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Recent Advances in Cell Membrane-Derived Biomimetic Nanotechnology for Cancer Immunotherapy

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Immunotherapy will significantly impact the standard of care in cancer treatment. Recent advances in nanotechnology can improve the efficacy of cancer immunotherapy. However, concerns regarding efficiency of cancer nanomedicine, complex tumor microenvironment, patient heterogeneity, and systemic immunotoxicity drive interest in more novel approaches to be developed. For this purpose, biomimetic nanoparticles are developed to make innovative changes in the delivery and biodistribution of immunotherapeutics. Biomimetic nanoparticles have several advantages that can advance the clinical efficacy of cancer immunotherapy. Thus there is a greater push toward the utilization of biomimetic nanotechnology for developing effective cancer immunotherapeutics that demonstrate increased specificity and potency. The recent works and state-of-the-art strategies for anti-tumor immunotherapeutics are highlighted here, and particular emphasis has been given to the applications of cell-derived biomimetic nanotechnology for cancer immunotherapy.

1. Introduction

Cancer immunotherapy has emerged as a vital therapeutic platform for the treatment of a variety of cancers.[1] It has entered the mainstream in research and clinics to overcome the limitations of other treatment modalities such as chemotherapy, radiotherapy, and surgery. Immunotherapy functions by modifying the body's immune system to target and remedy the tumor cells. The therapy uses therapeutic substances to induce or suppress an immune response to help the body fight against cancer. Cancer immunotherapy possesses potent therapeutic efficacy and strengthens antitumor immunity, particularly to antigen present tumor cells without serious side effects.[2] The intrinsic ability of anti-tumor immunotherapy has brought new insights into the development of novel strategies. Many practical strategies for cancer immunotherapy have evolved during the last years, for example, monoclonal antibodies, adoptive cell transfer, immune checkpoint blockade, and vaccines.[1b,3]

Despite the encouraging clinical outcomes of cancer immunotherapy, the efficiency is still limited due to several factors, and only a small fraction of patients respond to the treatments.[4] The immunosuppressive tumor microenvironment mainly accounts for treatment failure. It generally prevents the activation and infiltration of cytotoxic T lymphocytes (CTLs) that play an essential role in tumor eradication.[5] Many immunosuppressive cells such as myeloid-derived suppressive cells (MDSCs), tumor-associated macrophages (TAMs) and regulatory T cells (Tregs) are present at the tumor site, which leads to tumor aggressiveness, poor prognosis, and proliferation. These cells support tumor growth through the production of factors that stimulation new vessel formation, metastasis and lead to T cell and natural killer (NK) cell dysfunction.[6] The use of immunomodulatory compounds such as antibodies, adjuvants and cytokines to reshape tumor microenvironment also resulted in treatment failure due to lack of therapeutic efficacy and undesired side effects in local and systemic dissemination.[7] For instance, some patients treated with immunomodulatory compounds can experience complete tumor eradication, while others receiving the same treatment often see little improvement. The reason for this is the complexity of cancer pathogenesis with multiple mutations that leads to uncontrolled tumor growth. Therefore more personalized therapeutic modalities that aim to promote systemic and long-lasting anti-tumor immunity are required to completely eradicate malignancies and prevent metastasis as well as recurrence.[8]

Cancer immunotherapy can be innovated through more specific delivery of immune modulators to the lymph nodes (LNs) in immune cells, enhanced immunotherapeutic uptake by antigen-presenting cells (APCs), safe and efficient engineering of T cell using novel carriers and effective combination of different strategies to boost the immune system. Recent advances in immune nanotechnology have led to new prophylactic and treatment plans that can improve the current clinical standards. Nanomedicine can uniquely solve the key challenges in

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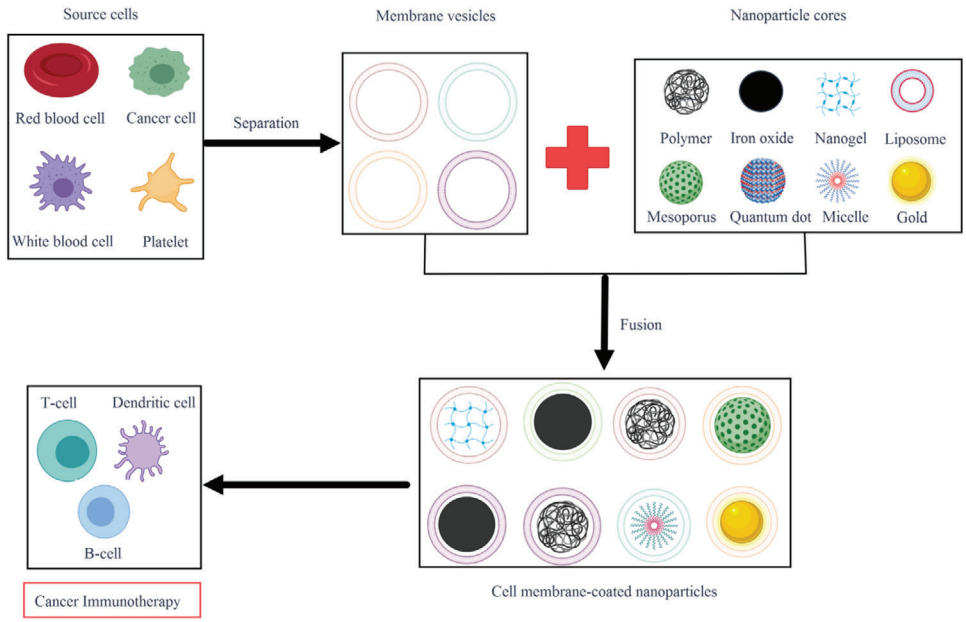

Figure 1. Schematic illustration of sources and types of cell-derived biomimetic nanoparticles for cancer immunotherapy.

cancer immunotherapy. Nano-immunotherapy is rapidly growing in the context of cancer due to a wide range of advantages over conventional immunotherapies. This includes delivery of multiple immunomodulatory compounds,[9] specific delivery via passive or active targeting with reduced side effects,[10] protection of therapeutic agents from degradation,[11] retention of immune-modulatory compounds and their sustained release via the stimuli-responsive delivery system.[12] Nano-immunotherapy is an innovative approach that modulates the immune profile by selectively targeting or depleting immunosuppressive cells or inducing immunogenic cell death by modulating tumor microenvironment and potentiating cancer immunity. It aims to activate the inherent ability of the immune system to initiate highly specific responses against tumors in a safe and reliable manner. Nanomaterials are successfully used in the targeted delivery of tumor antigens and adjuvants.[13] To further enhance the utility of the nanoscale platforms, biomimetic design principles have emerged to fabricate multifunctional nanoparticles with significant interactions with the biological systems.[14] The term biomimetic refers to two aspects mainly: endogenous substances that are extracted and purified from human, animal and microorganism, synthesis of endogenous substances with same structure and functions and imitation of micro environmental conditions of particular disease. These strategies mimic the natural system in many possible ways. In cell-based approaches, the cell membrane is innovatively separated and introduced in nanoparticles or the whole cell is uniquely utilized to produce biomimetic nanosystem.[15] Biomimetic nanotechnology is widely utilized due to its potential applications in drug delivery and cancer eradication.[15,16] This technology addresses the hurdles faced by traditional nanomedicine in cancer immunotherapy with a modality that can produce specific and durable anti-tumor responses.[17] Compared with the traditional approach, biomimetic nanoparticles have prolonged circulation and unique physical and material properties ideal for immune modulation.[18] These nanoparticles also display several advantages including biocompatibility, low immunogenicity, high targeting ability and minimum toxicity. Moreover, the therapeutic outcome increases with the use of biomimetic nanomedicine.[19] Regarding immunotherapy, biomimetic nanotechnology holds promise to enhance the efficacy and safety of existing methods. It can increase the fraction of patients who can achieve durable, long term response.[20] Through purposeful engineering, biomimetic anti-cancer nano immunotherapeutics are prepared with maximum adjuvant and antigen payload to enhance the immune response and reverse tumor burden. This top-down strategy uses nature's principles to develop multifunctional and multiantigenic nanosystems that can be used in the future for cancer immunotherapy.

In this review, we cover some necessary information about cancer immunotherapy using biomimetic nanotechnology. Then we discuss design parameters of biomimetic nanotechnology required for efficient cancer immunotherapy and finally, we introduce recent applications of cell-derived biomimetic nanotechnology for cancer immunotherapy. As shown in **Figure 1**, biomimetic nanotechnology platforms, utilizing red blood cells (RBCs) membrane, cancer cell membrane (CCM), white blood cells (WBCs) membrane, platelet membrane and hybrid membranes, have been developed with the limitless number of potential applications in cancer immunotherapy.

2. Background of Biomimetic Nanotechnology for Cancer-Immunotherapy

2.1. Cancer-Immunotherapy

Cancer is a severe threat to the human population worldwide and the leading cause of death. By the year 2030, the estimated figure of cancer deaths each year is predicted to be 11 million.[21] Cancer is the uncontrolled division of cells caused by several mutations.

The immune system is in a constant battle with cancer as the cancer cells proliferate. In contrast, the tumor cells try to escape the immune system by developing different mechanisms over time.[22] The immune system is made up of a complex network of cells, physical barriers, and proteins that work in collaboration to prevent diseases. Cancer and the immune system are linked together via a complex biological process. It is believed that due to the unique properties of the immune system, it will spontaneously reject cancer cell formation by recognizing it as a foreign body. The immune system of our body has two arms including innate immunity and adaptive immunity. Innate immunity is made up of macrophages and neutrophils that defend against the entry of pathogens while adaptive immunity consists of CD8+ cytotoxic T cells, B cells, T-regulatory (Treg) cells and NK cells that identify and diminish the harmed cells or memorize the antigens to fight against them in the future.[23] In vaccination, which is a type of adaptive immunity, the B cells produce antibodies against antigens and neutralize the pathogens to attack host cells.[24] Because of this specific response of antigens, they are termed as adaptive immunity.[25] APCs such as dendritic cells (DCs) are another fundamental type of immune cells that remain in peripheral tissues and capture lymphatic fluid antigens to activate the immune response of T cells. The main receptors of innate immunity on DCs, NK cells and macrophages are toll-like receptors (TLRs) that play a prominent role in fighting against pathogens.[26] When working correctly, the whole immune system recognizes and eliminates foreign invaders with high specificity. As in the case of tumorigenesis, the immune system continuously prevents the proliferation of cancer cells by its unique mechanisms. Malfunctioning and underactive immunity leads to the development of many diseases. For example, autoimmunity is caused by an overactive immune system, which is characterized by the destruction of healthy tissues and pro-inflammatory states.[27] Whereas in the case of the underactive immune system, the susceptibility to infections is enhanced that gives rise to drug resistance. The unique characteristics of the tumor microenvironment play a significant role in evading the immune system by producing different immunosuppressive cytokines through the activation of immune checkpoint molecules.[28] Cancer cells usually go through a prolonged evolutionary process to develop mechanisms against immune evasion.[29] Tumor cells grow by altering the surrounding microenvironment and generate cytokines, growth factor secretions, and extracellular matrix. This, in turn, suppresses the immune response.[29] It is for this reason that a significant amount of research is required in supporting the immune system to fight against cancer.

Cancer immunotherapy has made remarkable progress in recent years.[30] Immunotherapy for cancer treatment usually induces the host immune response that can differentiate between normal and cancer cells.[31] A number of therapeutic modalities have been used to treat cancer. These include blocking immunotherapy, cytokine therapy, chimeric antigen receptor T cell therapy (CAR-T), and adoptive immunotherapy of T cells. In the immune system, the distinctive characteristics of dendritic cells make it crucial for the treatment of cancer immunotherapy. DCs are considered the major APCs to produce cytotoxic T cell-derived immunotherapy against cancer. To activate T cells, DCs capture antigen and have to move to LNs where they release inflammatory cytokines.[32] Provenge is the first FDA approved vaccine with prostatic acid phosphate as a cancer antigen.[33] Despite the fact that DC-based immunotherapies induce specific antigen response in clinical studies of humans and animals, the therapy is still labor-intensive, less reproducible and expensive in terms of isolation, culture and antigen pulsing of DCs. Also, the transferred DC in LN is only 0.5 – 2%, which could not produce effective T cell response.[1b,34] Moreover these therapeutic options are not applicable to all of cancers and have certain drawbacks in clinical applications because of complex tumor microenvironment, patient heterogeneity, and systemic immunotoxicity. For this purpose the development of durable, tumor specific and effective immune response without any toxicity still remains a challenge.[33,35]

2.2. Evolution of Biomimetic Nanotechnology for Cancer Immunotherapy

To overcome the problems and tedious procedures of conventional immunotherapeutic strategies, nanotechnology has been developed for the sustained and targeted delivery of antigens.[36] To enhance the effectiveness of therapeutics for antigen delivery, natural or synthetically based nanoparticles are used.[37] Nanotechnology is widely used in cancer immunotherapy for preclinical and clinical trials.[38] Early nanoparticles were utilized as delivery adjuvants for traditional vaccines such as DNA, RNA and proteins that were subcutaneously administered to form a depot and activate the immune response for a prolonged time. A considerable improvement in immune stimulation and efficacy has been achieved with novel nanovaccine formulations that deliver the therapeutic antigen to the circulating DCs, tumor tissues, T cells macrophages, and immune organs such as lymph nodes. Still, there are problems associated with effective cancer immunotherapy, as the tumor microenvironment (TME) contributes a crucial role to cancer cell invasion and repression of T cell activation and proliferation. Adoptive cell transfer (ACT) of modified T cells has been recently used for cancer immunotherapy for specific cancers in a personalized way. For example, the nanoformulations act as artificial antigen-presenting cells for recognition and activation of T lymphocytes against specific tumors. Also, soluble antigens are incorporated in nanoparticles to prevent proteolytic degradation, improve stability and enhance the uptake by APCs. Stronger DC maturation and T cell response can be achieved by co-encapsulation of antigen and adjuvants in the nanoformulation. Nanoparticles for antigen delivery have shown significant potential in cancer immunotherapy. In this regard, many types of nanoparticles have been produced, such as polymer-based nanoparticles, liposomes, nanospheres and cells derived vesicles.[39] Poly (lactic-co-glycolic) acid (PLGA) nanoparticles have received much attention as an active carrier for antigen delivery.[13,40]

Recently, cell-based nanovesicles have been developed as biomimetic nanoparticles for antigen delivery for cancer immunotherapy. These biomimetic nanoparticles have been derived from RBCs, WBCs, cancer cells and platelets.[41] The biomimetic nanoparticles are fabricated by isolating the cell membranes from the individual cells and coating them over anticancer agent-loaded nanoparticles. The cell membrane provides a pivotal function to enhance the antitumor effect. Furthermore,

the interest is increasing in understanding the biological system to make the nanoparticles more effective with improved functionalities.[42] The importance behind this strategy depends on the main characteristic functions of natural components that evolved slowly and can't be easily re-created with synthetic material. The distinctive features of different cell types are rare because of the antigen profile displayed over the cell membrane. By complete the identification of individual factors on the membrane, researchers can enhance the synthetic platform for advanced drug delivery applications with special biomimetic features.[43] The tumor antigens displayed on the cell membrane can be used to enable the immune system to identify and fight against cancer. For this purpose, cancer mimicking nanoparticles with surface modification is used to improve the potency of vaccines.[44] This shows the considerable potential of biomimetic nanomedicine. The development and design of such nanoparticles can be widened by recognizing cell surface markers. The coating of nanoparticles with varying cell membranes present a unique top-down approach with the ability to completely replicate the surface antigen profile of source cells.[45] The strategy of directly utilizing cell membranes for nanoparticle preparation prevents the hurdles of nanoparticle functionalization.[46] By applying this unique strategy, researchers have devised nanoparticulate systems with excellent characteristics. For example, nanoparticles coated in RBCs membrane (RBCM) have been prepared to enhance blood circulation. Similarly, the tumor-targeting ability has been displayed by stem cell-derived nanoghosts, while silica NPs coated in WBCs membrane (WBCM) have the capability to transverse the endothelium layer.[47] This approach led to many more new applications with the same therapeutic properties as traditional therapy. For example, toxin nanosponges utilize particle stabilize RBCM to neutralize virulence factors.[42a] The recent work performed in cell membrane-derived biomimetic nanoparticulate formulations enables many new possibilities in this field. Membrane-bound vesicles and drug delivery systems have gained much attention because of their unique properties, including antigenic components, biological functions, and physicochemical properties. Cell-based biomimetic delivery systems can significantly improve the selectivity of the drug for different types of cancer. Cell-based biomimetic delivery systems use naturally derived cell membranes or cell as their functional parts to endow the drug delivery systems with more distinctive features and advantages. Cell-based biomimetic delivery systems specifically extend the blood circulation time and bypass the immune system in vivo.[19] As glycans, CD47 and sialic acid moieties on the surface of RBCs prolong the circulation time and reduce the immunogenicity of nanoparticles.[21,48] Many examples of nanoparticles coated in RMCM are available in which the membrane was utilized to prolong the circulation time of such nanoparticles. These include gold nanocages,[49] Fe_3O_4 nanoparticles,[50] and hybrid polymeric nanoparticles.[45a]

Cell membrane-derived biomimetic nanoparticles have evolved as a perfect platform for cancer immunotherapy. In this strategy, the biomimetic nanoparticles are used for antigen presentation and drug delivery.[51] The most prominent examples include RBCM coated nanoparticles. RBCM vesicles are usually more appropriate for antigen delivery because of their biocompatibility and easy isolation. RBCM vesicles are considered an exciting tool for antigen delivery to target dendritic cells for significant cytotoxic T cell response.[52] As a carrier of antigen, RBCs provide protection to reduce blood clearance of antigen, deliver it to the target site and present the antigen to the immune system. Similarly, tumor cell-based micro/nanoparticles can be utilized as the best vehicles for anti-cancer drugs with minor adverse effects. Cancer cell membrane-bound nanoparticles carry all the membrane-associated antigens that can be effectively used for cancer therapy. Particles coated in such cancer cell membranes also provide homotypic targeting for specific delivery of therapeutic agents.[53] This strategy also enables the incorporation of natural antigens and immunological adjuvants that can be utilized for vaccine applications to promote a tumor-specific immune response. Membranes from other cell sources have also been developed for cancer immunotherapy. For example, the surface of platelets can be engineered with anti-PD-L1 by covalent conjugation. The activation of platelets to release anti-PD-L1 can be triggered in animal models to evaluate the functional properties.[54] Such engineered platelets can effectively be used in cancer-immunotherapy to eliminate metastasis and tumor recurrence. In addition to many advantages, several disadvantages have also been observed regarding cell membrane biomimetic nanotechnology as shown in **Table 1**. However, many efforts are being made to improve this technology and overcome the obstacles in near future.

3. Design Parameters of Biomimetic Nanotechnology for Efficient Cancer Immunotherapy

The design parameters of biomimetic nanoparticles are essential for nanoparticle delivery and fate in vivo. In this section, we focus on the major physicochemical properties (shape, surface charge, size, surface chemistry and responsive release of biomimetic nanoparticles, as shown in **Figure 2**. We discuss how these properties contribute to achieving lower side effects, effective delivery and enhanced immunity.

3.1. Optimal Size

Size is the most important parameter which is investigated and manipulated for proper drug encapsulation, prolonging blood circulation, smoothing movement through leaky vasculature, organ/tissue accumulation and tissue/cell targeting. Nanoparticles with a diameter of less than 5 nm are usually cleared out via renal clearance after IV injection, whereas nanoparticles with a diameter greater than 200 nm are filtered out by the spleen because of the similar size of inter-endothelial slits (200–500 nm).[40,59] Therefore the nanoparticles with a size range of 20–200 nm are considered best for significant results. Also for biomimetic nanoparticles, where 20–200 nm sizes have the potential to evade the off-target organ accumulation and pass through tumor vascular fenestrations. For example, the biological profile and biodistribution of nanoparticles with a size of 20, 50, and 200 nm have shown minimum systemic clearance, efficient tumor internalization and higher tumor accumulation.[60] The drug delivery of biomimetic nanoparticles is based mainly on the EPR effect. This feature changes with respect to the anatomy of vasculature

Table 1. Advantages and disadvantages of various cell membrane-derived biomimetic nanoparticles.

Cell membrane type	Advantages	Disadvantages	References
RBCM	Prolonged blood circulation, evade the immune response, simple techniques for membrane surface decoration, controllable drug release and enhanced tumor-specific cellular uptake	Complicated and time-consuming purification procedures, no standard protocols for preparation and storage	[55]
Cancer cell membrane	Homotypic tumor targeting, evade the immune response, possess tumor-specific antigen, trigger tumor-specific immune response as an anticancer vaccine, improved transfection	Potential concerns regarding safety, time-consuming purification methods	[56]
WBCM	Strong selectivity at particular disease areas and regulation of inflammatory response, evading immune response, metastatic tumor targeting	Inadequacy in reproducing the integrality and complexity of WBC membrane	[56a,57]
Platelet membrane	Good immunocompatibility, Efficient properties in homeostasis therapy, hemorrhage and targeted drug delivery, evading immune response, targeting vascular wounds	Complex synthetic and purification routes, limited assessment of immunogenic potential, lack of standardized protocols to produce in sufficient amount	[56a,58]
Hybrid membrane	Prolonged blood circulation, evading immune response, homotypic targeting	Time-consuming preparation and purification procedures	[56b,58]

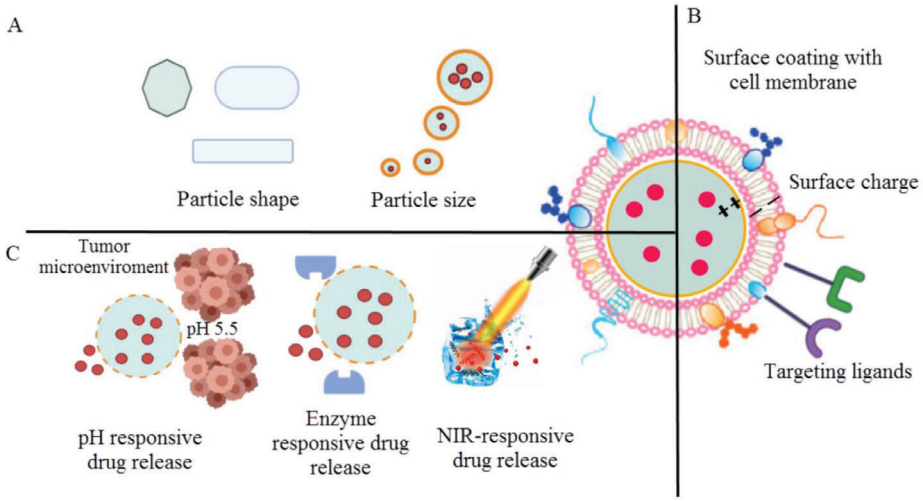

Figure 2. Design parameters for biomimetic nanoparticles. A) Size and shape of nanoparticle. B) Surface modification. C) Responsive drug release.

and its permeability. A continuous penetration through vasculature of highly permeable tumors has been observed for polymeric micelles with a particle size of 30, 50, 70, and 100 nm, whereas only 30 nm nanoparticles accumulated in poorly permeable tumors. The injected nanoparticles can be easily tracked and quantified by labeling with fluorescent dyes.[61] The particle size of biomimetic nanoparticles is considered an important feature that determines its biodistribution in organs and tumor tissues. Therefore an optimal size should be formulated to target the biomimetic nanoparticles to specific organs and tumor tissues at a particular stage.

3.2. Proper Morphology

As recent clinical nanotechnology has focused on improving the size consent of drug-loaded biomimetic nanoparticles, much work has also been done to tailor the shape of nanoparticles. Much research has been conducted on improving the shape of biomimetic nanoparticles by studying various morphologies, including rod, sphere, cubic, star, prism and disc shape. The geometry of nanoparticles plays an important role in macrophage internalization. For example, nanoparticles with discoidal shape accumulate in lung and spleen, while rounded nanoparticles are less prone to accumulation in MPS organs.[61] It is important to note the shape of biomimetic nanoparticles, because various morphologies can activate different intracellular signaling pathways. For example, they can promote the secretion of multiple cytokines or increase the chances of cytotoxicity to cancer cells depending individually on their shape.[62] Therefore it is necessary to investigate the shape of biomimetic nanoparticles for an efficient understanding of biological effects.

3.3. Balance Surface Charge

Charge on the surface of biomimetic nanoparticles is important because surface charges can alter the vital properties of nanoparticles.[63] For example, nanoparticles with a positive charge are more prone to systemic toxicity and are rapidly eliminated from circulation. Whereas negatively charged nanoparticles have prolonged circulation time with lower systemic toxicity. Also, negatively charged nanoparticles have a lower accumulation in the spleen and lungs.[64] Besides prolonged circulation time, adherence to cancer tissues and membrane-mediated endocytosis is also necessary for nanoparticles, which can be achieved via cationic surface charge. Moreover, cationic nanoparticles can escape endosomes via the proton sponge effect and release the cargo in the cytoplasm.[65] Because of this behavior, biomimetic nanoparticles are specifically designed nanoparticles that retain its negative charge to increase the circulation time and reverse to the positive charge surface at the target site to enhance the cellular delivery.[66]

3.4. Targeting Ligand

For most biomimetic nanoparticles, the EPR effect plays a significant role in localization at the tumor site, in a phenomenon which is termed passive targeting. In some cases, passive targeting is not sufficient for effective drug delivery. Thus active cellular targeting is required for achieving higher retention at the target sites.[67] This retention can be achieved by ligand-mediated biomimetic nanoparticulate drug delivery. Various types of ligands are available and can be attached to biomimetic nanoparticles to achieve active targeting at the tumor sites. Some examples include folate, transferrin, mannose, etc.[68] Similarly, cell-penetrating peptides (CPPs) such as TAT and iRGD (CRGDKGPDC) are also used for surface modification of biomimetic nanoparticles for effective targeted anti-tumor drug delivery.[69] For example, the surface of RBCM was modified with cyclic arginine-glycine-aspartate (cRGD) to achieve the targeted delivery of the anti-cancer drug to the tumor site.[70] The results demonstrated that the ligand significantly enhanced tumor-specific internalization and increased the efficacy of treatment compared to unmodified nanoparticles. It is important that the formation of protein species during circulation may mask attached ligands that might compromise the targeting ability, lose the specificity of conjugated ligand and produce toxicity.[71] A recent study reported that tumor-associated macrophages (TAMs) capture the actively targeted nanoparticles because of their phagocytic nature and only 0.0014% of nanoparticles interact with tumor cells after intravenous administration.[72] Another barrier for biomimetic nanoparticles is the extracellular matrix (ECM), which restricts the nanoparticles to penetrate deep cancer cells and tissues. For this purpose, it is important to prevent these hurdles and increase the interactions between ligand attached biomimetic nanoparticles and tumor cells.

3.5. Responsive Drug Release

Biomimetic nanoparticles are used to control the delivery of drugs and provide responsive drug release to improve the efficacy of treatment and reduce side effects.[73] It is important for biomimetic nanoparticles to hold the loading agents during circulation to avoid the unnecessary drug release at off-target sites. Also, proper release of drug molecules from the carrier is necessary with suitable pharmacokinetic behavior at the intended target site. The controlled drug release from biomimetic nanoparticles at the tumor site can be achieved using different approaches, such as the use of stimuli-responsive nanoparticles. Both internal and external stimuli-responsive material can be incorporated in a nanoparticle system to achieve tumor-specific drug release.[74] The internal stimuli include enzymes, pH, redox changes, matrix metalloproteinases (MMPs), whereas temperature, light, magnetic field and ultrasound are used as external stimuli.[75] Such responsive nanoparticles can elicit an effective anti-tumor response with lower off-target toxicity and prolonged tumor retention.[76]

4. Challenges of Biomimetic Nanotechnology for Cancer Immunotherapy

Biomimetic nanotechnology for cancer immunotherapy has gained a lot of importance in recent years owing to the greater potential in the treatment and preventing recurrence of the tumor. Much success has been achieved in clinical trials of cancer immunotherapy.[77] A variety of treatment strategies, as mentioned earlier, are used to elicit an anti-tumor response in the body.[78] However, these treatment approaches still face many challenges in the clinical translation of cancer immunotherapy. For example, the optimization of biomimetic nanotherapeutics is required to achieve productive results. Also, a combination of biomimetic nanotechnology with conventional therapies is needed to elicit a more powerful response. A monitoring system must be devised to predict the immune response more critically. The immune system is immensely complicated with multiple components involved. It is important to conduct basic research to understand the mechanism of action for biomimetic nanoparticle-based cancer immunotherapeutics.[79] Although biomimetic nanotechnology plays a vital role in cancer immunotherapy, the effectiveness is still lagging because of antigenicity of nanoparticles, adjuvant properties and inflammatory properties that must be designed and engineered to optimize the efficacy. Furthermore, the physicochemical properties such as size, shape, surface charge, etc. must be tuned to decrease the off-target accumulation of nanoparticles.[75] This will not only optimize the therapeutic efficacy but also minimize the unwanted immune response. For this purpose, stimuli-responsive biomimetic nanoparticles hold greater potential to provide targeted drug release of immunotherapeutics. This model can result in decreased toxicity of immunotherapeutics into healthy tissues.

It is worth noting that various biomimetic nanoparticles do not always maximize the targeted release efficacy, minimize toxicity or optimize the therapeutic efficiency of cancer immunotherapeutics. The toxicity of biomimetic nano-immunotherapeutics is the major hurdle that can lead to a lower response rate in the patient. Therefore a selective design of the biomimetic drug delivery system is required to address the issue. More effective immunotherapeutic procedures must be developed to minimize toxicities. The biomimetic approach can be utilized to develop

more novel immunotherapies. In biomimetic nanotechnology, homotypic targeting is considered a novel method to minimize the toxicities up to a greater extent.[21] This can be achieved by nanoparticles coated in the cancer cell membrane to achieve personalized immunotherapeutics. However, there is still a need for actual proof of concept that can be demonstrated by utilizing resected cancer cells rather than commercial cell lines. A thorough screening of different cancer cell types is required to unveil the targeting ability and establish a higher degree of universality of homotypic targeting.

Another important challenge is good manufacturing practice (GMP) which must be adopted to scale up the cell membrane nanotechnology. This can be the right way forward for the biomimetic nanotherapeutics to enter the clinic. To achieve a therapeutic dose and higher efficacy, the amount and quality of the material should be critically evaluated.

Moreover, the stability of the cell membrane coating must be ensured to prevent the loss of membrane coating during circulation. The stability of the membrane coating will retain the personalized aspect of nano immunotherapeutics and avoid unwanted side effects. Also, there are issues related to standard control in the field of biomimetic nano immunotherapeutics. The biomimetic nanoparticle of interest for cancer immunotherapy must be compared to better control when designing experiments.

5. Applications of Cell-Derived Biomimetic Nanotechnology for Cancer Immunotherapy

The field of nanomedicine has shifted toward the principles of biomimetic nanotechnology.[17b,80] The design of cancer immunotherapy using biomimetic nanotechnology offers several key advantages to improve the available clinical therapeutics. Researchers have turned toward nature to enhance the properties of nanotherapeutics further. Many nanotechnologies are now adopting aspects from nature to perform complex functions in highly efficient ways. Cell membrane coating with biomimetics can create nanotechnology with unique properties that can be leveraged in the design of cancer immunotherapy.[17b,80c] Cell-derived biomimetic nanoparticles perform cell-like functions depending on the source of the membrane. These functions are employed in a number of ways with much success in targeted drug delivery, bio detoxification and cancer immunotherapy. A wide range of cargoes can be used as the inner core of these biomimetic nanoparticles.[81] Most notably, in cancer immunotherapy, the NPs coated in cell membranes provide a rich source of antigen material to confer broader therapeutic potential. The cell mimicking properties are adapted from the transfer of membrane proteins to the surface of nanoparticles. The outer membrane layer can be further functionalized to provide more flexibility to NPs coated in cell membrane.[80c,82] The membrane of such nanoparticles can be derived from a plethora of cell types, resulting in unique formulations with novel properties. These biomimetic nanotherapeutics can significantly alter the landscape of cancer immunotherapy with improved efficacy as compared to traditional therapies.[29,83] Here, a comprehensive view of various cell-based biomimetic nanotechnology for cancer immunotherapy is discussed.

5.1. Red Blood Cell Membrane (RBCM)

Nanomedicine is mostly cleared from the body by the mononuclear phagocyte system (MPS). Earlier, these problems were addressed and solved by nanoparticle modification such as self-peptide decoration and PEGylation. However, the issues of MPS capturing and clearance were raised again as anti-PEGylated antibodies were formed against the PEGylated nanoparticles [84] In order to address the issues, RBCs-derived biomimetic nanotechnology emerged to utilize the cell and cell membrane to improve the circulation time. RBCs are the most common circulating cells in the blood, with an average life of 120 days due to glycans and proteins on the cell surface.[85] RBCs are the best cell-mediated drug delivery carriers due to their inherent biocompatibility.[86] In 2011, Zhang and co-workers, for the first time, developed long-circulating NPs coated in RBCM for cancer treatment.[45a] The half-life of these nanoparticles improved up to 50% that is significant as compared to PEGylated nanoparticles. The nanoparticles were detected in blood circulation even after 72 h of injection. Several biomarkers are expressed on the surface of RBCs which account for an easy escape from MPS organs (liver and spleen) and phagocytosis by macrophages in blood. These biomarkers include "don't eat me" marker CD47 and signal regulatory protein α (SIRP α) receptor. Such remarkable properties of RBCs allow the nanoparticles to achieve prolonged blood circulation and membrane functions in vivo.[87] These RBCs are recently utilized by biomimetic nanotechnology for cancer immunotherapy. In cancer immunotherapy, such biomimetic nanoparticles expand host anti-cancer immune reactions that can differentiate between cancer and normal cells.[30a] RBCs-derived biomimetic nanoparticles have been engineered to develop personalized cancer immunotherapies that can help to overcome the cancer heterogeneity. As discussed earlier, various strategies are used for cancer immunotherapy. These strategies can be used successfully in the regression of multiple types of tumors. Here we discuss the applications of RBCM based nanoparticles on the basis of these strategies for better understanding of cancer immunotherapy.

5.1.1. Immune Check Point Inhibitors

Immune checkpoint inhibitors are a novel class of anti-tumor drugs that block molecules expressed on the tumor cell surface for deactivating T cells. Thus they improve T cell-based immunity. The main targets of immune checkpoint inhibitor therapy are programmed cell death 1 (PD-1), programmed cell death 1 ligand (PD-L1) and cytotoxic T lymphocytes antigen 4 (CTLA-4).[88] This therapy ultimately increases the immune response of the patient against tumor cells. T and B immune cells express PD-1, whereas PD-L1 is present on tumor cells. The interaction between PD-1 and PD-L1 often results in the immune response of T and B cells.[1b] Similarly, CTLA-4 is expressed on regulatory T cells. This antigen interacts with CD80 and CD86 on APC and eliminates CD28 engagement to switch off T cell and APC mediated immune response.[89] Various antibodies are used to target these molecules and improve survival in different types of cancer.[88] For example, immune checkpoint blockade (ICB) therapy unleashes the patient's immune response to treat cancer.[90] However, the response rate of ICB therapy is still low in several

cancers and many times it results in immune-related adverse reactions. This indicates that the treatment requires more improvement to maximize efficacy and reduce toxicity.[88,91] The combination of ICB therapy with other treatment approaches has been demonstrated to improve the response rate.[92] For example, cancer vaccines are used in combination with immune checkpoint blockade therapy to elicit an anti-cancer immune response. However, still, the major objective of the clinical response has not been reached. The inefficient delivery of tumor antigen contributes to the reduced potency of cancer vaccines.[93] Possible reasons for the lower response could be the expression of PD-L1 in tumor cells that accounts for the immunosuppressive nature of the tumor microenvironment. Similarly, PD-L1 expression also occurs in APCs, which ultimately fail to induce T cell proliferation.[94] For this purpose, anti-PD-L1 has been proposed in combination with ICB and vaccine therapy to circumvent the problems. In order to overcome these problems, biomimetic nanoparticles using RBCs derived vesicles have been developed as effective antigen/adjuvant delivery systems for cancer immunotherapy. These systems could generate a robust anti-tumor immune response compared to conventional nanoformulations.[95] By utilizing RBCM nanotechnology for immune check point inhibitors, the accumulation of therapeutic agents in the tumor, drug delivery monitoring and combination therapy can be improved as follows.

For efficient cancer immunotherapy, Han et al. prepared an antigen delivery system based on nanoerythrosomes. The system was derived from RBCs with antigen-presenting targeting ability. Tumor antigen was loaded on to nanoerythrosomes by fusion of tumor-associated antigen. PD-L1 blocker was used with antigen-loaded nanoerythrosome (nano Ag@erythrosome) in a combination that resulted in a strong in vivo antigen response. The combination therapy inhibited the cancer growth in B16F10 and 4T1 cancer models. These cancer models revealed that personalized nanoAg@erythrosome based immunotherapy could be achieved by fusing surgically removed tumors and RBCs. The system was found to effectively inhibit cancer recurrence and metastasis.[96]

Biomimetic nano-immunotherapy has been found to treat triple-negative breast cancer effectively. The triple-negative phenotype of breast cancer usually has a poor prognosis and shows a lower response toward traditional chemotherapy and anti-human epidermal growth factor receptor (HER) therapy. The mutation rate of this type of tumor is high, which makes it suitable for immunotherapy. On the other hand, photothermal therapy (PTT) has been found as a highly efficient method to induce the release of tumor neoantigen in situ. Thus it has excellent potential to be used in combination with cancer immunotherapy. For this purpose, Liang et al. developed biomimetic-based photothermal cancer immunotherapy. They formulated RBCM-derived black phosphorus (BP) quantum dot nanovesicles (BPQD-RMNVs) that demonstrated triple-negative breast cancer apoptosis in situ through exposure to NIR radiations. The therapy was then combined with PD-1 antibody (aPD-1) to enhance immune response and eradicate residual and metastatic cancer. The NIR radiation was found to induce DCs recruitment and release neoantigens. It activated CD8+ T cells against primary and secondary tumors. Moreover, the combination of aPD-1 potentiates the CD8+ T cells and eliminated the metastatic and residual cancer cells, as shown in **Figure 3**. Overall, the BPQD-RMNVs mediated photothermal therapy combined with the immune checkpoint blockade antibody can be used successfully in cancer immunotherapy. This will increase the infiltration and activity of CD8+ T cells and reduce the growth of triple-negative breast cancer.[97]

Photodynamic therapy (PDT) has been recently found to initiate an immune response. And it is a promising way to be used in combination with chemotherapy. However, insufficient tumor penetration, retention and immature drug release restrict the anti-tumor effect. Size tunable nanoparticles play an important role in efficient drug delivery in such treatment approaches. Thus Yu et al. prepared a size reducible hyaluronidase responsive RBCs derived biomimetic nanoparticulate system (pPP-mCAuNCs@HA) as shown in **Figure 4**. The size analysis showed an optimal size of 150 nm suitable for prolonging circulation and enhanced tumor penetration. Pheophorbide A photosensitizer was co-loaded with ROS sensitive paclitaxel dimer prodrug (PTXK). Cinnamaldehyde was produced as a result of the hydrolysis of PTXK, which in turn stimulates the production of ROS by mitochondria to maintain the equilibrium. The biomimetic nanoparticles were further co-loaded with anti-PD-L1 peptide (dPPA) to increase the immune reaction by alleviating the activity of PDT mediated cytotoxic T cells. This, in turn, led to significant immunogenic based cell death. The combined therapy activated CD8+, CD4+ and NK cells and enhanced the production of different cytokines such as TNF-α and IL-12. The treatment was found to increase the cancer cell inhibition rate up to 84.2% with metastasis elimination. Thus it provides a better strategy for combining biomimetic immune and anti-metastasis therapy.[98]

5.1.2. Cancer Vaccines

Vaccines are a form of active immunization that elicits an artificial immune response against pathogens to prevent infections in the future. A vaccine is basically composed of a carrier, antigen and adjuvant to boost antigen activity. Cancer vaccines induce an endogenous immune response to treat or prevent the development of tumors.[99] Vaccines are simple and more cost-effective than immune checkpoint blocker and adoptive T cell therapies. The side effects are well controlled in cancer vaccines because they are specifically targeted at tumor-specific antigens.[100] Various types of cancer vaccines such as protein antigens, synthetic proteins, cell-derived vaccines or DNA-based vaccines are under investigation for accurate delivery to the target site. Cancer vaccines can incorporate antigens from whole tumor lysate that are overexpressed on cancer tissues specifically or mutated neo antigens specific to tumor cells.[101] Different types of carriers can be used for antigen loading. For example, polymeric nanoparticles, liposomes and emulsions. RBCM based nanoparticles provide a novel strategy to incorporate vaccines with high efficiency that can be prophylactic, prevent or eliminate tumors.[102]

For example, to enhance the immune response to recognize and destroy cancer cells, Guo et al. developed a biomimetic nanovaccine formulation for efficiently targeting the antigen to APCs, especially DCs and induce an antigen-specific T cell response as shown in **Figure 5**. The nanoparticles were based on RBCM-coated PLGA nanoparticles. These biomimetic nanoparticles were co-loaded with toll like receptor-4 agonist monophosphoryl lipid and antigen peptide (hgp10025-33). The membrane

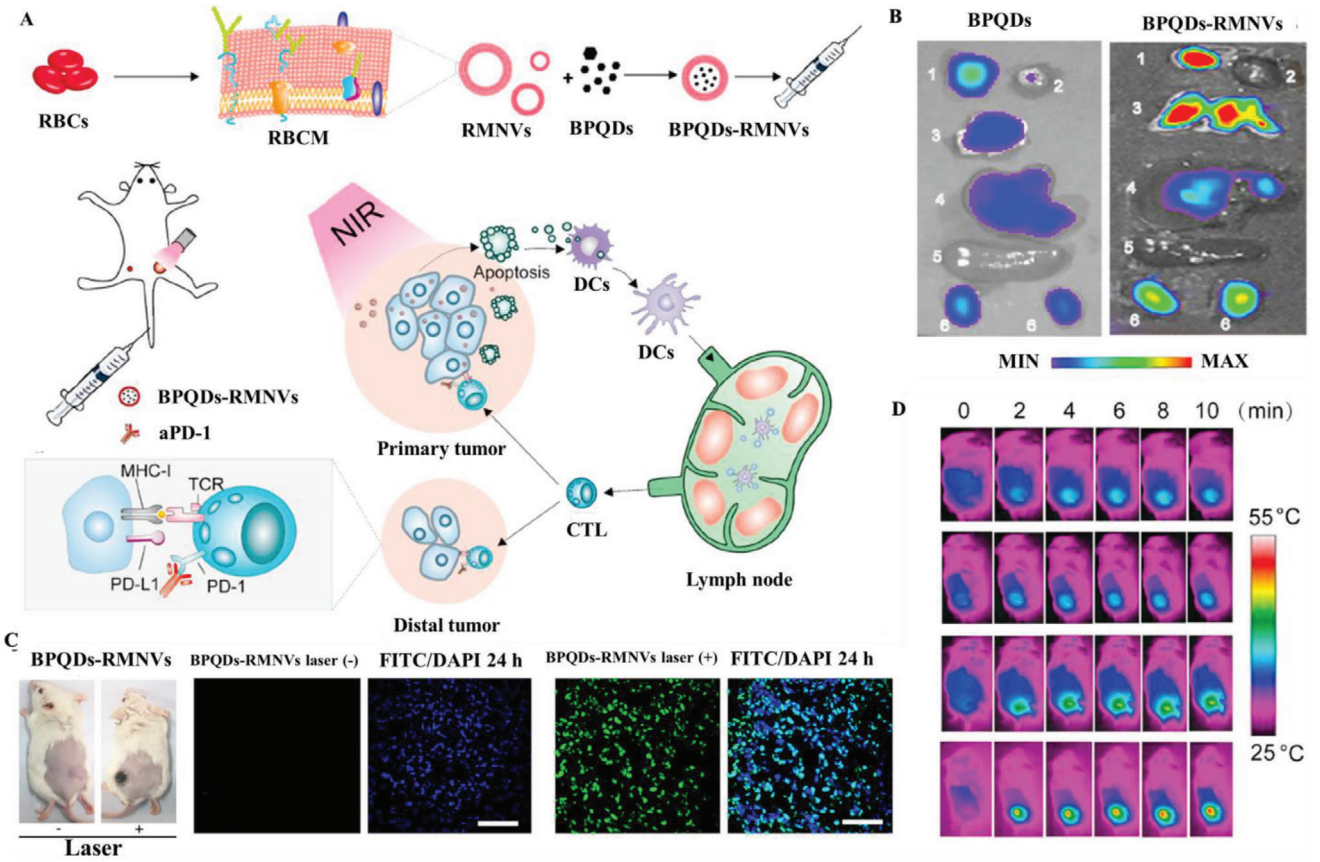

Figure 3. A) Schematic representation of photothermal cancer immunotherapy via RBC cloaked black phosphorous (BP) quantum dot nanovesicles (BPQD-RMNVs) and aPD-1. B) In vivo biodistribution images of nanovesicles and BPQDs distribution in organs and tumors. 1) Tumor, 2) heart, 3) lungs, 4) liver, 5) spleen, and 6) kidney. C) Cancer cell death in the mice treated or untreated with NIR radiation after 24 h; green fluorescence shows tumor cell death, (D) IR thermographic maps. Reproduced with permission.[97] Copyright 2019, Elsevier.

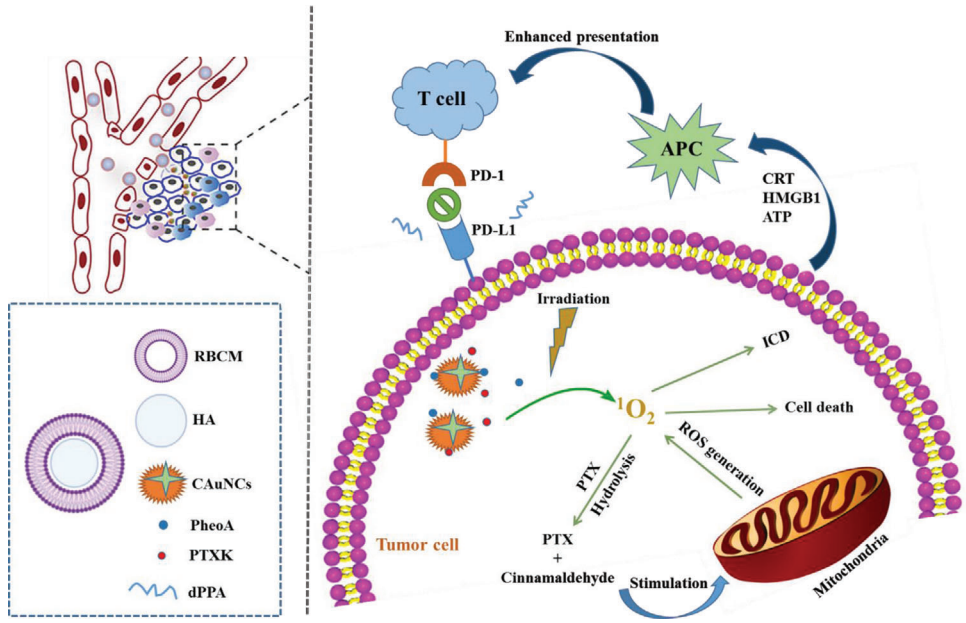

Figure 4. A diagrammatic overview of size reducible biomimetic nanoparticles (pPP-mCAuNCs@HA) in combination with chemotherapy, pharmacodynamics treatment and immunotherapy. Reproduced with permission.[98] Copyright 2019, Elsevier.

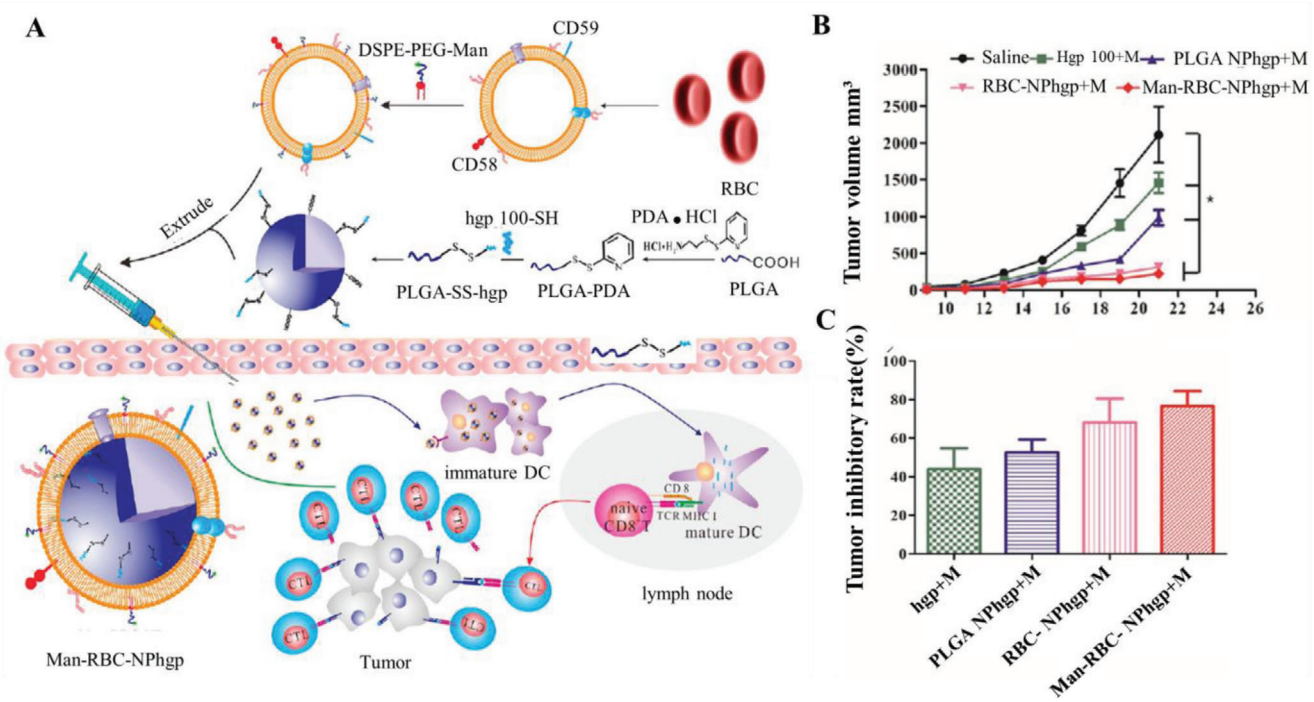

Figure 5. A) Man-RBCs membrane coated PLGA-SS hpg100 nanoparticles (man-RBCs-NPhpg) preparation for cancer immunotherapy. B) Tumor volume curves. C) Inhibition rate of tumor in different groups in comparison with saline. Reproduced with permission.[32] Copyright 2015, American Chemical Society.

was modified with mannose as an adjuvant for functionalization and active targeting of APC in the lymphatic system. The redox responsive peptide-bound biomimetic PLGA nanoparticles were sensitive to tumor microenvironment. Such a vaccine exhibits enhanced in vitro cell uptake and promoted antigen retention in draining lymph nodes. Tumor growth was significantly inhibited and metastasis was suppressed in melanoma models. Moreover, the biomimetic nanovaccine effectively enhanced the infiltration of CD8+ T cell and IFN-γ secretion. Overall, the results demonstrated the viable potential of RBCM-coated polymer-based nanoparticles for the best delivery of antigen in cancer immunotherapy.[32]

Cancer cells are transformed cells that possess diverse modifications with the production of various neoantigens, such as cell surface carbohydrates. Cancer immunotherapy can be accessed efficiently by targeting such tumor-associated carbohydrate antigen (TACA). Such immunotherapy aims to support the immune system in combating malignant tumors. One example of an immunogenic carbohydrate is *N*-glycolylneuraminic acid (Neu5Gc), a dietary carbohydrate that generates neoantigens. The anti-Neu5Gc antibody can elicit passive immunotherapy and inhibit the growth of the Neu5Gc positive tumor. Therefore Reuven et al. designed a biomimetic-based cancer vaccine to target Neu5Gc positive tumors in **Figure 6**. They prepared biomimetic glyconanoparticles using engineered αGal knockout porcine RBCs to form nanoghosts (NG) with positive (NGpos) or negative (NGnegs) Neu5Gc-glycoconjugate expression. The nanovaccine demonstrated optimized immunization of Neu5Gc-deficient mice with NGpos glyconanoparticles that induced a strong, persistent and diverse anti-Neu5Gc IgG immune response. The resulted anti-Neu5Gc IgG antibodies were detected in Neu5Gc positive tumors and stopped cancer growth in vivo. Taken together, the results specified the potential of TACA neoantigens and dietary sialic acid Neu5Gc in cancer immunotherapy.[30b]

5.1.3. Cytokine Therapy

Various cytokines and immune adjuvants are used to enhance the immune response of cancer therapy. For example, interleukin-2 was developed in mid 90s to induce strong immunity against cancer. Encouraging results were found in the pre-clinical stage of this development. However, it was associated with various toxicities. To improve the therapy with reducing toxicity, targeted delivery of cytokines is required that can be achieved by utilizing RBCM based nanotechnology.

Cancer immunotherapy using artificial antigen-presenting cells (aAPCs), which have a similar function as APCs such as DCs, is used to activate T lymphocytes and produce antitumor response. It has gained much interest in recent years. RBCs can be used to develop artificial antigen-presenting cells (aAPCs). This is because of several advantages of RBCs such as biocompatibility, high surface to volume ratio and remarkable membrane elasticity to facilitate the interaction between RBCs -based aAPCs and T cells.[103] Moreover, RBCs have a suitable size of 5–8 µm, which can easily cover the micro size immune synapse and provide adjustment to rearrange the membrane-anchored biomolecules through membrane fluidity.[104] The long-circulating life of RBCs also provides more interaction time with T cells when administered intravenously.[105] Keeping this

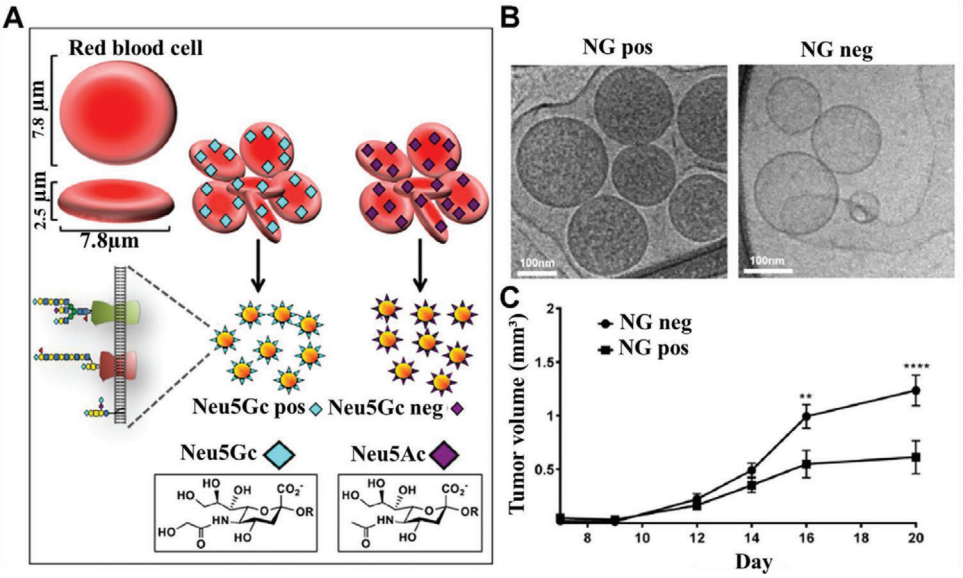

Figure 6. A) Schematic illustration of erythrocytes and nanoghost (NG) with either terminal Neu5Gc (NGpos) or terminal NeuAc (NGneg). B) Transmission electron micrographs of NGpos or NGneg. C) Tumor volumes showing growth inhibition of tumor of NGpos vaccine treated group. Reproduced with permission.[30b] Copyright 2019, American Chemical Society.

background, Sun et al. developed a unique RBCs-based aAPCs system by attachment of antigen peptide-loaded major histocompatibility complex and CD28 activation antibody on the RBCM. These were then further engineered with interleukin-2 (IL2) as differentiation and proliferation signals. Such an RBCs based aAPC-IL2 (R-aAPC-IL2) system was able to provide an elastic cell surface with appropriate biophysical parameters in **Figure 7**. The novel system also mimics the functions of matured DCs and facilitates the proliferation of antigen-specific CD8+ T lymphocytes and stimulates the production of cytokines. R-aAPC-IL2 induced cancer cell-specific lysis in splenocytes from C57 mice, thus providing a strong anti-cancer immune response. Overall, this work represents a novel cell-derived biomimetic RBCs based aAPC system that can behave similarly to antigen-presenting DCs to activate and induce T cell response for cancer immunotherapy.[106]

Biomimetic nanogels have been recently designed for safe and effective drug delivery. Nanogels are superior carriers for co-encapsulation of both hydrophilic and hydrophobic drugs due to their chemical composition.[107] Such a biomimetic nanogel was developed by Song et al. with tumor microenvironment responsive properties in **Figure 8**. It was used to combine anti-tumor effect chemotherapy and immunotherapy. The gel was formulated with pH-responsive hydroxypropyl-β-cyclodextrin acrylate and two opposite charge chitosan derivatives to load paclitaxel. The nanogel was further coated with the RBCM to achieve nanosponge characteristics for delivering interleukin-2 without minimizing its bioactivity. In response to the tumor microenvironment, the nanogel releases the drugs, which significantly enhances anti-tumor activity with the induction of calreticulin exposure, improves drug penetration and increases immunity against tumor. The microenvironment of the tumor was also modified by a combination of drugs that promoted immune effector cell infiltration and reduced the immune-suppressive factors.[108]

5.2. Cancer Cell Membrane

Besides RBCs, cancer cells can also be used as a source of membrane for biomimetic nanotechnology in cancer immunotherapy. Cancer cells are malignant cells that can be cultured and produced efficiently by in vitro methods because of their ability of infinite proliferation.[109] Many unique features of cancer cell membranes account for its use as a promising coating material for cancer immunotherapies. These features include immune escape, infinite growth ability, and resistance to cell death, prolonged circulation time, and homologous targeting ability.[110]

Galectin-3 and carcinoembryonic antigen-presenting on the surface of cancer cell membrane have a greater homotypic affinity toward cancer cells.[111] Using this concept, tumor cell membrane cloaked biomimetic nanoparticles are designed to acquire homologous targeting capacity suitable for cancer-targeted drug delivery and effective cancer immunotherapy.[21] Furthermore, the tumor-specific antigens present on the membrane surface make it convenient for cancer cell membrane biomimetic nanotechnology to play an important role in efficient immunotherapy.[42a] The strategies of cancer immunotherapy have been improved by utilizing cancer cell membrane as discussed in the following examples.

5.2.1. Immune Check Point Inhibitors

Cancer cell membrane-based nanotechnology applied to immune checkpoint inhibitors has been used by various researchers to improve efficacy of anti-tumor immunotherapy. For this purpose, Jin et al. developed human glioblastoma CCM (U87)-coated PLGA nanoparticles for anti-tumor immunotherapy. The nanoformulation U87-CCM NPs was delivered via subcutaneous injection that produces tumor-specific immune

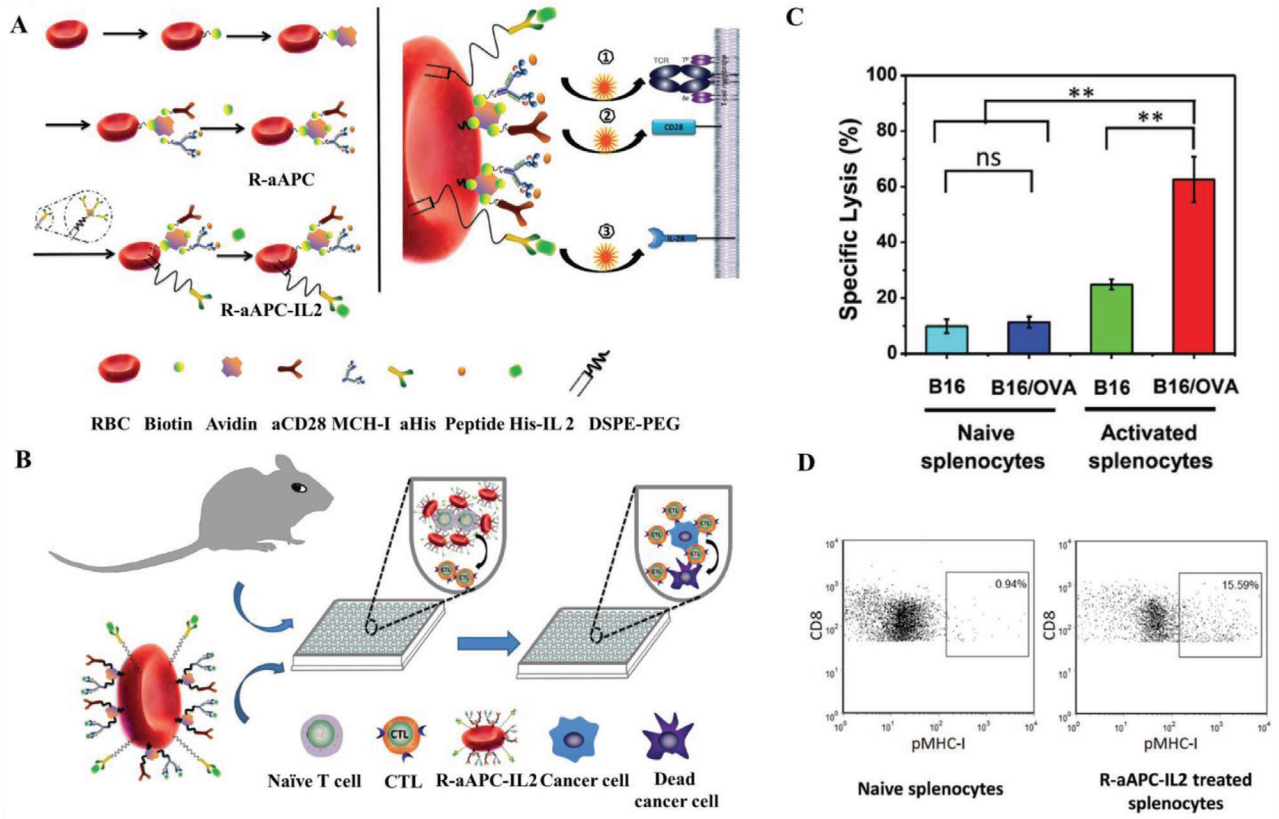

Figure 7. A) Fabrication of RBCs based aAPC modified with pMHC-I, aCD28 and IL2 with a mechanism to activate CD8+ T cells for cancer immunotherapy. B) In vitro T-cell reduction and cancer cell-specific killing. C) Efficacy of cancer-cell specific lysis by naive splenocytes and R-aAPC-IL2-activated splenocytes from C57 mice. D) Dimer staining to show the TCR specificity of CD8+ T cell populations in naive splenocytes and R-aAPC-IL2-treated splenocytes. Reproduced with permission.[106] Copyright 2017, Wiley-VCH GmbH.

reaction by activating CD4+ and CD8+ T cells in lymph nodes and spleen of Balb/c mouse model.[112] Although anti-PD-1 immunotherapy is used to treat melanoma, its efficacy is still limited due to its low targeting ability. To improve the therapeutic effectiveness and achieve a better anti-tumor response, Xie et al. developed a strategy that combines immunotherapy and starvation therapy, as shown in **Figure 9**. They designed mesoporous silica nanoparticles coated in cancer cell membrane (CMSN). The mesoporous silica nanoparticles were firstly loaded with glucose oxidase (GOx), and then the surface was modified with a cancer cell membrane to induce starvation therapy. By such biomimetic functionalization of MSN nanoparticles, the resulting system could escape the host immune response and target the homologous cells. It was found that the synthetic CMSN-GOx nanosystem can eliminate tumors and induce DC maturity to stimulate an antitumor immune response. In vivo analysis was performed to demonstrate a better anti-tumor therapeutic effect of combination therapy of CMSN-GOx and anti-PD-1 than using the therapies alone.[113]

5.2.2. Cancer Vaccines

CCM based nanotechnology has been used to improve the effectiveness of cancer vaccines. CCM-based nanovaccines are safer due to the absence of nuclear components of tumor cells.[42a] CCM has greater potential for cancer immunotherapy by offering a diverse range of tumor-associated antigens (TAAs) that induce a strong tumor-specific immune response.[42a,80b,114] Traditional anti-cancer vaccines deliver few antigens, which results in lower immune response. Cytotoxic T cells kill tumor cells specifically by interacting with receptors on the surface of tumor cells. It makes more sense to use the tumor cell membrane as a cancer-specific antigen. For example, Fang et al. explored a B16-F10 tumor cell membrane cloaked polymeric nanoparticles for biological functionalization, as shown in **Figure 10**. The resultant nanoparticles had a core–shell structure. The shell or outer layer of nanoparticles carried a full source of antigens of the tumor cell membrane, offering a potential toward different modes of cancer immunotherapy. They also functionalized the nanoparticles with immunological adjuvants that resulted in improved tumor-specific immune response for the use in vaccine applications. The nanoparticles showed homotypic targeting ability inherent to the membrane. Thus the membrane functionalization allows for unique tumor-targeting that can be used for anti-cancer immunotherapeutic applications.[42a]

Nanovaccines coated in cancer cell membrane are considered better therapeutics for cancer immunotherapy than using individual tumor-associated antigens (TAAs). These nanovaccines are able to elicit an immune response to various TAA.[115]

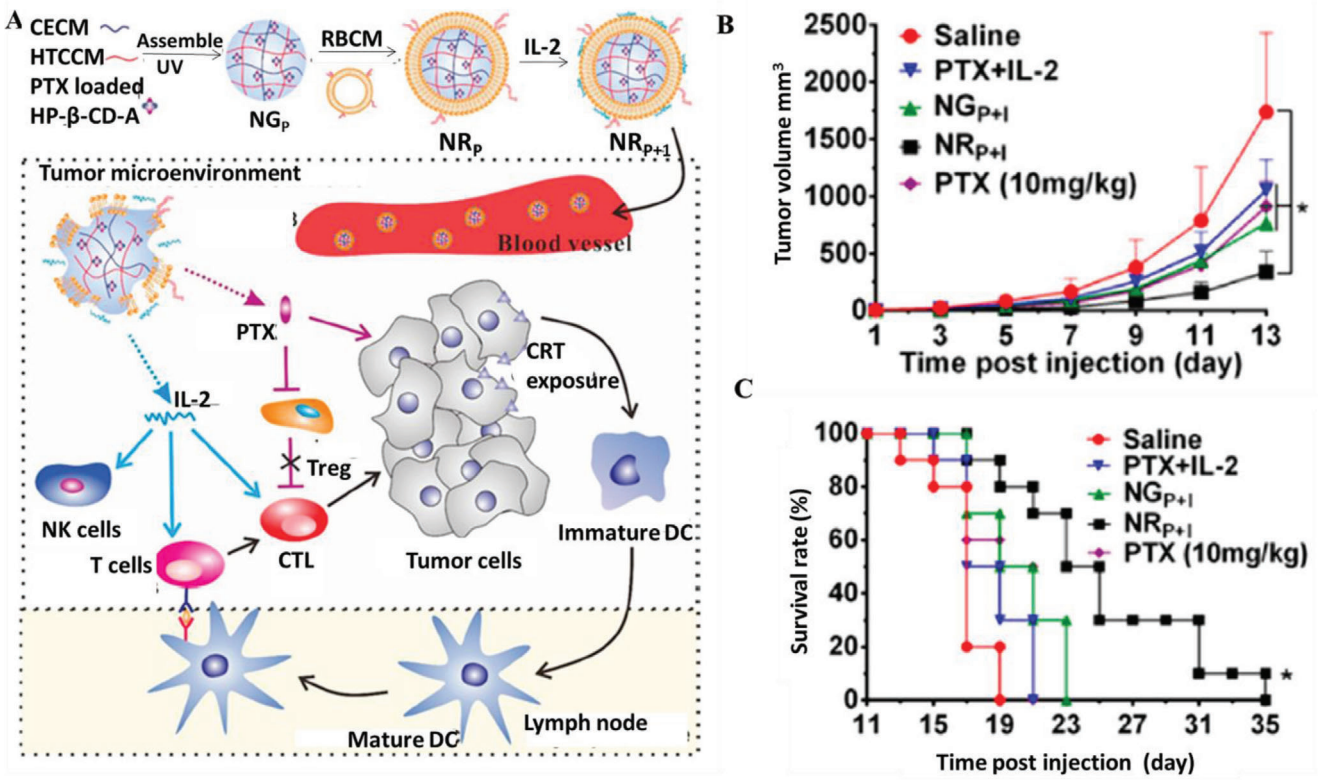

Figure 8. A) Cancer cell microenvironment sensitive biomimetic nanogel for combine the anti-cancer effect of immunotherapy and chemotherapy. B) Tumor growth curve. C) Mice survival rate treated with different formulation groups. Reproduced with permission.[108] Copyright 2017, American Chemical Society.

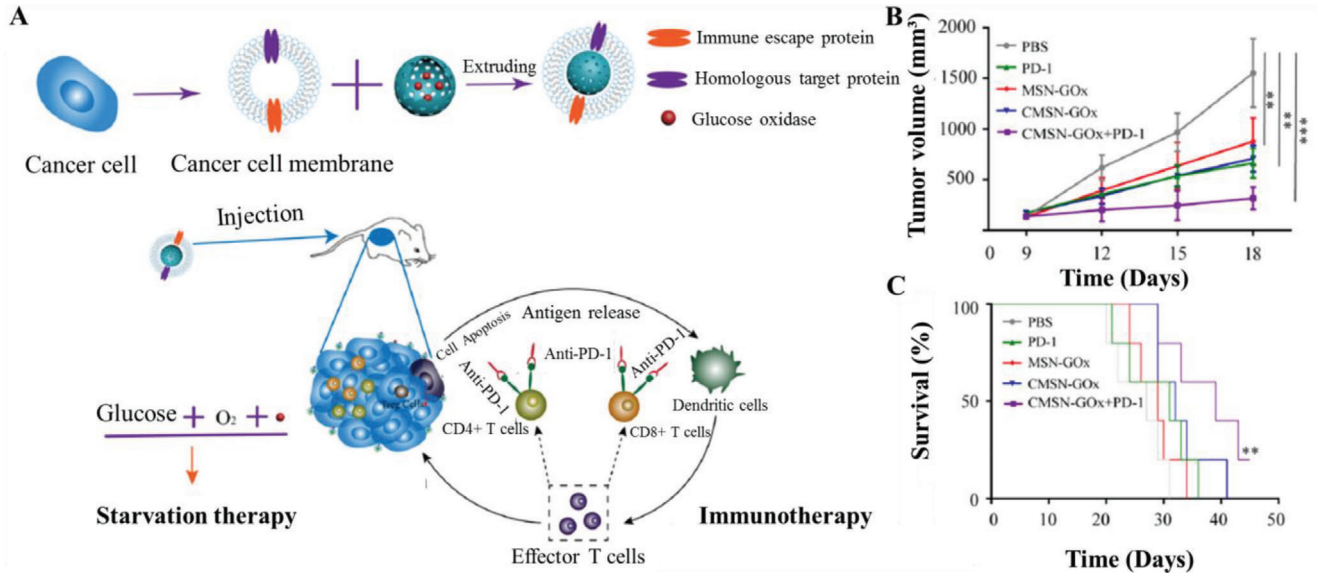

Figure 9. A) Schematic illustration of CMSN-GOx based enhanced anti-PD-1 immunotherapy against cancer. B) Tumor volume in the mice after different treatment. C) Mice survival curves after various treatments. Reproduced with permission.[113] Copyright 2019, American Chemical Society.

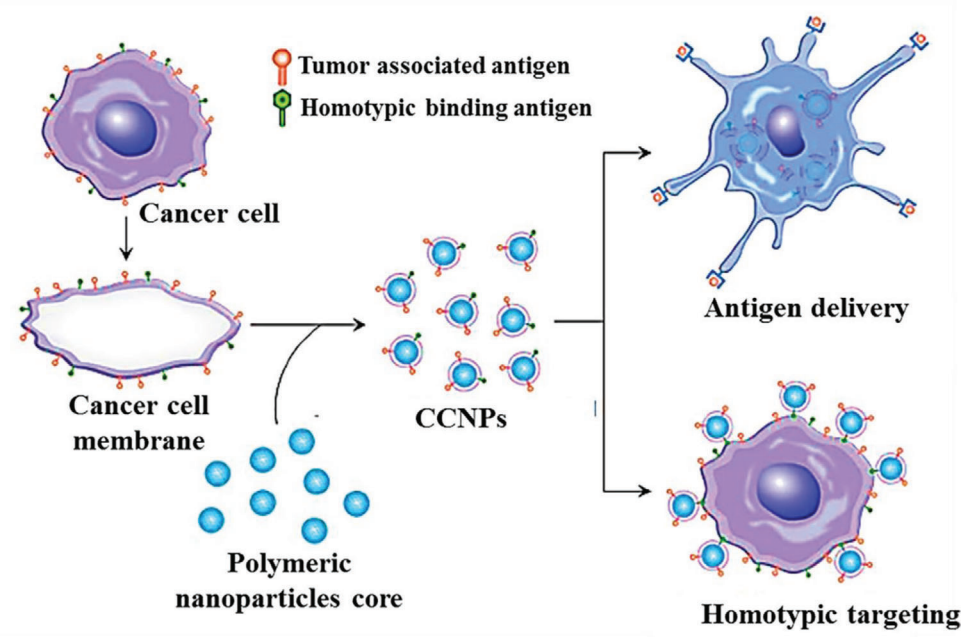

Figure 10. Schematic representation of PLGA nanoparticles with cancer cell membrane coating (CCNP) for delivering tumor-linked antigens to antigen-presenting cells or for homotypic targeting of source cells. Reproduced with permission.[42a] Copyright 2014, American Chemical Society.

A similar multistage nanovaccine was developed by Fontana et al. It is based on breast cancer cell membrane with conjugated immuno-adjuvant (dextran-coated porous silicon) for cancer immunotherapy.[114] The cancer cell membrane porous silicon-based nanovaccine stimulated the expression of stimulatory signals (CD80 and CD86) in immune cells and improved the production of inflammatory cytokines in peripheral blood monocytes that provoke Th1-mediated immune response. Another nanoparticle was developed by Noh et al., known as the immune-modulatory tumosome in **Figure 11**. The tumosome was designed using tumor cell-based antigens and lipids monophosphoryl, lipid adjuvant, combine with synthetic lipid. The resulted in tumosomes were multifaceted that deliver the cancer antigens with immuno adjuvants to stimulate prolong adaptive immune response in draining lymph nodes of tumor and spleen. Moreover, this hybrid tumosome was found to inhibit cancer growth following intravenous injection.[116]

To improve the efficacy of cancer immunotherapy, Kroll and colleagues developed the concept of tumor-derived biomimetic nanotechnology. For this purpose, they developed an anti-cancer nanovaccine based on cancer cell-derived biomimetic nanotechnology, as shown in **Figure 12**. The nanovaccine was capable of delivering autologous tumor antigens together with immunostimulatory adjuvant. The components of biomimetic nanovaccine are a tumor antigen and adjuvant which were present in such a fashion that maximizes their ability to promote the antigen presentation and activation of the immune response. Overall the formulation demonstrated a potent anti-tumor response in vivo. Other therapies such as checkpoint blockade can be combined with this strategy with tremendous therapeutic effect for cancer immunotherapy.[117]

As discussed earlier, the strategy of utilizing membrane derived from endogenous cells for immune stimulation offers multiple antigen exposure and is suitable for personalized cancer immunotherapy. To boost immune response, Jin et al. developed biomimetic PLGA nanoparticles coated with cancer cell membrane fractions (CCMFs) as shown in **Figure 13**. They evaluated the characterization and ability of these CCMF-PLGA NPs to induce an immune response. The antigen U87-CXCR4 loaded CCMF-PLGA NPs demonstrated the ability to stimulate the production of cytotoxic T cells. From near-infrared fluorescence imaging, the migration of NPs to proximal draining LNs was confirmed. Higher populations of CD8+ and CD4+ T cells were observed in spleen and LNs in immunized mice. Thus the CCMF-PLGA NPs hold the potential to disrupt cancer cell-stromal cell interactions and improve immune response in cancer immunotherapy.[118]

Cancer immunotherapy can be used in combination with chemotherapy to overcome tumor immune suppression. For this purpose, Wu et al. developed a surface layer (S-layer) protein-improved immunotherapy strategy based on cancer cell membrane coated (S-CM-HPAD) nanoparticles for malignant cancer therapy and metastasis inhibition as shown in **Figure 14**. The S-CM-HPAD nanoparticles could efficiently deliver the tumor antigen, DOX and immune adjuvant to the homotypic tumor by homotypic targeting ability of the outer tumor cell membrane. In addition to cancer cell death, DOX was found to improve the immunotherapeutic response by inhibition of myeloid-derived suppressor cells (MDSCs). The S-layer had intrinsic adjuvant property and displayed epitopes and proteins, which potentiated the immune response to antigen. The excellent combined therapeutic effect on inhibition of cancer and metastasis in melanoma cancer models demonstrated an enhanced therapeutic strategy for cancer immunotherapy.[119]

By inducing host immune response, biomimetic nanovaccines can specifically eliminate cancer by the display of a diverse range

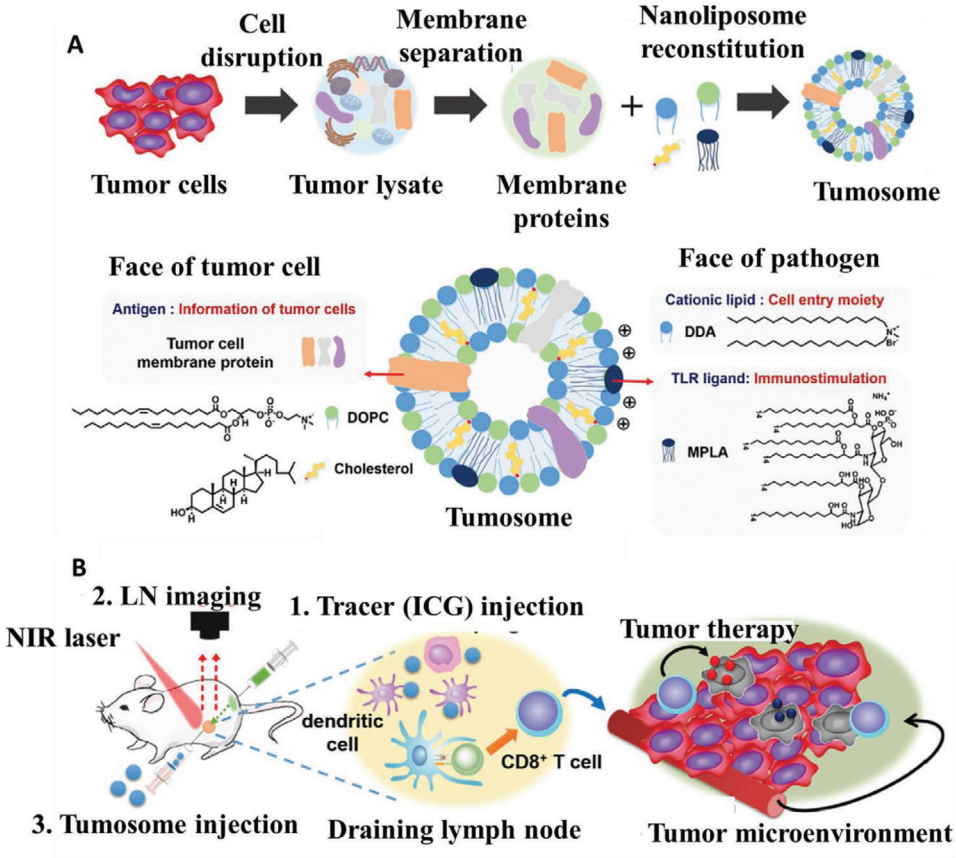

Figure 11. Schematic overview of multifaceted immunomodulatory nanoliposomes (tumosomes) for cancer immunotherapy. A) Synthesis of tumosomes by tumor-associated antigens, adjuvants (MPLA, DDA) and lipids (DOPC, cholesterol). B) Image-guided cancer immunotherapy. Reproduced with permission.[116] Copyright 2017, Wiley-VCH GmbH.

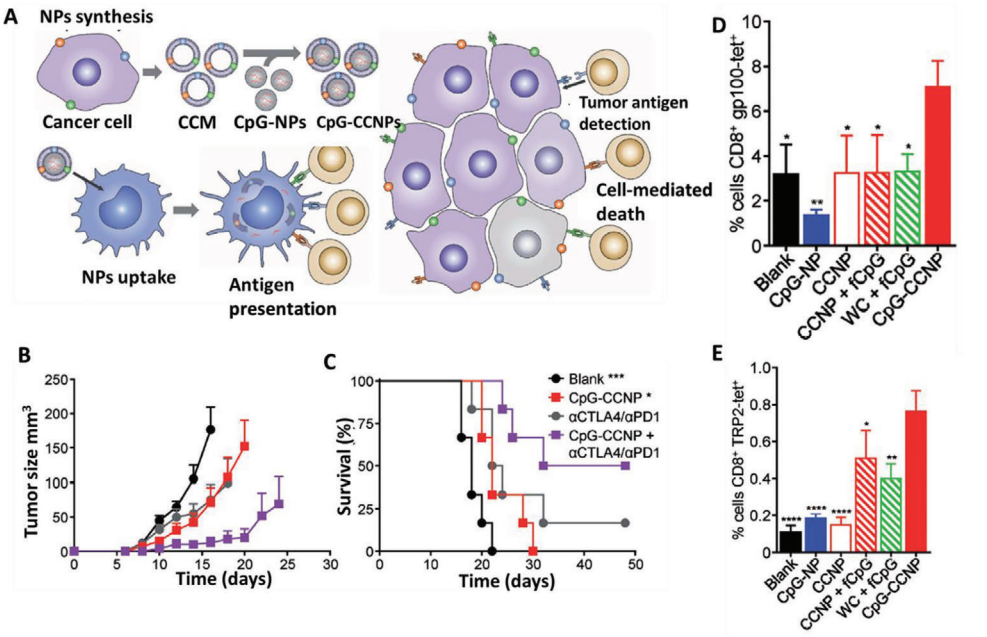

Figure 12. Cancer cell membrane coated nanoparticles (CCNPs) for multiantigenic anti-tumor vaccination. A) Coating of membrane onto polymeric nanoparticles with loaded CpG adjuvant to stimulate anti-tumor immunity. B) Tumor size. C) Survival rate curve. D,E) Tetramer staining analysis of T cells specific for gp 100 and TRP2. Reproduced with permission.[117] Copyright 2017, Wiley-VCH GmbH.

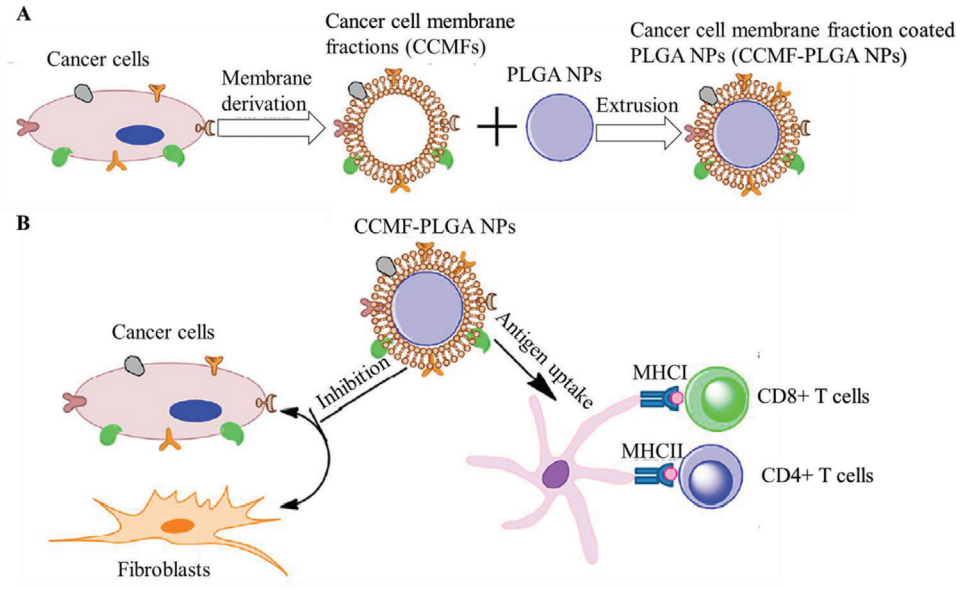

Figure 13. A) Cancer cell membrane fractions (CCMFs) preparation and translocation on PLGA nanoparticles. B) Ability of CCMF-PLGA NPs to induce anti-tumor immunity. Reproduced with permission.[118] Copyright 2019, American Chemical Society.

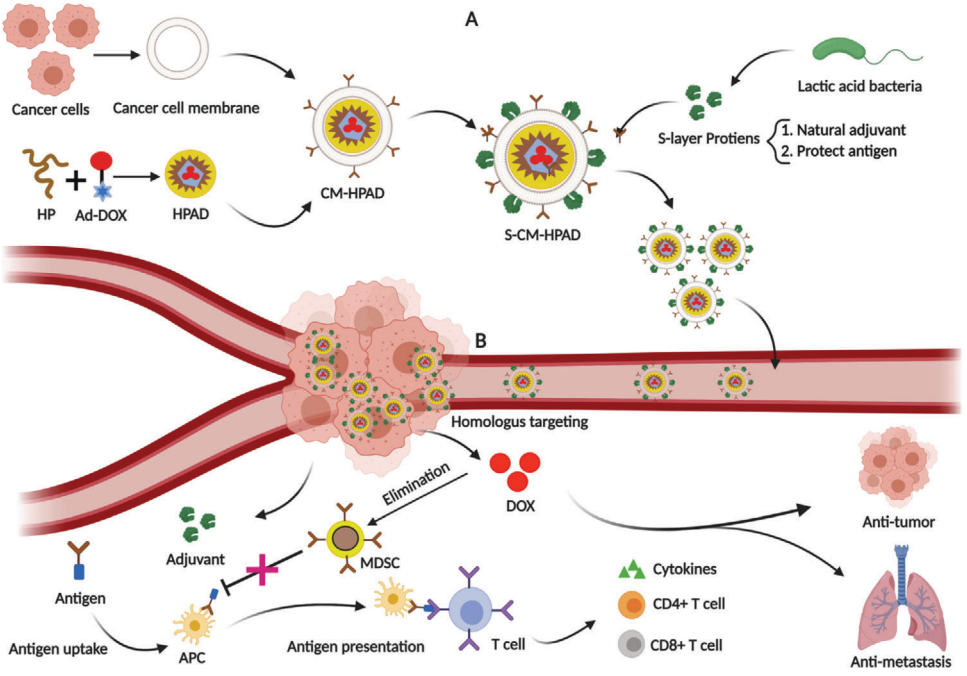

Figure 14. A) Formulation of S-CM-HPAD NPs. Cancer cell membrane extracted from B16F10 melanoma cell, hybridized with cationic polymers (HPAD) and then self-assembly of surface layer protein (S) on CM-HPAD to form S-CM-HPAD NPs. B) S-CM-HPAD NPs based chemotherapy and immunotherapy. Reproduced with permission.[119] Copyright 2019, American Chemical Society.

of antigens.[99] Given this, Li et al. developed a novel vaccine by coating a magnetic nanocluster (MNC) surface with azide pre-engineered tumor cell membrane. The surface of the nanoclusters was preadsorbed with toll-like receptor agonist CpG oligodeoxynucleotide (CpG-ODN), immune adjuvant and then the cancer cell membrane was decorated with anti-CD205. This conferred the nanovaccine with preferentially recognized CD8+ DCs as shown in **Figure 15**. By applying a magnetic field, the nanovaccine was drained and efficiently preserved in lymph nodes for more than three weeks. The significant improvement in retention at lymph nodes provided higher chances for recognition and uptake of nanovaccine of DCs and CD8+ stimulation. A large amount of T cells proliferated as a result of cancer cell membrane-derived antigens. As a result, an enhanced

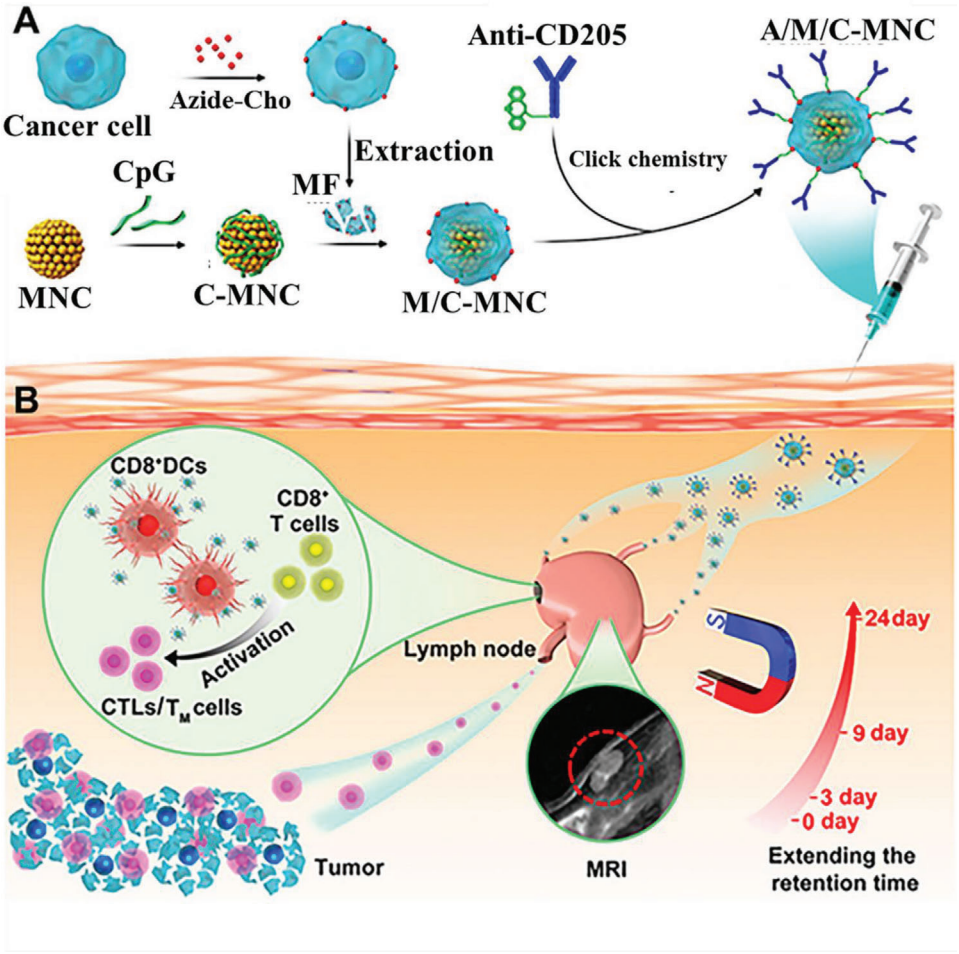

Figure 15. Formulation of magnetosome for anti-cancer vaccination. A) Cancer cell membrane coated CpG loaded MNCs fabrication with anti-CD205 decoration (A/M/C-MNCs). B) A/M/C-MNCs mediated immune response for cancer immunotherapy. Reproduced with permission.[120] Copyright 2019, American Chemical Society.

prophylactic and therapeutic effect was demonstrated in five cancer models. Therefore, such a tumor-based magnetosome carries promise for effective cancer immunotherapy.[120]

5.2.3. Combination Therapy

The immune therapy strategies can be combined to modulate the tumor microenvironment and enhance the efficacy to further strengthen the immune response. To explore this strategy and improve the targeting efficiency of APC, Liu and co-workers prepared a shell and core nanostructure using PLGA as a core component. TLR-7 agonist R837 was loaded in the nanoparticles, and the core was coated with cancer cell membrane shell with mannose modification as shown in **Figure 16**. The developed nanoparticles were efficiently retained in lymph nodes and targeted to DCs. It showed that the novel biomimetic nanovaccine could generate the production of CD3+, CD8+ and CD107a T cells and enhance the production of IFN-γ. Immune checkpoint blockers can be used in combination, which may boost the priming anti-tumor immunity of the vaccine and further enhance the therapeutic effect. When single anti-PD-1 therapy was used, it inhibited the growth of tumors in the early stage and failed to eliminate cancer in later stage. The biomimetic nanovaccine, in combination with anti-PD-1 therapy, was found to significantly regress melanoma. This indicated that the combinational strategy could be an attractive method for cancer immunotherapy.[121]

5.3. White Blood Cell Membrane (WBCM)

WBCs, commonly known as leukocytes, are defensive cells with a diameter of 7–20 µm, which is larger than RBCs. Most of the WBCs have an amoeboid movement that helps in their migration from blood vessels to extravascular tissues. Thus WBCs have a widespread distribution in blood vessels, lymphatic vessels and other tissues.[122] Limited work has been done on WBCs derived from biomimetic nanotechnology.[123] Therefore, it is important to understand the depth of these cells in order to utilize their efficacy in biomimetic nanotechnology. WBCs consist of many different subclasses, including T cells, granulocytes, monocytes/macrophages and NK cell. They are located

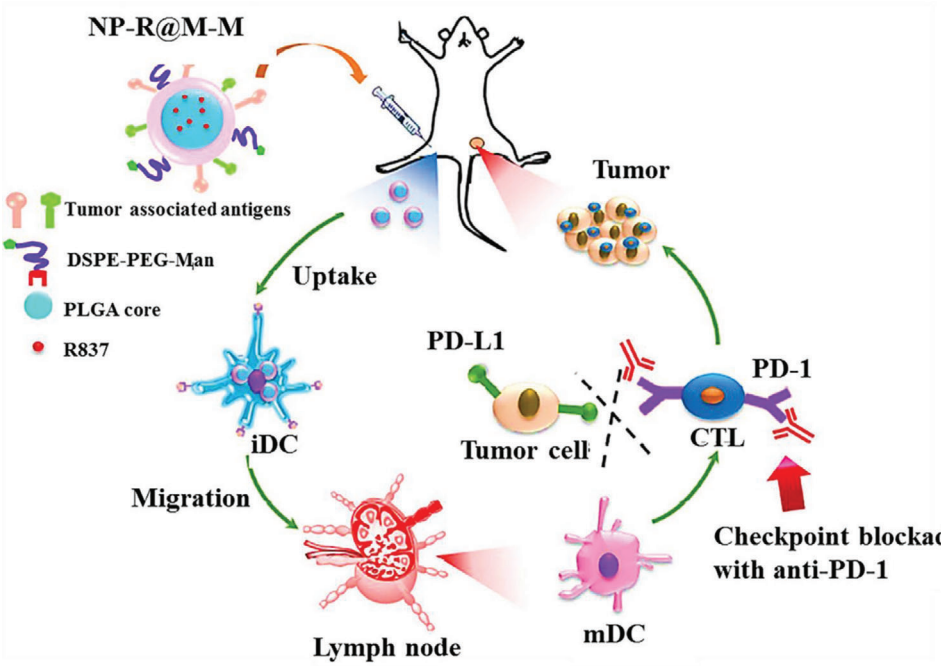

Figure 16. Schematic diagram of R873 loaded mannose modified PLGA nanoparticles with tumor cell membrane coating (NP-R@M-M) to produce immunity against cancer anti-cancer Reproduced with permission.[121] Copyright 2018, American Chemical Society.

in the bloodstream and body tissues. The nanoparticle can be coated with the WBCM, which provides many superior functions to the nanoparticles. For example, nanoparticles coated with macrophage/monocyte or neutrophil membrane reduces the opsonization and self-recognition mechanism that delay phagocytic uptake.[47a] Similarly, cytotoxic T-cells hunt for antigen, whereas NK cell provides host defense. These cells have adequate circulation and their membranes can be used to prolong the circulation life of nanoparticles by a coating process. These cells can recognize and accumulate in disease regions purposefully.[124] WBCs are recruited toward tumors during their substantial growth and activated to provide host response to the disease.[43] WBCs have unique site-specific targeting properties that can be used for cancer targeting. A wide range of chemokines is expressed on tumor cells that provide interaction with the WBCM. Thus WBC-derived nanoparticles are immensely useful to enhance the therapeutic efficacy because of the presence of a chemokine component that gives an intrinsic property to the target tumor.[125]

5.3.1. Immune Check Point Inhibitors

Immune check point inhibitor-based therapies were developed recently using biomimetic nanotechnology to improve their effectiveness. These are known to reduce the immunosuppressive effect of the tumor microenvironment and increase the cytotoxicity in cancer. In order to mimic the functions, WBCs biomimetic nanoparticles are constructed for cancer immunotherapy. Similar work was done by Zhang et al., who constructed biomimetic magnetosomes to improve immunomodulation/ ferroptosis synergy in cancer. The magnetosome was composed of magnetic nanocluster (NC) Fe_3O_4 as a core and coat with a pretreated WBCM. TGF-β inhibitor (Ti) was loaded inside the membrane, and the PD-1 antibody (Pa) was anchored on the membrane surface in **Figure 17**. Following IV injection, the membrane cloaked nanoparticles resulted in prolonging circulation, whereas the NC with magnetization and superparamagnetic core allows for magnetic resonance imaging (MRI). An immunogenic environment was created by the cooperation of Pa and Ti, which increased the amount of H_2O_2 in polarized M1 macrophages and promoted the Fenton reaction by releasing Fe ions from the NC. The hydroxyl ions (·OH) induced lethal ferroptosis that exposed tumor antigens and improved immunogenicity of the microenvironment. Together the synergism led to potential therapeutic effects and supports a promising combination modality for cancer immunotherapy.[126]

5.3.2. Adoptive Cell Therapy

Adoptive cell therapy is the removal of immune cells from a cancer patient or a healthy individual. These cells are then expanded by ex vivo procedure and injected in patients again to fight against cancer.[127] Adoptive cell therapies can use various effector cells to combat cancer. These cells include chimeric antigen receptor T cells, T cell receptor transduced (TCR) T cells, tumor-infiltrating lymphocytes, NK cells and negative T cells.[127,128] In cancer immunotherapy, adoptive T cell transfer depends on both in vivo targeting ability and ex vivo T cell expansion. To accomplish this challenge, multifunctional artificial antigen-presenting cells (aAPCs) were developed by Zhang et al. They prepared a biomimetic magnetosome as versatile aAPC by cloaking magnetic nanoclusters with azide engineered WBCM

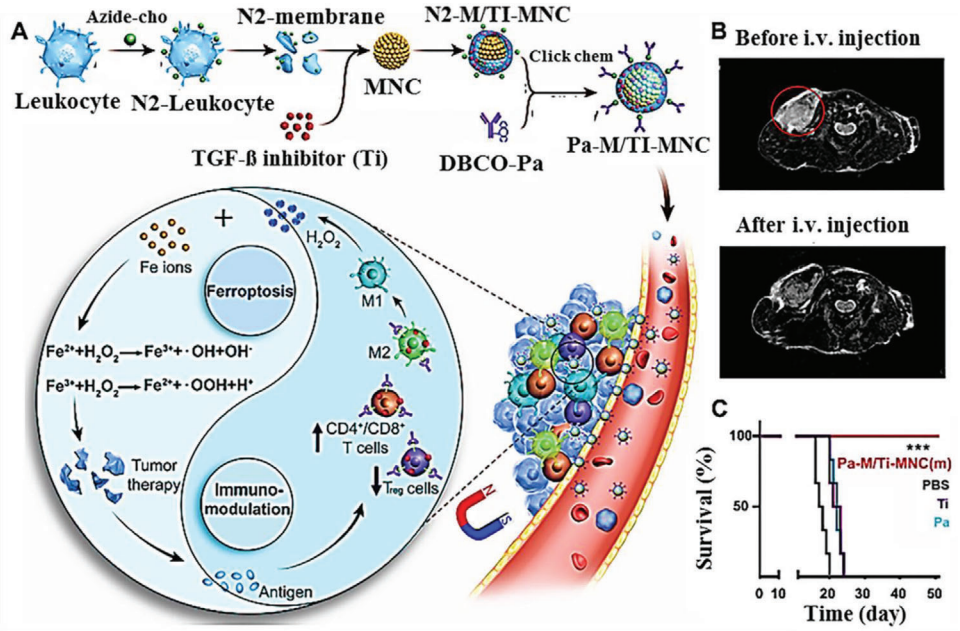

Figure 17. Biomimetic magnetosomes for immunomodulation/ferroptosis synergy in cancer. A) Diagrammatic illustration; N3-M/Ti- MNC, Ti loaded M-MNC; Pa-M/Ti-MNC, Ti-loaded and Pa-decorated M-MNC. B) T2 weighted MRI of mice before and after IV injection with Pa-M/Ti-NCs (m). C) Mice survival after treatments. Pa-M/Ti-NCs (m), Pa-M/Ti-NC with an additional magnetic field. Reproduced with permission.[120] Copyright 2019, American Chemical Society.

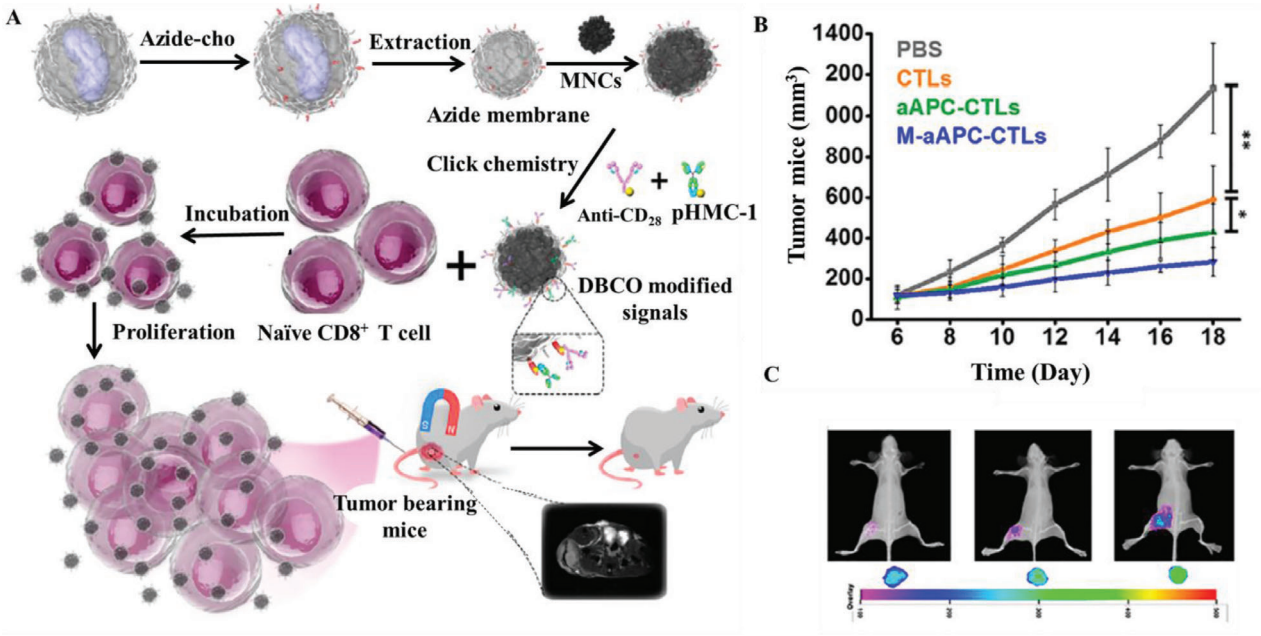

Figure 18. Biomimetic magnetosomes as aAPC for cancer immunotherapy. A) Fabrication of biomimetic magnetosome. B) Tumor size change curves. C) Visualization of the tumor-targeting ability treated with different CTL based formulations at 6 h after iv injection with DiR labeled CTLs. Reproduced with permission.[129] Copyright 2017, American Chemical Society.

as shown in **Figure 18**. The membrane was further decorated with T-cell through copper-free click chemistry. The biomimetic nano aAPCs exhibited high functionality for antigen-specific cytotoxic T-cell expansion and stimulation and effectively guided CTLs to tumor tissues via magnetic resonance imaging and magnetic control. The T cells were able to inhibit tumor growth in murine lymphoma model. This represents a significant potential of aAPC platform for T cell-based cancer immunotherapy.[129]

The aim of battling against cancer is to develop effective immunotherapy with high tumor specificity and low toxicity. For this purpose, Deng et al. developed NK cell membrane camouflaged photosensitizer TCPP loaded nanoparticles (NK-NPs)

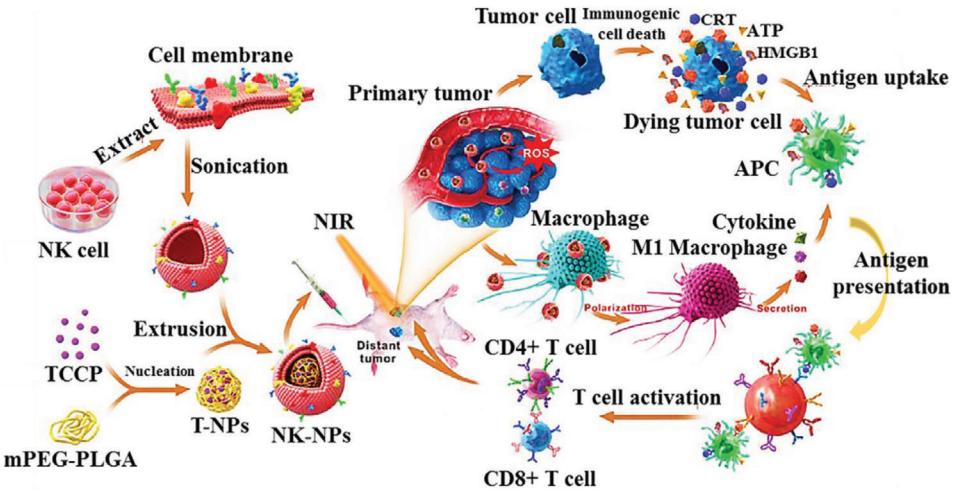

Figure 19. Schematic diagram of NK cell membrane-based nanoparticles for PDT-enhanced cancer immunotherapy. Reproduced with permission.[34b] Copyright 2018, American Chemical Society.

in **Figure 19**. This strategy was able to remove the primary tumor and inhibited distant tumors. Shotgun proteomics was performed to profile the proteomics of the NK cell membrane. The NK cell membrane enabled the nanoparticles to target tumors and enhance M1-macrophage polarization to induce anti-cancer immunity. The photosensitizer TCPP produced tumor cell death through PDT and enhanced anti-cancer immunity of the NK cell membrane. The NK-NPs was selectively accumulated in tumor with the ability to remove the primary tumor and produce an abscopal effect in distant tumors. This offers an effective membrane-based approach for tumor immunotherapy.[34b]

5.4. Platelet Cell Membrane

Many cell types are currently studied for cell-derived biomimetic nanotechnology and their properties have been investigated for cancer immunotherapy. One important cell type is platelets, also known as thrombocytes. Platelets are small, discoidal shape, non-nucleated blood cells with a diameter between 2–4 µm. These cells are derived from mature megakaryocytes in the bone marrow.[38] Platelets perform a variety of vital functions. For example, they are essential components in thrombosis and homeostasis during vessel injuries, play significant roles in the development of lymphatic vasculature and mediate adaptive or innate immune response.[130] Platelets express CD47 receptors on their surface, similar to RBCs, so they can be utilized in nanoparticles to evade the uptake by macrophages. These cells also have other surface proteins such as CD55 and CD59 that suppress the immunological complement system.[131] Thus biomimetic nanotechnology derived from platelets membrane has demonstrated to prolong circulation time and avoid clearance by the reticuloendothelial system (RES).[131b]

5.4.1. Immune Check Point Inhibitors

Platelet-based nanotechnology can be applied to immune checkpoint inhibitors in order to address the improvement in cancer immunotherapy. One biomimetic nanosystem Fe_3O_4-SAS@PLT was developed by Jiang et al. with immune evasion and tumor targeting properties, as shown in **Figure 20**. The nanoparticles can maximize the ferroptosis reaction, generate mild immunogenicity and thus enhance the response rate in cancer immunotherapy. The Fe_3O_4-SAS@PLT was prepared from sulfasalazine (SAS) loaded mesoporous magnetic nanoparticles Fe_3O_4 with a coating of platelet (PLT) membrane. These nanoparticles cause ferroptosis based cell death via inhibiting the glutamate-cysteine antiporter system Xc pathway. The Fe_3O_4-SAS@PLT mediated ferroptosis improved the efficacy of PD-1 immune checkpoint blockade therapy and inhibited the metastatic tumor in the 4T1 model. Thus the therapy could provide greater potential in the treatment of tumor metastasis.[132]

Immunotherapy with checkpoint inhibitors has a better response in several types of cancers, and it represents an ideal treatment option after surgery. Cell-based platforms have a natural ability of migration and reduce non target toxicity. They can be used to enhance the targeting efficiency of conjugated anti-PD antibodies at the desired sites. For this purpose, Zhang et al. developed engineered platelets from megakaryocytes to express the PD-1 protein as shown in **Figure 21**. The PD-1 platelet-derived microparticles were found to accumulate in tumors and this revert exhausted T cells that result in the inhibition of tumor growth. By loading Cyclophosphamide in PD-1 expressing platelets to eliminate regulatory T cells, an increasing population of reinvigorated CD8+ lymphocytes was observed in the tumor microenvironment to prevent tumor relapse. The results suggest an ideal strategy of using platelet-derived nanotechnology in cancer immunotherapy.[133]

In another study, Wang et al. conjugated platelets with anti-PD-L1 antibodies by covalent maleimide linkage that was released in response to activated platelet-derived microparticles. The microparticles possessed the characteristics to target residual cancer lesions to prevent cancer recurrence. They accumulate specifically in tumor wound and deliver anti-PD-L1 antibody to the residual tumor lesions to eliminate and inhibit tumor growth. Interestingly, platelets were capable of identifying circulating

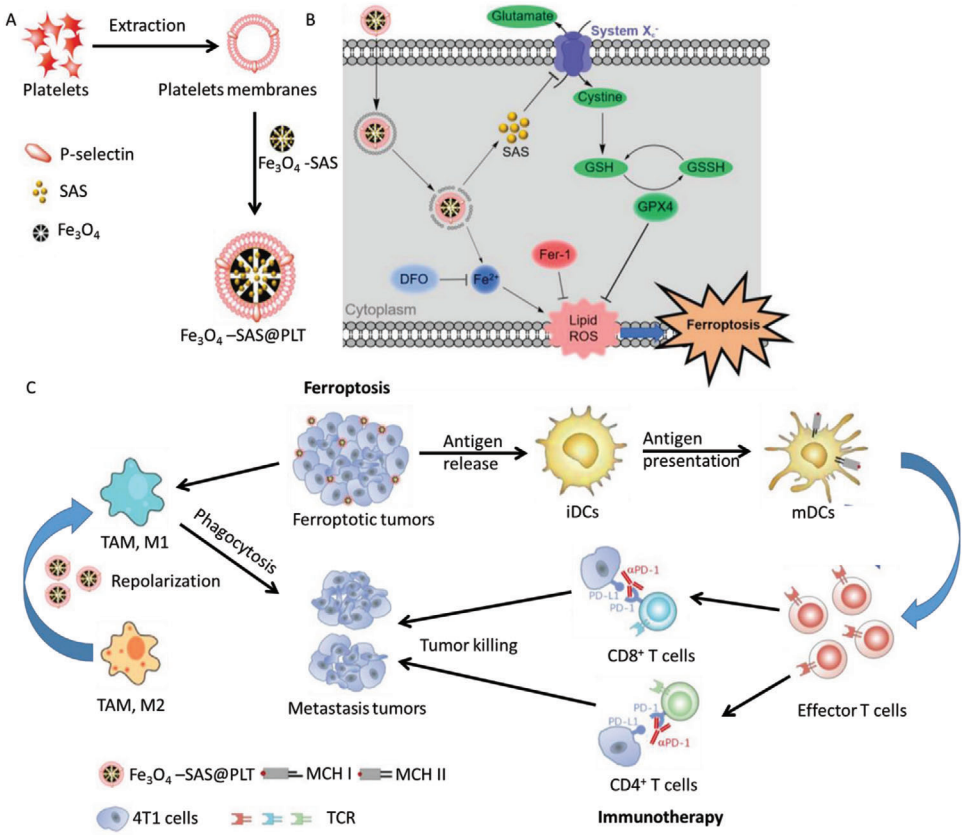

Figure 20. Schematic illustration of platelet membrane camouflaged magnetic nanoparticle for ferroptosis to improved tumor immunotherpy. A) Formulation of Fe_3O_4-SAS@PLT. B) Fe_3O_4-SAS@PLT induced cell death by ferroptosis. C) Mechanism of Fe_3O_4-SAS@PLT mediated ferroptosis improved immune checkpoint blockade in metastatic tumors. Reproduced with permission.[132] Copyright 2020, Wiley-VCH GmbH.

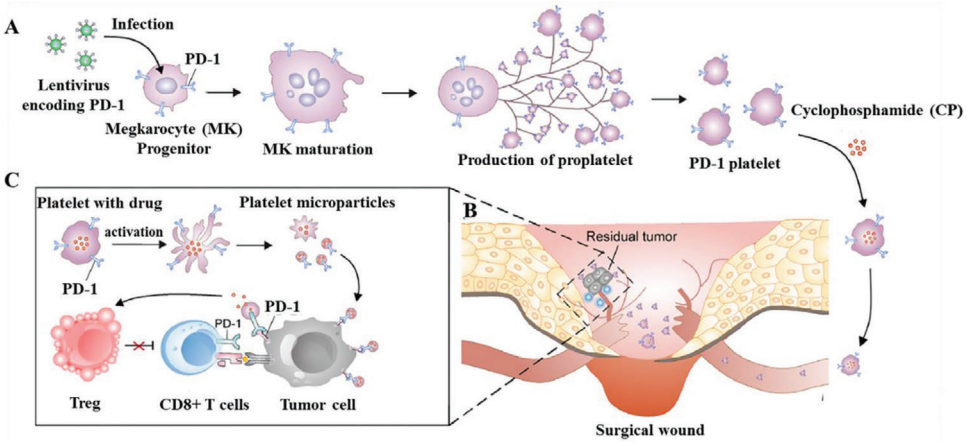

Figure 21. Preparation of PD-1 expressing platelets and reinvigoration of CD8+T cells. A) L8057 cell line expressing murine PD-1 and production od platelets. B) PD-1 expressing platelets target tumor cells within the surgical wound. C) PD-L1 blockade by PD-1 expressing platelets revert exhausted CD8+ T cells to attack tumor cells. Reproduced with permission.[133] Copyright 2018, American Chemical Society.

tumor cells (CTCs) derived from primary tumors and captured by anti-PD-L1 antibody in the bloodstream to inhibit tumor metastasis. Moreover, the activated platelets release the cytokines and boost immune cells to develop a pro-inflammatory environment and enhance the function of immune cells in combination with anti-PD-1 therapy. In short, the platelet conjugated anti-PD-L1 demonstrated better response and lower off-target toxicity.[54]

The research also demonstrated that platelets based anti-PD-L1-based carriers could migrate and distribute in physically treated tumors, i.e., PDT, PTT, ultrasound, or radiotherapy. Thus

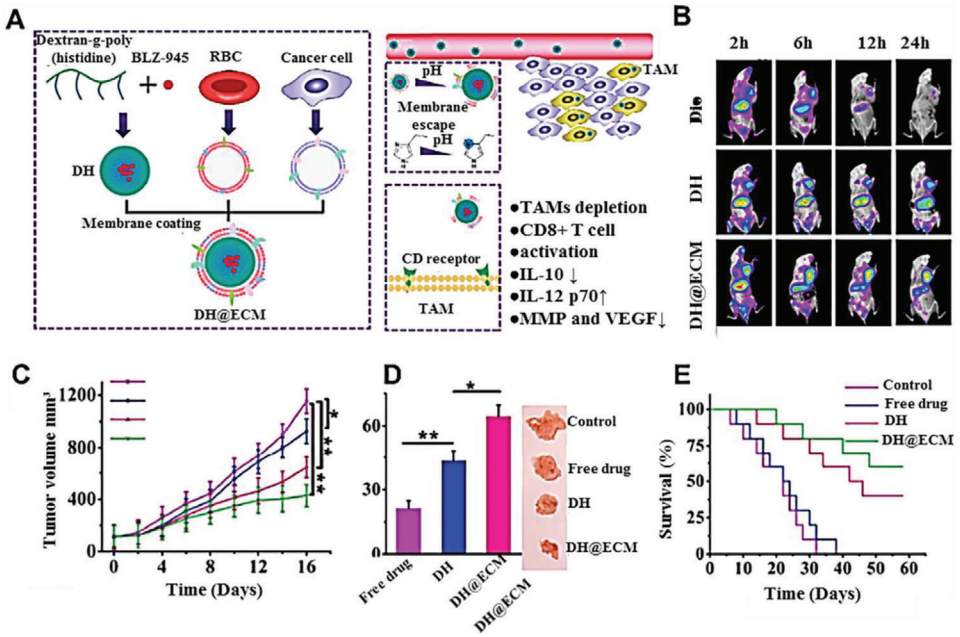

Figure 22. A) Diagrammatic illustration of RBC-cancer cell hybrid membrane wrapped pH-sensitive micelle for cancer immunotherapy. B) In vivo biodistribution images in tumor bearing mice. C) Tumor volume changes of different formulation in 4T1 tumor bearing mice. D) Tumor images and inhibition rate of different preparation. E) Survival rate curve of different preparation groups against 4T1 tumor-bearing mice. Reproduced with permission.[137] Copyright 2019, Elsevier.

it could further improve the biomimetic application of nanotechnology in personalized therapy.[134]

5.5. Hybrid Membrane

The cell types discussed previously to highlight the unique properties that can be utilized in cell-based biomimetic nanoparticles. Recently, the desire for the development of nanoparticles with multiple functionalities from different cell types has increased. In order to prove the concept, much work has been done in which modified nanoparticles with two cells hybrid membrane were used to achieve enhanced functionality.[135] The first dual membrane was developed by incubation of two pure membranes with mild agitation at 37 °C. Forster resonance energy transfer (FRET) pairs can be used to label the membrane in order to confirm the hybrid membrane in one nanoparticles.[135] Earlier, the hybrid membrane composed of platelet and RCM was used to cloaked PLGA nanoparticle. The biomimetic nanoparticle resulted in enhanced colocalization of two dyes observed through fluorescence microscopy. This indicated that the nanoparticles contain both types of membranes. The physicochemical properties of the dual membrane cloaked nanoparticles were similar to both membrane-based preparations and demonstrated characteristic core–shell morphology. Moreover the hybrid membrane was stable in aqueous medium, phosphate buffer, and serum and even after lyophilization.[38] Hybrid membrane-bound nanoparticles have the property to retain the macrophage uptake-suppressing property of both cell types. Also, it binds preferentially to cancer cells, similar to single membrane coated nanoparticles.[38]

Similarly, Zhang and co-workers fused membrane material from RBCs and melanoma tumor cells to the advantage and homotypic targeting ability of the membrane. They coated the membrane over doxorubicin-loaded copper sulfide nanoparticles for the combination therapy of melanoma. The resulted hybrid wrapped nanoparticles preferentially recognized the source cells, with prolonging circulation life and achieve specific targeting of homologous cancer cells in vivo that lead to the complete removal of cancer cells.[56b] The dual characteristic came from both the membranes. RBCM prolongs the circulation life because of self-markers such as proteins, glycans, and sialic acid that suppress the immune attack.[136] Whereas, cancer cell membrane increases the homologous binding.[56b] Thus the hybrid membrane from RBCs and cancer cells possess the immune camouflaged and tumor-targeting ability.

Taking advantage of the hybrid membrane, Wang et al. designed hybrid membrane cloaked pH-sensitive micelle based on RBCs and cancer cell membrane as shown in **Figure 22**. The micelle was fabricated from copolymer dextran-grafted-poly histidine loaded with colony-stimulating factor-1 receptor (CSF-IR) inhibitor BLZ 945. The nano micelle (DH@ECm) targeted the tumor-associated macrophages (TAM), a potential target for cancer chemotherapy. The micelle possessed a suitable particle size of 190 nm with immune camouflaged and tumor targeting ability after intravenous administration. In the acidic tumor microenvironment, the micelle showed membrane escape effect to facilitate recognition and interaction with TAMs. DH@ECm also reverses the tumor-immune system and elevated CD8+ T cells, thus possess sufficient cancer immunotherapy potential with a 64% inhibition rate.[137] Altogether, a wide range of cell types is available to design hybrid membrane coated biomimetic nanoparticles for the use in cancer immunotherapy. Special considerations are needed to be taken while choosing multiple types of membrane in different applications.

Table 2. Summary of cell membrane-based biomimetic nanoparticles for cancer immunotherapy.

Types of cell membrane	Core material	Applications	References
RBCM	Nanoerythrosome	Reduced tumor recurrence and metastasis after surgery, cancer immunotherapy	[96]
	Black phosphorus quantum dot	PTT, cancer immunotherapy	[97]
	Hyaluronidase-responsive nanoparticles	Metastasis, PDT, cancer immunotherapy	[98]
	PLGA nanoparticles	Cancer immunotherapy, tumor metastasis	[32]
	Red blood cell-based artificial antigen-presenting cells interleukin-2	Cancer immunotherapy	[30b]
	Nanogel	Improved drug penetration, induction of calreticulin exposure, Cancer immunotherapy	[108]
Cancer cell membrane	PLGA nanoparticle	Anticancer vaccination and drug delivery	[42a]
	Silicon nanoparticle	Cancer immunotherapy	[114]
	Nanoliposome	Cancer immunotherapy	[116]
	PLGA nanoparticle	Multiantigenic antitumor immunity	[117]
	Mesoporous silica nanoparticles	Starvation therapy and cancer immunotherapy	[113]
	PLGA nanoparticle	Anticancer vaccination	[121]
	PLGA nanoparticle	Cancer immunotherapy	[118]
	Cyclodextrin nanoparticle	Tumor immunotherapy and metastasis	[118]
WBCM	Fe_3O_4 magnetic nanocluster	Ferroptosis/immunomodulation synergism for anticancer therapy, cancer immunotherapy	[126]
	Magnetosomes	Cancer immunotherapy	[129]
	Natural killer nanoparticle (NK-NPs)	PDT, cancer immunotherapy	[34b]
Platelet membrane	Mesoporous magnetic nanoparticles	Cancer immunotherapy, tumor metastasis	[132]
	Genetically engineered platelets- PD-1	Cancer immunotherapy	[133]
	Conjugation of anti-PDL-1 onto the surface of platelets	Reduce post-surgical tumor recurrence and metastasis, post-surgical cancer immunotherapy	[54]
Hybrid membrane	Micelle	Cancer immunotherapy	[137]

Overall, the cell-derived biomimetic nanoparticles have shown greater potential in cancer immunotherapy. The summary of this biomimetic approach is shown in **Table 2**.

6. Conclusion and Future Prospects

In this review, we highlighted cell membrane-derived biomimetic nanotechnology and its applications in cancer immunotherapy. Cancer immunotherapy has shown its efficacy in many cancer types. However, only a limited number of patients exhibit positive responses. In order to broaden its application, the use of nanoparticulate systems represents an attractive strategy to enhance the efficacy of immunotherapeutics by targeting and increase accumulation in tumor tissues. Most recently, novel types of biomimetic platforms have emerged to further improve the nano-drug delivery system for cancer immunotherapy. Membrane coating from different source cells presents a facile means of introducing multiple functionalities onto the same nanoparticle without the need for complicated synthetic techniques. The cell membrane cloaking of nanoparticles innovatively decreases the gap between synthetic nanomaterial and biological systems to further inspire the cancer immunotherapy approaches with a biological perspective. In cancer immunotherapy, biomimetic nanoparticles potentiate the immune response and easily target it to antigen-presenting cells to achieve potent inhibition of tumor growth. The cell membrane coating also provides unique properties such as prolonging blood circulation, RES escape, and tumor-specific targeting to the nanoparticles.

In theory, biomimetic nanotechnology-based cancer immunotherapy represents an attractive option, but in practice, there are many challenges to be overcome to achieve widespread clinical applications. Generally, it is difficult for the immune system to generate potent responses against established tumors. With the help of optimized biomimetic nanoparticles, researchers can explore the design of novel formulations to elicit an immune response for overcoming tumor immunosuppression. Cell membrane-derived biomimetic nanotechnology has many advantages for in vivo drug delivery and regenerative medicine for cancer immunotherapy. In the future, unique methodology can be utilized by introducing comprehensive biological moieties and functions that will possess synergistic behavior and enhance the performance of biomimetic nanoparticles. For example, ligands composed of antibodies, peptides, and proteins can be incorporated into cell membranes to improve functionality in cancer immunotherapy. Dual membrane approaches are also used for further increasing the behavior of biomimetic nanoparticles such

as homotypic targeting, prolonged circulation and evade immune response. On the other hand, stimulus sensitive agents can be fabricated over cell membrane surface by facile means to develop nanoparticles with responsive behavior. Similarly, phototherapy is also be accessed by the biomimetic approach to enhance the therapeutic performance. The cell membrane biomimetic nanotechnology is limited by various factors such as complex preparation methods, low yield, low synthesis scale and difficult preservation. Hence these factors should be considered and improved more in the future. Cell membrane-based nano-immunotherapy should be evaluated in terms of the integrity of cell membranes, optimize the circulation of nanoparticles in blood and prolong biological effects. The nucleus and genetic material of source cells should be separated from the cell membrane, especially in cancer cells. The researcher should focus on the translation of biomimetic nanoparticles from synthesis to clinical applications. Looking toward clinical translation, the main task is to scale up the biomimetic nanoparticles production and efficiency in a cost-effective manner. The workflow also needs to be aligned with acceptable manufacturing practices to meet the quality requirements for regulatory approval. Significant work is required in order to evaluate the synergy between biomimetic nano-immunotherapy and other types of modalities against cancer. Finally, the biomimetic nanomedicine should be tailored in such a way to develop personalized cancer immunotherapies.

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Conflict of interest

The authors declare no conflict of interest.

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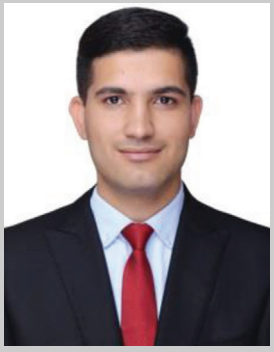

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