular Immunology E-Book*. Elsevier Health Sciences; 2014.
68. Kloetzel PM. The proteasome and MHC class I antigen processing. *Biochim Biophys Acta*. 2004;1695(1–3):225-233.
69. Gruhler A, Fruh K. Control of MHC class I traffic from the endoplasmic reticulum by cellular chaperones and viral anti-chaperones. *Traffic*. 2000;1(4):306-311.
70. Kube S, Hersch N, Naumovska E, et al. Fusogenic liposomes as nanocarriers for the delivery of intracellular proteins. *Langmuir*. 2017;33(4):1051-1059.
71. Apostolopoulos V, Thalhammer T, Tzakos AG, Stojanovska L. Targeting antigens to dendritic cell receptors for vaccine development. *J Drug Deliv*. 2013;2013:869718.
72. Song H, Huang P, Niu J, et al. Injectable polypeptide hydrogel for dual-delivery of antigen and TLR3 agonist to modulate dendritic cells in vivo and enhance potent cytotoxic T-lymphocyte response against melanoma. *Biomaterials*. 2018;159:119-129.
73. Atri C, Guerfali FZ, Laouini D. Role of human macrophage polarization in inflammation during infectious diseases. *Int J Mol Sci*. 2018;19(6):1801.
74. Yuan A, Hsiao Y-J, Chen H-Y, et al. Opposite effects of M1 and M2 macrophage subtypes on lung cancer progression. *Sci Rep*. 2015;5:14273.
75. Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. *Nat Immunol*. 2010;11(10):889-896.

76. Pyonteck SM, Akkari L, Schuhmacher AJ, et al. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. *Nat Med*. 2013;19(10):1264-1272.
77. Reichel D, Tripathi M, Perez JM. Biological effects of nanoparticles on macrophage polarization in the tumor microenvironment. *Nanotheranostics*. 2019;3(1):66-88.
78. Tan H-Y, Wang N, Tsao S-W, Che C-M, Yuen M-F, Feng Y. IRE1α inhibition by natural compound genipin on tumour associated macrophages reduces growth of hepatocellular carcinoma. *Oncotarget*. 2016;7(28):43792.
79. Bader JE, Enos RT, Velazquez KT, et al. Macrophage depletion using clodronate liposomes decreases tumorigenesis and alters gut microbiota in the AOM/DSS mouse model of colon cancer. *Am J Physiol Gastrointest Liver Physiol*. 2017;2017:00229.
80. Shen L, Li H, Shi Y, et al. M2 tumour-associated macrophages contribute to tumour progression via legumain remodelling the extracellular matrix in diffuse large B cell lymphoma. *Sci Rep*. 2016;6:30347.
81. Shen KY, Song YC, Chen IH, Chong P, Liu SJ. Depletion of tumor-associated macrophages enhances the anti-tumor immunity induced by a toll-like receptor agonist-conjugated peptide. *Hum Vaccin Immunother*. 2014;10(11):3241-3250.
82. Wu X, Schulte BC, Zhou Y, et al. Depletion of M2-like tumor-associated macrophages delays cutaneous T-cell lymphoma development in vivo. *J Invest Dermatol*. 2014;134(11):2814-2822.
83. MacParland SA, Tsoi KM, Ouyang B, et al. Phenotype determines nanoparticle uptake by human macrophages from liver and blood. *ACS Nano*. 2017;11(3):2428-2443.
84. Arvizo RR, Rana S, Miranda OR, Bhattacharya R, Rotello VM, Mukherjee P. Mechanism of anti-angiogenic property of gold nanoparticles: role of nanoparticle size and surface charge. *Nanomedicine*. 2011;7(5):580-587.
85. Hossen MN, Rao G, Dey A, Robertson JD, Bhattacharya R, Mukherjee P. Gold nanoparticle transforms activated cancer-associated fibroblasts to quiescence. *ACS Appl Mater Interfaces*. 2019;11(29):26060-26068.
86. Wang C, Sun W, Ye Y, Bomba HN, Gu Z. Bioengineering of artificial antigen presenting cells and lymphoid organs. *Theranostics*. 2017;7(14):3504-3516.
87. Latouche JB, Sadelain M. Induction of human cytotoxic T lymphocytes by artificial antigen-presenting cells. *Nat Biotechnol*. 2000;18(4):405-409.
88. Li H, Shao S, Cai J, et al. Artificial human antigen presenting cells are superior to dendritic cells at inducing cytotoxic T cell responses. *Immunology*. 2017;152(3):462-471.
89. Zhang Q, Wei W, Wang P, et al. Biomimetic magnetosomes as versatile artificial antigen-presenting cells to potentiate T-cell-based anticancer therapy. *ACS Nano*. 2017;11(11):10724-10732.
90. Perica K, De Leon MA, Durai M, et al. Nanoscale artificial antigen presenting cells for T cell immunotherapy. *Nanomedicine*. 2014;10(1):119-129.
91. Kim KS, Suzuki K, Cho H, Youn YS, Bae YH. Oral nanoparticles exhibit specific high-efficiency intestinal uptake and lymphatic transport. *ACS Nano*. 2018;12(9):8893-8900.
92. Perica K, Tu A, Richter A, Bieler JG, Edidin M, Schneck JP. Magnetic field-induced T cell receptor clustering by nanoparticles enhances T cell activation and stimulates antitumor activity. *ACS Nano*. 2014;8(3):2252-2260.
93. Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumours. *Nat Rev Mater*. 2016;1:16014.
94. Golombek SK, May JN, Theek B, et al. Tumor targeting via EPR: strategies to enhance patient responses. *Adv Drug Deliv Rev*. 2018;130:17-38.
95. Benasutti H, Wang G, Vu VP, et al. Variability of complement response toward preclinical and clinical nanocarriers in the general population. *Bioconjug Chem*. 2017;28(11):2747-2755.
96. Alvarez R, Oliver L, Valdes A, Mesa C. Cancer-induced systemic myeloid dysfunction: implications for treatment and a novel nanoparticle approach for its correction. *Seminar Oncol*. 2018;45:84-94.
97. Corbo C, Molinaro R, Parodi A, Toledano Furman NE, Salvatore F, Tasciotti E. The impact of nanoparticle protein corona on cytotoxicity, immunotoxicity and target drug delivery. *Nanomedicine*. 2016;11(1):81-100.
98. Lu X, Xu P, Ding H-M, Yu Y-S, Huo D, Ma Y-Q. Tailoring the component of protein corona via simple chemistry. *Nat Commun*. 2019;10(1):1-14.
99. Li L, Li Y, Ijaz M, Shahbaz M, Lian Q, Wang F. Review on complement analysis method and the roles of glycosaminoglycans in the complement system. *Carbohydr Polym*. 2015;134:590-597.
100. Ding T, Sun J. Formation of protein Corona on nanoparticle affects different complement activation pathways mediated by C1q. *Pharm Res*. 2020;37(1):1-9.
101. Vu VP, Gifford GB, Chen F, et al. Immunoglobulin deposition on biomolecule corona determines complement opsonization efficiency of preclinical and clinical nanoparticles. *Nat Nanotechnol*. 2019;14(3):260-268.
102. Winzen S, Schoettler S, Baier G, et al. Complementary analysis of the hard and soft protein corona: sample preparation critically effects corona composition. *Nanoscale*. 2015;7(7):2992-3001.
103. Mo J, Xie Q, Wei W, Zhao J. Revealing the immune perturbation of black phosphorus nanomaterials to macrophages by understanding the protein corona. *Nat Commun*. 2018;9(1):2480.
104. Fornaguera C, Calderó G, Mitjans M, Vinardell MP, Solans C, Vauthier C. Interactions of PLGA nanoparticles with blood components: protein adsorption, coagulation, activation of the complement system and hemolysis studies. *Nanoscale*. 2015;7(14):6045-6058.
105. Coty JB, Noiray M, Vauthier C. Assessment of complement activation by nanoparticles: development of a SPR based method and comparison with current high throughput methods. *Pharm Res*. 2018;35(7):129.
106. Dobrovolskaia MA, Shurin M, Shvedova AA. Current understanding of interactions between nanoparticles and the immune system. *Toxicol Appl Pharmacol*. 2016;299:78-89.
107. Neun BW, Barenholz Y, Szebeni J, Dobrovolskaia MA. Understanding the role of anti-PEG antibodies in the complement activation by Doxil in vitro. *Molecules*. 2018;23(7):1700.
108. Dezsi L, Meszaros T, Orfi E, et al. Complement activation-related pathophysiological changes in anesthetized rats: activator-dependent variations of symptoms and mediators of pseudoallergy. *Molecules*. 2019;24(18):3283.
109. Moghimi SM. Cancer nanomedicine and the complement system activation paradigm: anaphylaxis and tumour growth. *J Control Release*. 2014;190:556-562.
110. Markiewski MM, DeAngelis RA, Benencia F, et al. Modulation of the antitumor immune response by complement. *Nat Immunol*. 2008;9(11):1225.
111. Tavano R, Gabrielli L, Lubian E, et al. C1q-mediated complement activation and C3 opsonization trigger recognition of stealth poly (2-methyl-2-oxazoline)-coated silica nanoparticles by human phagocytes. *ACS Nano*. 2018;12(6):5834-5847.
112. Quach QH, Kah JC. Complement activation by gold nanoparticles passivated with polyelectrolyte ligands. *RSC Adv*. 2018;8(12):6616-6619.
113. Hamad I, Al-Hanbali O, Hunter AC, Rutt KJ, Andresen TL, Moghimi SM. Distinct polymer architecture mediates switching of complement activation pathways at the nanosphere−serum interface: implications for stealth nanoparticle engineering. *ACS Nano*. 2010;4(11):6629-6638.
114. Wibroe PP, Moghimi SM. Complement sensing of nanoparticles and nanomedicines. Functional nanoparticles for bioanalysis, nanomedicine, and bioelectronic devices. *ACS Publ*. 2012;2:365-382.

115. Moghimi SM, Simberg D. Complement activation turnover on surfaces of nanoparticles. *Nano Today*. 2017;15:8-10.
116. Reddy ST, van der Vlies AJ, Simeoni E, et al. Exploiting lymphatic transport and complement activation in nanoparticle vaccines. *Nat Biotechnol*. 2007;25(10):1159-1164.
117. Szebeni J, Alving CR, Rosivall L, et al. Animal models of complement-mediated hypersensitivity reactions to liposomes and other lipid-based nanoparticles. *J Liposome Res*. 2007;17(2):107-117.
118. Marangoni VS, Cancino Bernardi J, Reis IB, Fávaro WJ, Zucolotto V. Photothermia and activated drug release of natural cell membrane coated plasmonic gold nanorods and β-lapachone. *ACS Appl Bio Mater*. 2019;2(2):728-736.
119. Su J, Sun H, Meng Q, et al. Long circulation red-blood-cell-mimetic nanoparticles with peptide-enhanced tumor penetration for simultaneously inhibiting growth and lung metastasis of breast cancer. *Adv Funct Mater*. 2016;26(8):1243-1252.
120. Hu C-MJ, Zhang L, Aryal S, Cheung C, Fang RH, Zhang L. Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. *Proc Natl Acad Sci*. 2011;108(27):10980-10985.
121. Rao L, Meng Q-F, Bu L-L, et al. Erythrocyte membrane-coated upconversion nanoparticles with minimal protein adsorption for enhanced tumor imaging. *ACS Appl Mater Interfaces*. 2017;9(3):2159-2168.
122. De La Cruz GG, Rodríguez-Fragoso P, Reyes-Esparza J, Rodríguez-López A, Gómez-Cansino R, Rodriguez-Fragoso L. Interaction of nanoparticles with blood components and associated pathophysiological effects. *Unraveling the Safety Profile of Nanoscale Particles and Materials-from Biomedical to Environmental Applications*. IntechOpen; 2018.
123. Lund R, Leth-Larsen R, Jensen ON, Ditzel HJ. Efficient isolation and quantitative proteomic analysis of cancer cell plasma membrane proteins for identification of metastasis-associated cell surface markers. *J Proteome Res*. 2009;8(6):3078-3090.
124. Zhu J-Y, Zheng D-W, Zhang M-K, et al. Preferential cancer cell self-recognition and tumor self-targeting by coating nanoparticles with homotypic cancer cell membranes. *Nano Lett*. 2016;16(9):5895-5901.
125. Chen Z, Wang Z, Gu Z. Bioinspired and biomimetic nanomedicines. *Acc Chem Res*. 2019;52(5):1255-1264.
126. Zou S, Wang B, Wang C, Wang Q, Zhang L. Cell membrane-coated nanoparticles: research advances. *Nanomedicine*. 2020;15(06):625-641.
127. Li S, Xu J, Qian J, Gao X. Engineering extracellular vesicles for cancer therapy: recent advances and challenges in clinical translation. *Biomater Sci*. 2020;8(24):6978-6991.
128. Li R, He Y, Zhang S, Qin J, Wang J. Cell membrane-based nanoparticles: a new biomimetic platform for tumor diagnosis and treatment. *Acta Pharm Sin B*. 2018;8(1):14-22.
129. Alving CR. Liposomal vaccines: clinical status and immunological presentation for humoral and cellular immunity. *Ann N Y Acad Sci*. 1995;754:143-152.
130. Fries LF, Gordon DM, Richards RL, et al. Liposomal malaria vaccine in humans: a safe and potent adjuvant strategy. *Proc Natl Acad Sci USA*. 1992;89(1):358-362.
131. Verma JN, Rao M, Amselem S, et al. Adjuvant effects of liposomes containing lipid a: enhancement of liposomal antigen presentation and recruitment of macrophages. *Infect Immun*. 1992;60(6):2438-2444.
132. Yang R, Xu J, Xu L, et al. Cancer cell membrane-coated adjuvant nanoparticles with mannose modification for effective anticancer vaccination. *ACS Nano*. 2018;12(6):5121-5129.
133. Allison A, Gregoriadis G. Liposomes as immunological adjuvants. *Nature*. 1974;252(5480):252-252.
134. Kroll AV, Fang RH, Jiang Y, et al. Nanoparticulate delivery of cancer cell membrane elicits multiantigenic antitumor immunity. *Adv Mater*. 2017;29(47):1703969.
135. Kang T, Zhu Q, Wei D, et al. Nanoparticles coated with neutrophil membranes can effectively treat cancer metastasis. *ACS Nano*. 2017;11(2):1397-1411.
136. Govaere O, Petz M, Wouters J, et al. The PDGFRalpha-laminin B1-keratin 19 cascade drives tumor progression at the invasive front of human hepatocellular carcinoma. *Oncogene*. 2017;36(47):6605-6616.
137. Weber GF. Molecular genetics of metastasis. *eLS*. 2008;270(2):181-190.
138. Oldenborg P-A, Zheleznyak A, Fang Y-F, Lagenaur CF, Gresham HD, Lindberg FP. Role of CD47 as a marker of self on red blood cells. *Science*. 2000;288(5473):2051-2054.
139. Dodge JT, Mitchell C, Hanahan DJ. The preparation and chemical characteristics of hemoglobin-free ghosts of human erythrocytes. *Arch Biochem Biophys*. 1963;100(1):119-130.
140. Ihler GM, Glew RH, Schnure FW. Enzyme loading of erythrocytes. *Proc Natl Acad Sci USA*. 1973;70(9):2663-2666.
141. Marchesi VT, Palade GE. The localization of mg-Na-K-activated adenosine triphosphatase on red cell ghost membranes. *J Cell Biol*. 1967;35(2):385-404.
142. Chai Z, Hu X, Wei X, et al. A facile approach to functionalizing cell membrane-coated nanoparticles with neurotoxin-derived peptide for brain-targeted drug delivery. *J Control Release*. 2017;264:102-111.
143. Luk BT, Fang RH, Hu CM, et al. Safe and Immunocompatible Nanocarriers cloaked in RBC membranes for drug delivery to treat solid tumors. *Theranostics*. 2016;6(7):1004-1011.
144. Grabowski N, Hillaireau H, Vergnaud J, et al. Toxicity of surface-modified PLGA nanoparticles toward lung alveolar epithelial cells. *Int J Pharm*. 2013;454(2):686-694.
145. Mura S, Hillaireau H, Nicolas J, et al. Influence of surface charge on the potential toxicity of PLGA nanoparticles towards Calu-3 cells. *Int J Nanomed*. 2011;6:2591-2605.
146. Heo MB, Cho MY, Lim YT. Polymer nanoparticles for enhanced immune response: combined delivery of tumor antigen and small interference RNA for immunosuppressive gene to dendritic cells. *Acta Biomater*. 2014;10(5):2169-2176.
147. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. *Nat Rev Immunol*. 2013;13(3):159-175.
148. Xuan M, Shao J, Dai L, He Q, Li J. Macrophage cell membrane camouflaged mesoporous silica nanocapsules for in vivo cancer therapy. *Adv Healthc Mater*. 2015;4(11):1645-1652.
149. Gao J, Chu D, Wang Z. Cell membrane-formed nanovesicles for disease-targeted delivery. *J Control Release*. 2016;224:208-216.
150. Molinaro R, Corbo C, Martinez JO, et al. Biomimetic proteolipid vesicles for targeting inflamed tissues. *Nat Mater*. 2016;15(9):1037-1046.
151. Wiklander OP, Brennan MÁ, Lötvall J, Breakefield XO, Andaloussi SE. Advances in therapeutic applications of extracellular vesicles. *Sci Transl Med*. 2019;11(492):eaav8521.
152. Gehrmann U, Näslund TI, Hiltbrunner S, Larssen P, Gabrielsson S. Harnessing the exosome-induced immune response for cancer immunotherapy. *Semin Cancer Biol*. 2014;28:58-67.
153. Kang M, Hong J, Jung M, et al. T-cell-mimicking nanoparticles for cancer immunotherapy. *Adv Mater*. 2020;32(39):2003368.

How to cite this article: Comparetti EJ, Ferreira NN, Ferreira LMB, Kaneno R, Zucolotto V. Immunomodulatory properties of nanostructured systems for cancer therapy. *J Biomed Mater Res*. 2022;1-16. doi:10.1002/jbm.a.37359