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T-cell Membrane-Coated Nanomaterials in Cancer Treatment

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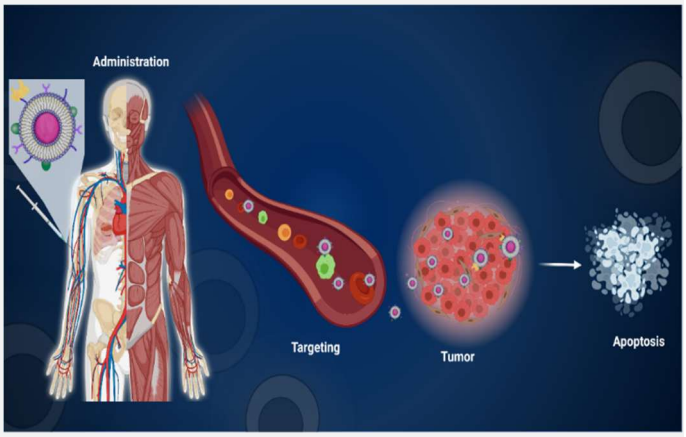
ABSTRACT



To date nanoparticles (NPs) have been widely explored for their use in cancer. These are classified as highly efficient drug delivery systems because of their exceptional properties and design flexibility that rendered them highly targeted and safe. However, nanoparticles still face challenges regarding biological stability, non-specificity, recognition as a foreign substance, and speedy clearance that limits their applications in clinical use. To overcome these drawbacks, advanced biomimetic nanotechnology has been proposed using T-cell membrane-coated NPs as superior drug delivery systems which can increase their circulation time and prevent rapid clearance from the body by the immune system. The immune T-cells have specific surface proteins that transfer unique functionality to biomimetic NPs during the membrane extraction and coating process. Such proteins on the T-cells surface provide the nanoparticles various advantages including prolonging circulation, increasing the range of drug targets, controlled release, specified cellular interaction, and limited in vivo toxicity. In this review, T-cell membrane-based biomimetic nanosystems, their detailed extraction process, fabrication, coating over NPs, and the applicability of these biomimetic systems in cancer treatment are discussed. In addition, recent applications, future perspectives, and current challenges for their clinical translation are also presented.

Keywords: Cancer therapy, T-cell- decorated nanoparticles, T-cell membrane-coated, Trojan horse nanoparticles

1. Introduction

Cancer is the leading cause of mortality globally [1-5]. Although cancer therapy has improved over time, the rate of tumor recurrence and distant metastasis remains high, and cancer patients' prognoses have so far not improved [6-9]. Local treatment approaches such as surgical procedures and excision therapy cannot remove lingering tumor cells in the circulation. In contrast, systemic treatment options, including chemotherapy are hampered by variables such as cancer cells' poor responsiveness [10, 11]. Regional relapse and distant metastasis are nevertheless common, and patients with liver cancer have a dismal prognosis [12-18]. Also, the coating of the membrane and possible changes, such as the hybrid membrane of platelet-leukocyte and membrane of erythrocyte, may provide exceptional tumor-targeting abilities [19-26]. Unlike the native T-cell receptor, chimeric antigen receptors (CARs) give T-cells predefined properties of antigens that target malignancies. Single chain variable region (ScFv) generated using monoclonal antibodies produced on the CAR-T cells membrane may precisely detect cancer cell antigen and kill tumor cells in a non–major histocompatibility complex-restricted manner CAR-T cells. Recent breakthroughs in CAR-

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T cell treatment for CD19-positive hematopoietic tumors have emphasized the therapy's potential to treat solid tumors [27-29]. However, due to specific hurdles, this amazing therapeutic impact was not demonstrated when CAR-T cell treatment was applied to solid tumors [30-32]. Prolonged survival of CAR-T cell transit to tumor sites and tumor locations is also required. The combination of CAR-T cell treatment with cell membrane coating can be a potential technique due to its high specificity and selectivity [33].

Herein, the properties and function of the T-cell were introduced. In order to determine the types of nanomaterials, membrane fabrication techniques, core particles, and their uses in medical contexts, cell-specific targeting with membrane coating is presented. The principles of several cell membrane coating processes are then described along with preparation techniques. These procedures include T-cell membrane extraction and wrapping of T-cell membrane over nanoscale compounds. Then, the biomedical application of these nanosystems in cancer therapy was represented. Finally, the challenge and limitations of clinical translation were discussed. We hope to compile a thorough analysis of T-cell membrane-coated NPs for chemotherapy that targets specific tumors.

2. T-cell: Biology and functions

T-cells are required for the production and persistence of immunological responses, homeostasis, and memory. T cells have a receptor that can identify a variety of antigens in microorganisms, tumors, and the environment, along with maintaining immunological memory and tolerances. T-cells are also thought to have a role in a variety of inflammatory and autoimmune disorders. The functional involvement of T-cells in immunity and immunopathology and the underlying processes involved have mainly been explored using mice models, contributing to the emergence of immune-based therapy in humans [34]. T lymphocytes are progenitors of bone marrow (BM), which gets mature in the thymus and then are transported to peripheral tissues. Peripheral T-cells have different subgroups, including naive T-cells, that can respond to various antigens and memory cells. When naive T-cells contact antigen and co-stimulatory linkers displayed on dendritic cells (DCs), they produce different cytokines, which then travel to numerous locations to enhance pathogen removal by producing cytokines and toxins [35]. Activated effector cells have a shorter life span, but some survive as memory-T cells, which may be divided into different subsets depending on motility, tissue distribution, and self-renewal abilities. Although their origin and lineage connection are unknown, memory subsets can play a role in sustaining prolonged immunity and remembering protective responses [35].

The function of T lymphocytes in immunological responses and at various stages of life is not consistent throughout the body. T-cells can be found in lymphatic tissues, exocrine, mucus and barrier sites, fat, and the brain. Lymphoid organs such as the spleen, tonsils, and BM contain the bulk of T lymphocytes in the human body. High quantities can also be detected in mucosal locations such as the intestine, lungs, and skin, while peripheral blood contains around 2%–3% of the total T-cell component [36]. T-lymphocyte cells destroy emerging tumors and intracellular pathogens such as some bacteria and viruses and regulate the strength of adaptive immune responses and define by the profile of cytokines they secrete[37]. Newly created naïve-T cells and T-reg cells fill key lymphatic and mucosal sites early in development. Memory T-cells grow mostly in mucosal locations such as the intestinal tract and lungs [38]. Memory T-cells become the main subgroup all across the body after infancy; nevertheless, memory T-cell storage in lymphatic tissues begins at a slow rate compared to mucosal and barrier regions [38].

Lymphocyte classification is according to specific markers that are present on their surfaces and known as Cluster of Differentiation (CD), which are more than 300 types, and also contain T-Cell Antigen Receptors (TCRs)[39, 40]. The T-cell production starts from progenitor cells containing expressed biomarkers (CD7, CD5, CD2, and cytoplasmic CD3) which can enter the cortex of the thymus. The rearrangements of α, β, γ, and δ chains result in T-cells with αβ-chains (T-αβ) and T-cells with γδ-chains (T-γδ). The T-αβ and T-γδ cells can be characterized for CD3 and the αβ-TCR or γδ-TCR respectively. At this stage, NK-T cells arise from the precursor T-cells expressing CD3 by expressing a specific α-chain which pairs via a β-chain interaction with glycolipid-CD1d. Upon development, NK-T cells acquire the expression of CD56. However, precursor T-cells express minimal levels of CD3 on their surface and undergo a fast transition, where for expression first CD8 and then CD4 are required. As CD8 expression occurs before or after rearrangement of the TCRs, the separation of T-γδ cells from the αβ-path takes place, resulting in approximately 30% of the T-γδ cells being CD8+. The CD4+CD8+ double-positive T-αβ cells continue their development by undergoing

positive selection via interaction with either peptide-MHC I or peptide-MHC II complexes, resulting in a single expression of CD8 or CD4 respectively. Thereafter, T-αβ travels to the medulla from the thymic cortex, where they undergo negative clonal selection to remove T-cells that have a high-affinity interaction for self-antigens. Finally, mature single-positive CD4+ and CD8+ T-αβ cells are released into the blood [41].

After binding to antigen, T lymphocytes proliferate and give rise to different types of T-cells, including some killer- T cells and some memory-T cells. Killer-T cells directly attack virus-infected cells and cancer cells, and by producing a special protein called perforin, they create pores in these cells and cause their death. There are many T-cell subsets each of which has a different and related activity. It is divided into different types of cells such as Th1 (T-helper), Th2, Th3, Th9, T-Cytotoxic and regulatory-T cells, each of these cells has a special function in the immune system that is different from other lymphocytes. T-cells are regulatory cells in the immune system that play an important role in cancers, autoimmune diseases, and infectious diseases. The two main subtypes of regulatory-T cells (T-reg) consist of (I) natural T-reg cells (tT reg or nT reg) that are generated in the thymus during maturation and their suppressive activity is necessary to establish and maintain immune homeostasis in a stable state (**Figure 1A**). (II) Inducible T-reg (iT reg) cells that arise from incipient T-cells following self-antigen recognition outside the thymus (**Figure1B**) [42].

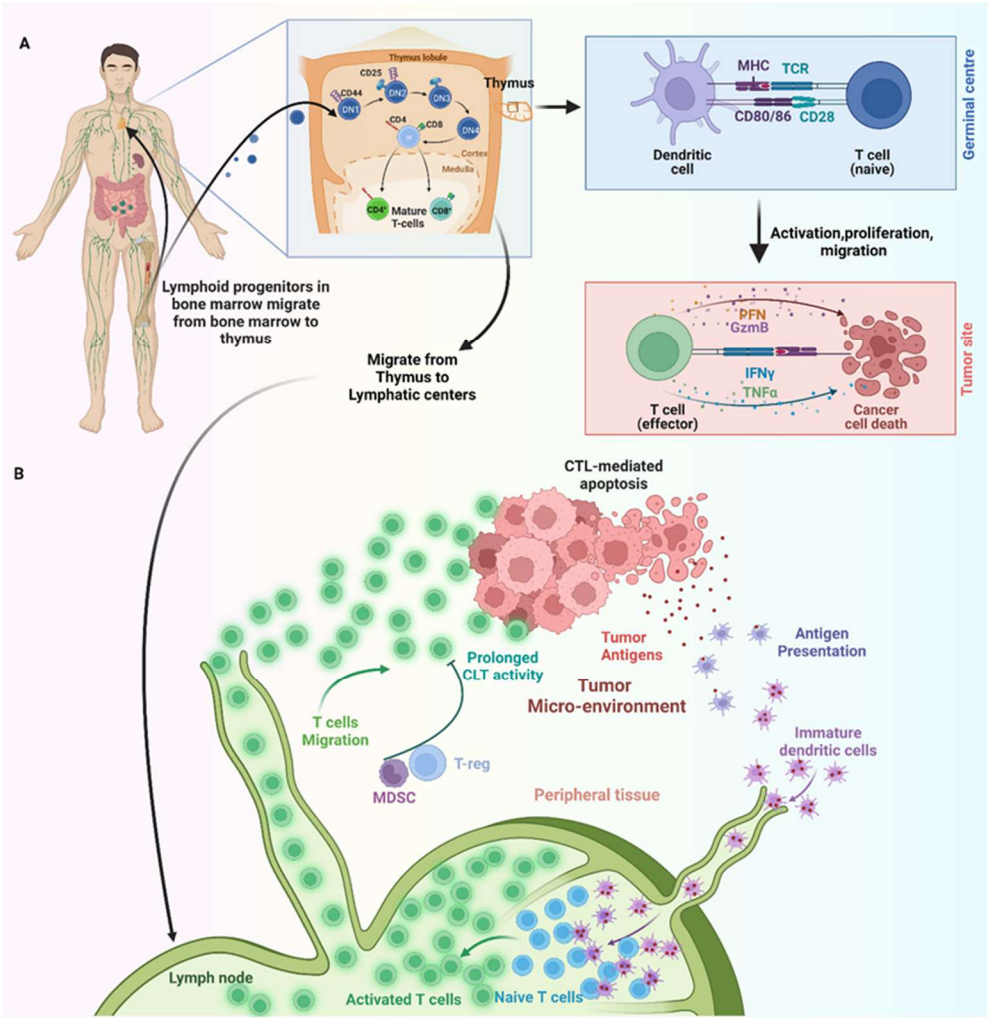

Figure 1 (**A**) T-cells development by lymphoid progenitors migration from Bone marrow to the thymus. (**B**) Naive T-cells continuously recirculate through secondary lymphoid organs such as lymph nodes, the spleen, and the tonsils, until they are finally activated by recognizing cognate MHC complexes/peptides on the surface of antigen-protecting cells.

Adoptive T lymphocyte transfer is a promising approach for cancer immunotherapy having genetically modified chimeric antigen receptor (CAR). Such chimeric antigen receptor T cells when targeted to the tumor surface recognize

the surface antigens independently and kill the tumor cells upon antigen contact [43]. CARs are composed of an external binding domain, one or more intracellular signaling domains, a hinge region, and a transmembrane domain. The most commonly used binding domains are antibody fragments (single-chain variable fragments (scFvs)) such as the B cell molecule CD19. Intracellular signaling domains of CARs consist of the CD3ζ chain.

While, co-stimulatory domains (e.g., CD28 and/or 4-1BB) are also present in second or third-generation chimeric antigen receptors to improve cell proliferation, resistance to apoptosis, cytokine secretion, and in vivo persistence. Third-generation CARs exhibit improved effector functions and in vivo persistence as compared to second-generation CARs. The fourth-generation CARs, also known as armored chimeric antigen receptors or T-cells redirected for antigen-unrestricted cytokine-initiated killing (TRUCKs), combine the expression of a second-generation CAR with factors such as co-stimulatory ligands, cytokines, or enzymes that enhance the anti-tumoral activity [44, 45].

3. Fabrication of T-cell membrane-coated nanoparticles

A crucial step in the extraction of T-cell membrane vesicles from cells is cell rupture or lysis. The lysate is prepared by rupturing the cell. There are two primary categories of cell lysis procedures: chemical and mild cell lysis techniques (such as chemical lysis and osmosis), and harsher protocols (e.g., pressure, mechanical and ultrasonic homogenization, and pistil and mortar [46-48]. Chemical lysis doesn't involve crushing or scraping and uses buffers, salts, detergents, and enzymes. When selecting a cell lysis method, there are numerous things to take into account. The cell type is the major factor. In particular, the studies indicate using sonication, extrusion, hypotonic treatment, and microfluidic electroporation to remove the cell membranes from RBCs (erythrocytes). The separation of cellular membrane vesicles from platelets has been carried out using sonication or multiple freeze-thaw procedures. The second element is the location and nature of the relevant proteins that may be peripheral or integral. Most extracting techniques aim to get a cell membrane with completely operational proteins. For big cell aggregates or tissue fragments, mechanical lysis is typically advised. Mechanical homogenization, which traditionally involves freezing tissues and then grinding them with a pestle and mortar to produce lysate uses direct physical restraint to produce lysate [49, 50]. The second phase includes overlaying the cell membrane vesicle onto NPs once the T-cell membrane has been removed from the source cell. The objective is to give NPs improved bio-interacting abilities. Recent years have seen a variety of coating techniques proposed. One of the most popular techniques involves physically extruding the pure membrane and NPs cores through a porous membrane. The mechanical force applied through the extruder results in the fusion of particles and vesicles. The extrusion is followed by a centrifugation process to remove the uncoated vesicles and the precipitate represents the final product [6, 39, 40]. Another option is to use sonication-based methods, which apply an ultrasonic-based destabilizing force to two components to create core-shell nanomaterials. Among the other methods suggested are a microfluidic device and in situ coating of NPs [51, 52].

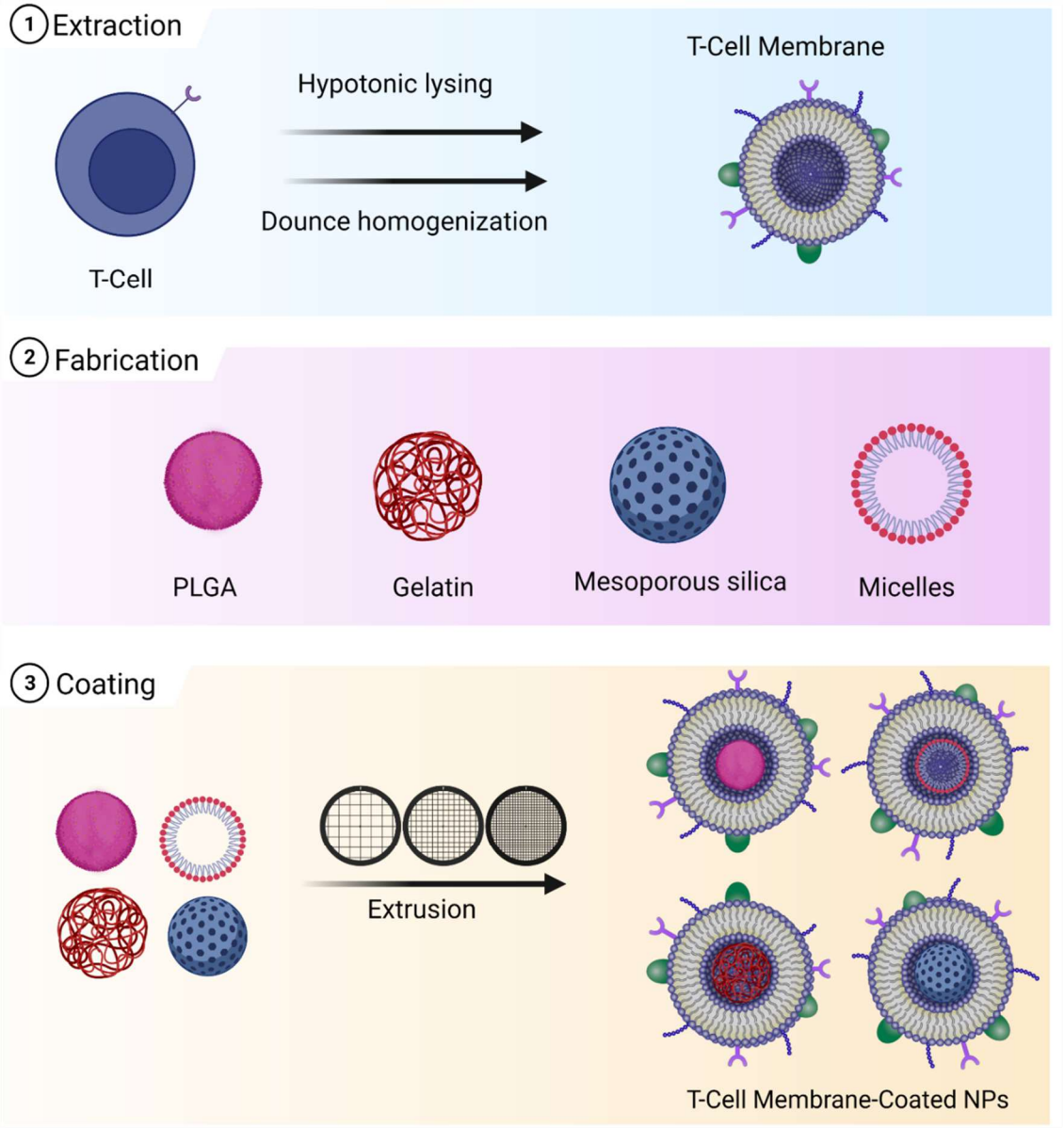

Figure 2 Schematic illustration of the process to manufacture T-cell membrane-coated NPs. This process consists of three steps including (**1**) extraction of the cell membrane, (**2**) fabrication of the core nanoparticle, and (**3**) coating of the nanoparticle with the cell membrane.

4. Cancer therapy

Due to the retention of intricate natural features of the donor cells, cell membrane-cloaked NPs have evolved as potential vehicles to target tumors [53]. T-cells have distinct targeting characteristics compared to other cells [54], which can be exploited to target tumors [55, 56]. Activated T-cells can display a strong affinity for tumors owing to the presence of specific immune detection molecules, such as T-cell receptors (TCRs), on their membranes. These molecules enable T-cells to identify associated chemicals on the tumor surface [57, 58]. Using T-cells' immunologic recognizing characteristics, their membrane might be viable for nano drug delivery to tumors [59]. This section provides a summary of recent advances in research on biomimetic T-cell membrane-coated NPs for cancer therapy. Based on the strategy of cancer therapy, we categorized these nanotherapeutics into four groups: (I) cancer chemotherapy; (II) cancer immunotherapy; (III) cancer photothermal therapy; and (IV) combinatorial therapy.

4.1. Chemotherapy

Despite breakthroughs in the development of cancer chemotherapeutics, it is becoming abundantly clear that cytotoxic chemotherapies will continue to be the cornerstone of cancer care [59]. However, existing chemotherapies are associated with nonspecific drug distribution, resulting in (off-target) unwanted effects and associated toxicity, which commonly restrict their effectiveness [60]. This necessitates a new paradigm in the treatment mode and the invention of newer therapeutic strategies. Therefore, to enhance chemo-drug therapeutic efficiency and address these mentioned constraints, novel multifunctional biomimetic NPs have been designed to efficiently target and treat cancer. These multifunctional nanocarriers are based on the T-cell membrane-cloaking approach and they have the potential to revolutionize the chemotherapy of various cancers. However, to the date of this review, only single research has been done in this chemotherapeutic domain [61].

According to the American Cancer Society, melanoma is among the deadliest skin diseases, with one person dying from it every hour. Since several treatments for melanoma are currently available (e.g., surgery, chemotherapy, immunotherapy, and radiation therapy), they all have drawbacks, including poor response rates, high toxicity, severe side effects from non-specific anticancer drug targeting, and the evolution of multidrug resistance over time. A multifunctional nanoparticle has been designed to efficiently target and treat melanoma to increase therapeutic effectiveness and overcome the aforementioned constraints. A cellular membrane with a melanoma-specific anti-gp100/HLA-A2 T-cell receptor (TCR) (19LF6) produced from a T-cell hybridoma was coated on PLGA NPs containing Trametinib, a chemotherapeutic medication (**Figure 3**). Trametinib-loaded PLGA NPs that were camouflaged with T-cell membranes showed excellent stability, hemocompatibility, and cytocompatibility. It was also discovered that drug release patterns from NPs are affected by membrane coating, with the greatest sustained-release corresponding to the amount of membrane utilized. Compared to the plain NPs, 19LF6 membrane-coated NPs generated a threefold increase in cellular absorption toward the melanoma cell lines *in vitro*. Furthermore, the binding kinetics and cellular absorption were found to be membrane/TCR concentration-dependent. These NPs had much greater *in vitro* cancer-killing efficiency than other nanoparticle groups, and their binding and uptake properties matched. When compared to free drugs and negative controls, particles having a higher membrane content are more effective. Theragnostic properties of these NPs were demonstrated using *in vivo* biodistribution experiments, with a more than two-fold increase in tumor retention compared to other groups. Based on these findings, T-cell membrane-bound NPs appear to be a promising theragnostic carrier for melanoma imaging and therapeutic applications [61].

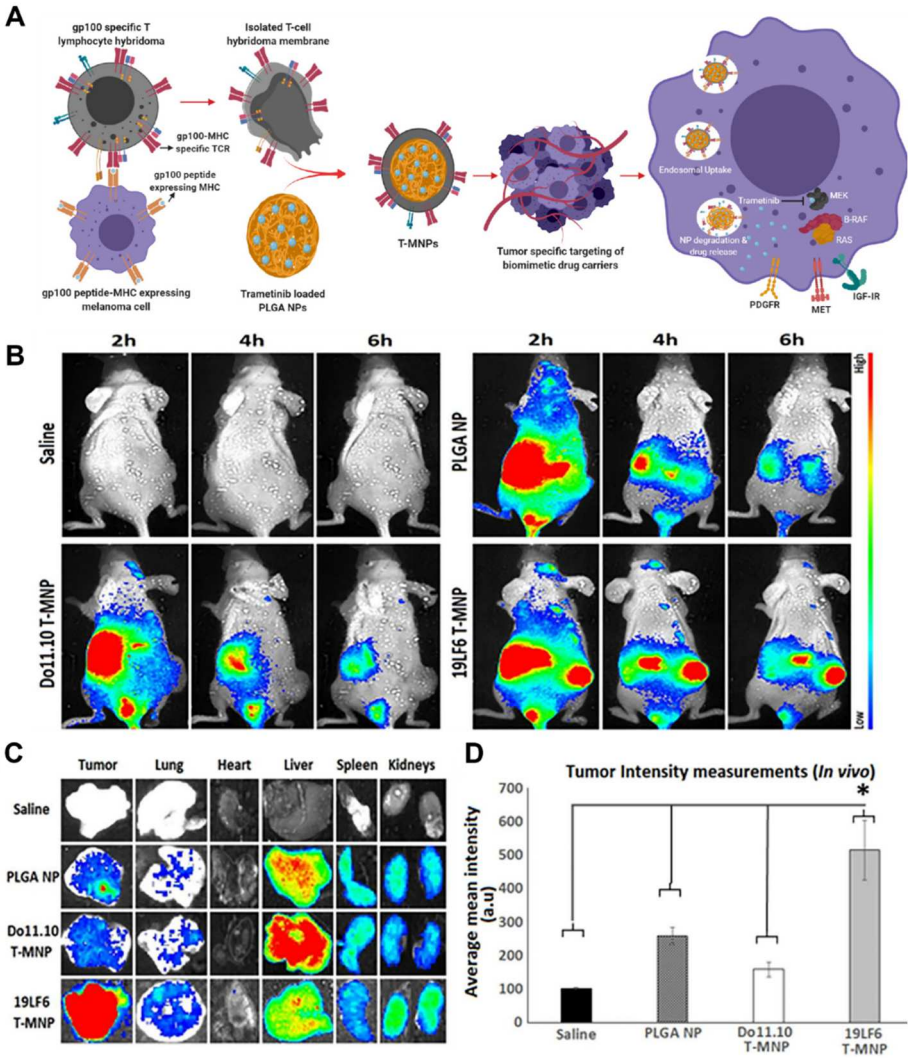

Figure 3. Schematic diagram of T-cell coated nanoparticles for melanoma. **A)** Graphical illustration of T-MNP. **B)** Real-time tumor targeting characteristics of IV injected NPs on melanoma tumor models. **C)** *Ex vivo* organ images of biodistribution in different study groups. **D)** Measured fluorescent intensity of *in vivo* biodistribution study groups in tissue homogenates. Reprinted from [61] with permission from Frontiers.

4.2. Immunotherapy

Immuno-oncology (cancer immunotherapy) is a treatment approach that aims to restore the immune system's ability to recognize and reject malignancy [62]. Immunotherapy is seen as a potential new era of therapy due to its ability to destroy cancer cells with more selectivity and less toxicity than traditional treatments. Unfortunately, despite its promising outcomes in the treatment of tumors, cancer immunotherapy still confronts a number of obstacles, which are mostly attributable to tumor heterogeneity, immune cell dysfunction, immunotherapy resistance, and immunotoxicity. Consequently, it is crucial to maximize the efficacy and safety of tumor immunotherapy [63].

Recent trends in cancer immunotherapy have focused on developing T-cell membrane-based nanomaterials. Targeting this goal, Kang *et al.* designed T-cell-membrane-coated NPs (TCMNPs) for immunotherapy to overcome some of the obstacles to existing cancer therapies (**Figure 4A**). TCMNPs, like cytotoxic-T cells, target tumors with T-cell-membrane-derived protein and destroy cancer cells by releasing antitumor chemicals and causing Fas-ligand-mediated death. TCMNPs, unlike cytotoxic-T cells, are impervious to immunosuppressive chemicals (e.g., TGF-1) and programmed death-ligand 1 (PD-L1) produced by cancer cells by eliminating TGF-1 and PD-L1. In the therapy of melanoma, TCMNPs are more effective than immune checkpoint blocking. Dynamic light scattering, electrophoretic

spectrophotometry, and transmission electron microscopy were used to characterize TCMNPs' physicochemical properties. TCMNPs' hydrodynamic size distribution increased slightly, but their surface zeta potential declined compared to uncoated PLGA NPs (**Figure 4B**). TCMNPs had a typical spherical core-shell structure when observed by TEM (**Figure 4C**). Nitrogen (N) and phosphorus (P), which are components of plasma membranes, were exclusively identified in the membrane section of TCMNPs (**Figure 4D**). Following NPs coating, fluorescent confocal pictures revealed that TCMNPs included both the plasma membrane and PLGA NPs, and the colocalization survived intact after therapy to B16F10 cancerous cells (**Figure 4E**). T-cell membrane proteins were well retained on TCMNPs, but those on trypsin-pretreated T-cell-membrane-coated NPs (trTCMNPs) were decreased (**Figure 4F**). TCMNPs were shown to have anti-tumor effects in the treatment of lung cancer. TCMNPs carrying T-cell membrane proteins can operate as a T-cell camouflage nanoparticle and boost cancer immunotherapy [64].

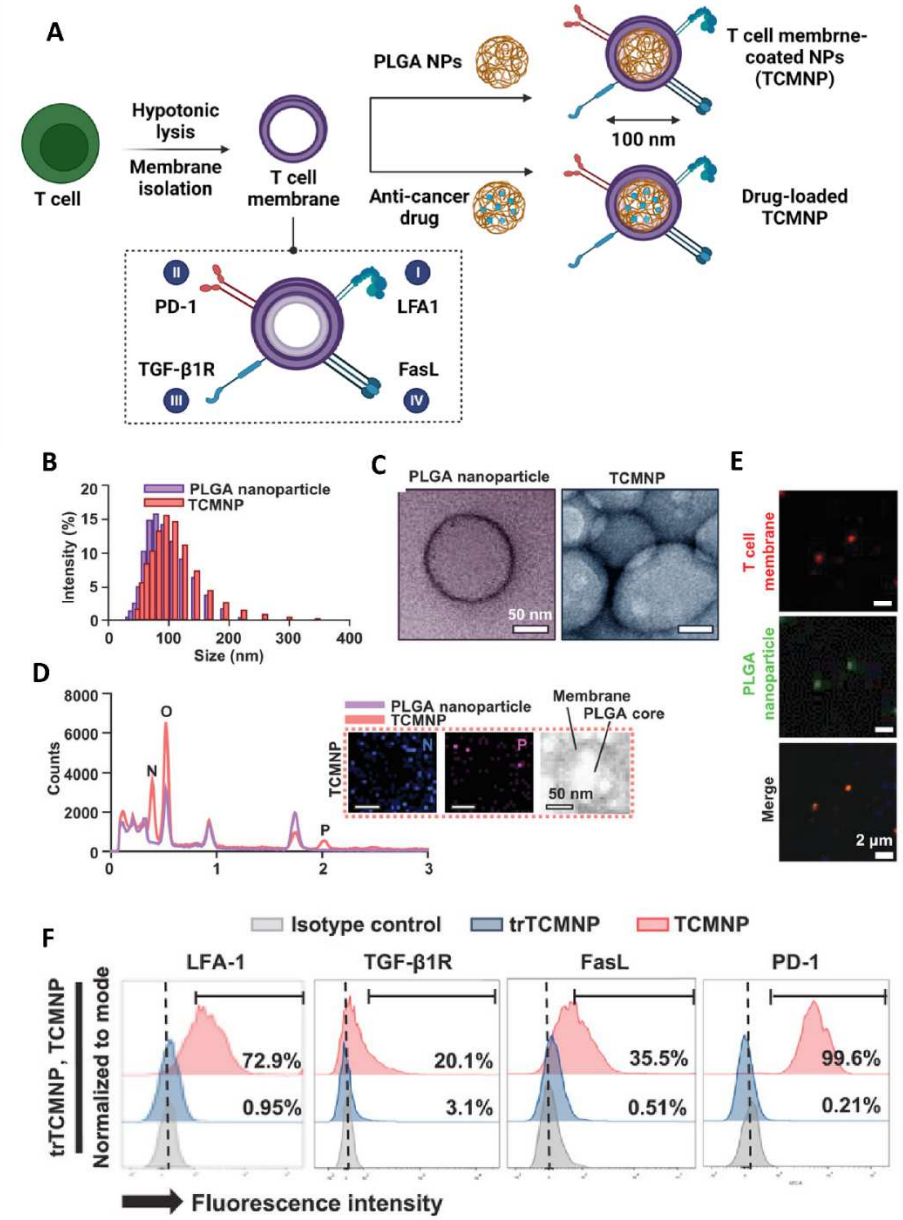

Figure 4. Production and suggested therapeutic mechanism of TCMNPs. **A)** Preparation of NPs. **B)** Size analysis. **C)** TEM analysis. **D)** Energy dispersive spectroscopy of NPs. **E)** Confocal laser microscopy. **F)** Flow cytometry Reprinted from [64] with permission from Wiley

Macrophage immunomodulation against tumors has been recognized as a highly potential treatment option. However, appropriately engaging macrophages for antitumor immunotherapy has two fundamental obstacles. First, binding macrophage signal regulatory protein alpha (SIRP) to CD47, a "don't eat me" signal on cancer cells, hinders phagocytosis of cancerous cells. Secondly, tumor-associated macrophages (TAMs) are polarized to a tumorigenic M2 state by colony-promoting substances released by tumor cells. Rao *et al.* found that genetically modified T-cell membrane-coated magnetic NPs (gCM-MNs) can prevent both pathways from functioning. The gCM shell suppresses the CD47-SIRP pathway by genetically enhanced expression of SIRP variants with exceptional affinity, while the magnetic NP center stimulates M2 TAM repolarization, resulting in combinatorial macrophage immune responses. Furthermore, the gCM coating protects the MNs from immune clearing, and the magnetic NP core, in turn, transports the gCMs into tumor tissues via magnetic guidance, thus boosting their systemic circulation and tumor accumulation (**Figure 5A-B**). Using tumor-bearing B16F10 mice, the antitumor effects were studied *in vivo*. Compared to magnetic NPs and gCMs treatments, the gCMs-MNs treatment significantly suppressed tumor growth, which was even more effective than the co-administration of gCMs and magnetic NPs in a cocktail (**Figure 5C-E**). gCM-MNs have been proven to prolong the overall lifespan in melanoma and breast cancer models by suppressing local tumor development and distant tumor metastasis. Therefore, the use of a combination of cellular membranes coating nanotechnology and genetic engineering to activate the body's immune function for cancer immunotherapy is a safe and effective method [65].

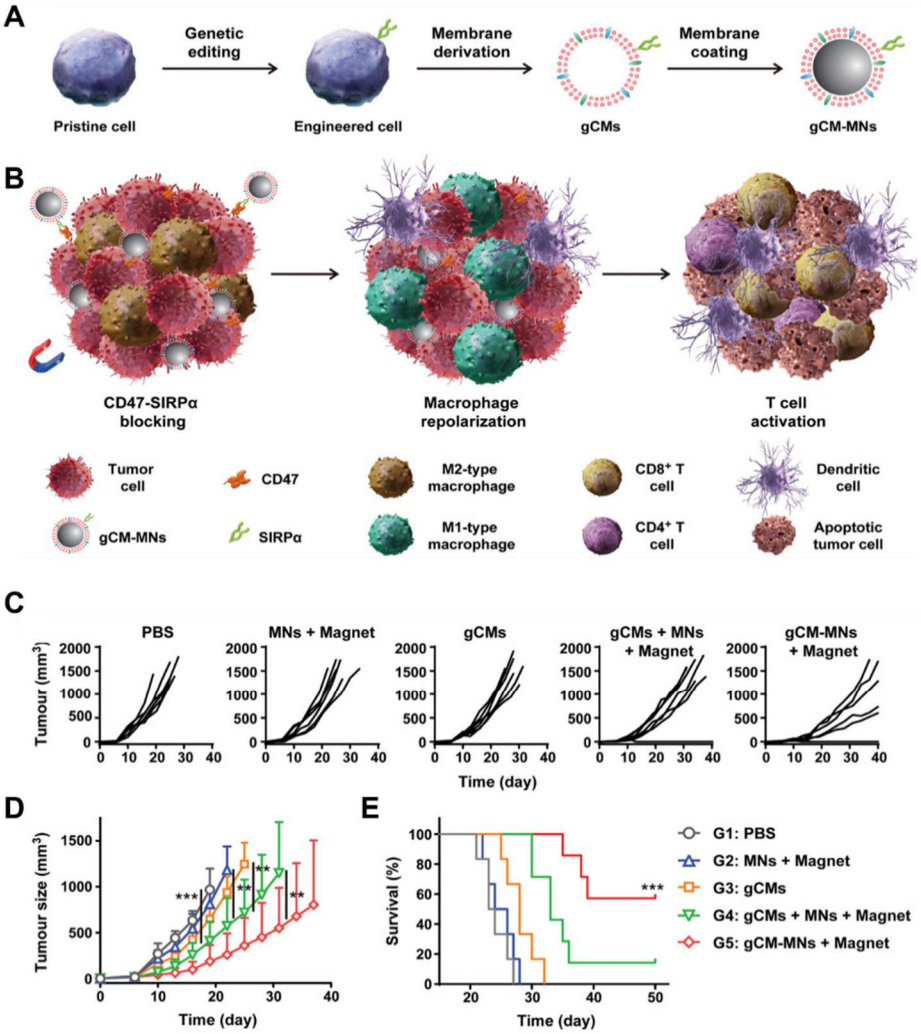

Figure 5. Representation of genetically edited cell membrane coated magnetic nanoparticles (gCM-MNs) for cancer immunotherapy. A) Isolation and coating of cell membrane B) Mechanistic pathways showing anti-tumor immunity. C-E) The results of *in vivo* antitumor action for different treatment groups. Reprinted from [65] with permission from Wiley.

Type I interferons (IFNs) are key regulators of tumor-immune system interaction. Impaired IFN signaling is coupled with poor patient prognosis. Current IFN supplemental therapy occasionally produces serious adverse effects and IFN-induced multigenic resistance programs to immune checkpoint blockade (ICB). Zhai *et al.* reported that the paradoxical effects of IFN supplementary therapy might be controlled by utilizing a T-cell membrane-coated epigenetic nanoinducer of IFNs (OPEN). The researchers genetically engineered a cytotoxic-T cell line to overexpress programmed death receptor 1 (PD1) and then utilized the membrane of these cells to coat protein NPs containing ORY-1001, an inhibitor of lysine-specific histone demethylase 1 (LSD1), to construct OPEN. They demonstrated that the OPEN enhanced intratumoral accumulation of ORY-1001 and local generation of IFNs after intravenous treatment, and the IFNs improved tumor infiltration, proliferation, and activation of tumor-specific cytotoxic-T cells, as well as tumor cell antigen presentation. In addition, they revealed that the IFN-induced programmed death ligand 1 (PDL1) and other immunological checkpoint molecules may be easily neutralized by OPEN. This sequential mechanism restored intratumoral IFNs and reduced IFN-induced immune evasion, thereby inhibiting tumor development in multiple tumor models. The study shows a promising strategy to solve the paradoxical effects of IFN supplementary treatment using an epigenetic nanoinducer. It is a milestone in nanomedicine for safer and more efficient cancer immunotherapy [66]. Taken together, T-cell membrane-coated NPs as a new biomimetic drug delivery platform have the potential to improve the current cancer immunotherapy.

4.3. Photothermal therapy

As a potential cancer therapeutic approach, photothermal therapy (PTT) demonstrates several advantages, such as enhanced efficiency, noninvasiveness, and minimal injury to normal tissues. Photothermal therapy exploits the photothermal conversion ability of nanomaterials to effectively convert optical energy to thermal energy and eradicate malignancies. However, the insufficient accumulation of NPs in the tumor site limited nanotechnology-mediated PTT [67-69]. To enhance the accumulation of nanomaterials and, subsequently, the PTT effect, T-cell membrane-coated NPs have recently emerged as a promising nano-photothermal approach for tumor targeting and eradication [69, 70]. A bioorthogonal metabolic glycoengineering-based customized targeting technique has recently been widely documented. With the treatment of artificial monosaccharides, metabolic glycoengineering is a robust approach for introducing diverse chemical groups to cell glycan. This method, in particular, can be used to create bioorthogonal groups on tumors as artificial "receptor-like" targets, which can then be used for specific binding in complex environments. A new bicyclo nonyne (BCN) altered artificial sugar (Ac4ManN-BCN) that can be integrated into tumor cell surface glycans effectively and nondestructive was presented. The BCN element over the membrane served as an outstanding tag for targeting and significantly improved the tumor identification of azide (N3) transformed T-cells. Based on this synthetic tumor-targeting strategy, NPs of indocyanine green with membrane coating of T-cells (N3-TINPs) and target tumor receptors were developed. The results showed high fluorescence intensity in the tumor. Furthermore, the photothermal therapeutic effectiveness of N3-TINPs *in vivo* was examined, and the tumor area temperature in the TINPs group raised to 44 °C, whereas the tumor area temperature in the N3-TINPs group increased significantly to 53 °C (**Figure 6**). As a result, these modifications may give an alternate targeting technique for tumor therapy with a photothermal effect [70].

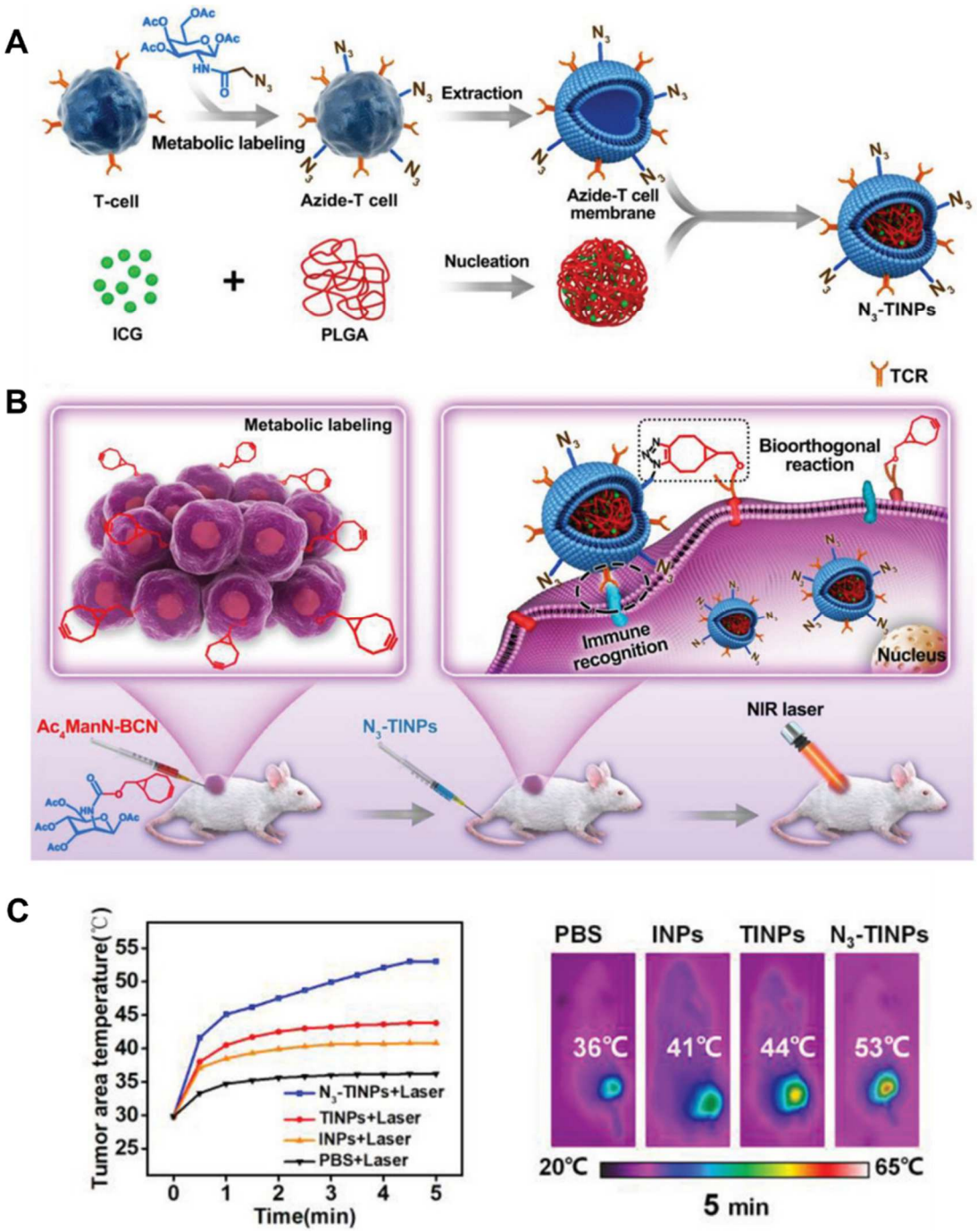

Figure 6. N3-labeled T-cell membrane-biomimetic nanoparticles with a dual-targeting mechanism for highly efficient photothermal therapy. **A**) Synthesis of N3-TINPs. Extracting N3-labeling T-cell membranes were coated on prepared ICG-PLGA polymeric cores by extrusion to form N3-TINPs. **B)** Tumor cells carrying the BCN group via natural glycometabolic labeling by pretreatment with Ac4ManN-BCN. N3-TINPs could target tumors through immune recognition of T-cell membrane and bioorthogonal reaction between BCN and N3 groups, and effectively eliminate mouse tumors through ICG-mediated photothermal effects. **C)** *In vivo* photothermal therapy efficacy. Reprinted from [70] under open access license from Wiley.

Hepatocellular carcinoma (HCC) is among the most common cancers. Aside from standard surgical removal, radiation, and chemotherapy, other treatments such as nano-photothermal and biotherapy are increasingly used to treat HCC. Ma *et al.* combined the benefits of nanoparticle drug delivery technologies with the targeting capacity of CAR-

T cells. CAR-T cell membrane selectively identifying GPC3^{+} HCC cells, was coated on mesoporous silica NPs containing IR780 NPs (a biodegradable, near-infrared photothermal dye) which resulted in a new nanomaterial based on cell membrane-targeting modification. The physical features of this nanoparticle were then investigated, and *in vitro* and *in vivo* targeting capabilities were confirmed. Transmission electron microscopy confirmed that the membrane was effectively coated on NPs. It was demonstrated that CAR-T cell membrane-coated NPs had better targeting ability than unmodified NPs, both *in vitro* and *in vivo* (**Figure 7**). This novel nanosystem provided photothermal anticancer properties and improved targeting ability, indicating that it might be a potential therapeutic option for HCC [69]. Overall, the above-mentioned studies provide a nondestructive targeting strategy, showing that T-cell membrane-camouflaged NPs can act as a novel delivery platform for effective drug accumulation and ultimately achieve a highly efficient PTT action

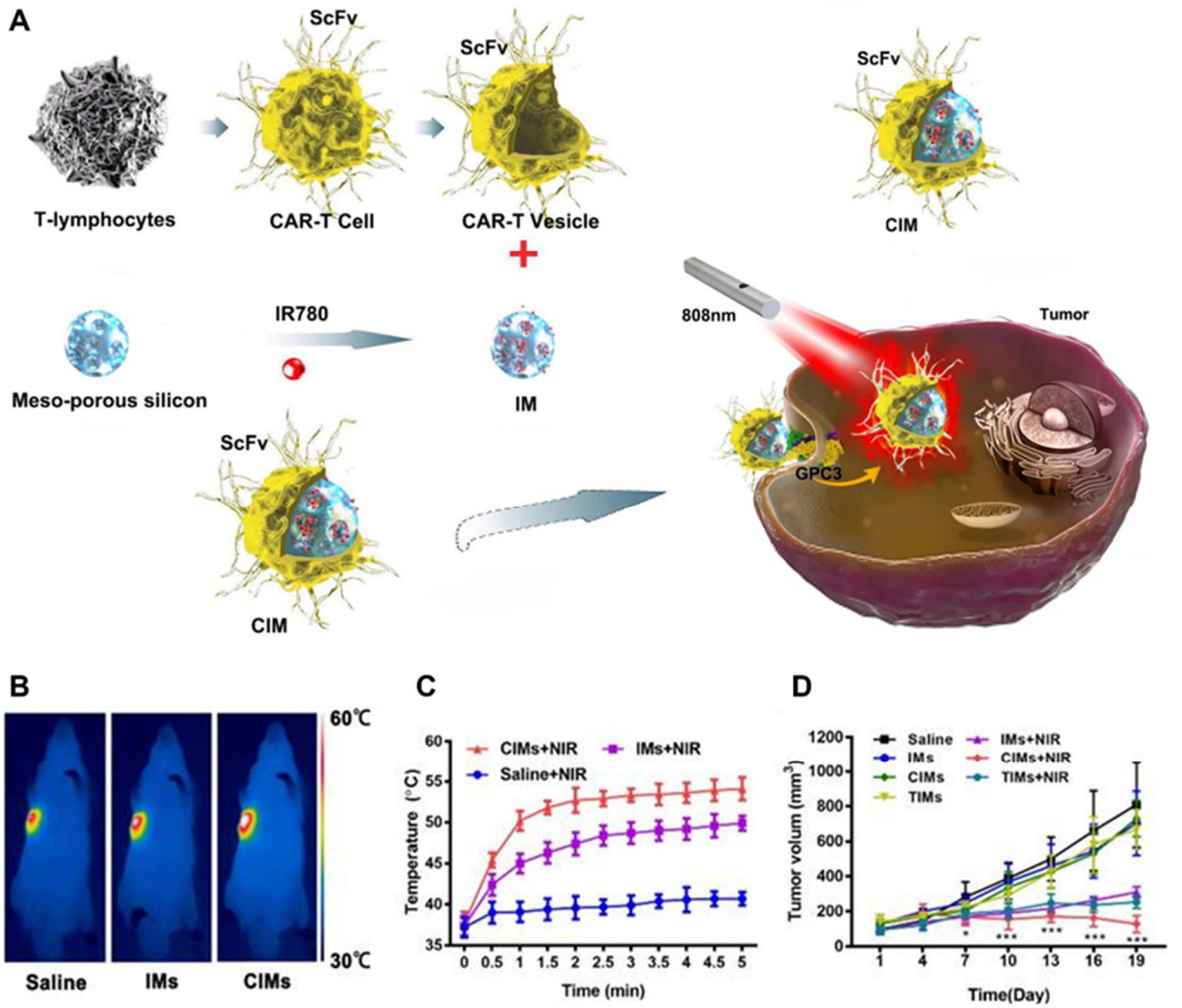

Figure 7. Photothermal applications of anti-tumor NPs coated with CAR-T membrane. **A)** Representation of NPs coated with CAR-T membrane with photothermal anti-tumor effect. **B**), **C),** and **D)** show the *in vivo* anti-tumor effects. **B)** Infrared thermographic images of Huh-7 tumor-bearing nude mice after NIR irradiation. **C)** Temperature increases the behaviors of the tumor tissues in the mice after receiving intravenous injections of different treatments with NIR irradiation. **D)** Tumor growth profiles. Reprinted from [69] under open access license from Ivyspring International Publisher.

4.4. Combinatorial therapy

Due to the inter- and intra-heterogeneity of tumors, a single therapeutic approach might be inadequate. Thus, combinatorial therapy may provide even more promising outcomes for eradicating tumors. Combinatorial therapy is

a complimentary combination of two different therapies, such as radioimmunotherapy, chemoradiotherapy, or a combination of medications that can target multiple cancer formation pathways [71].

Over the last three decades, chemoradiotherapy, which is the co-administration of chemotherapy and radiation, has evolved as a key treatment paradigm for the curative management of many solid tumors. Despite its success, this approach has several limitations. Chemoradiotherapy is not always capable of eradicating the primary tumor. Moreover, the combination of chemotherapy with radiotherapy has not lowered the dose of radiation required for a high probability of cure. Furthermore, utilizing both chemotherapy and radiation together has greatly increased the toxicity profile of cancer treatment [72]. Accordingly, the new invention of T-cell membrane camouflaged NPs provides a unique opportunity to improve the delivery of chemotherapy, which can in turn enhance the efficacy of chemoradiotherapy while lowering toxicity. In this regard, a biomimetic nanosystem with membranes of cytotoxic T-lymphocytes was proposed. T-lymphocyte membranes were employed to disguise the surface of PLGA NPs in this system. Local low-dose irradiation (LDI) was used as a chemoattractant for nanoparticle targeting. Transmission electron microscopy, dynamic light scattering, and confocal microscopy were used to confirm the T-lymphocyte membrane coating. Macrophage phagocytosis of NPs was decreased by 23.99% (P=0.002) using this novel technology. The development of human gastric cancer was suppressed by 56.68% in Balb/c nude mice after systemic treatment of paclitaxel-loaded T-lymphocyte membrane-cloaked NPs. The tumor growth inhibition rate jumped to 88.50% when LDI was applied to the tumor site, and two animals reached full remission. Furthermore, LDI can increase the activation of adhesion molecules in tumor vasculature, which is critical for leukocyte adherence and may help to localize T-lymphocyte membrane-coated NPs in tumors. As a result, this innovative drug-delivery system preserved human cytotoxic-T cells, extended circulation duration, and tumor site accumulation capabilities, whereas local LDI could significantly improve tumor localization [73].

A combination of chemotherapy and PTT has evolved as a promising cancer therapy approach. However, the intricacy of targeted delivery and the ability to activate drug release at specific tumor locations remains a challenging issue [72]. Accordingly, it is urgent to develop a combined chemo-photothermal therapy biomimetic nanoplatform that can simultaneously deliver chemotherapeutic drugs and photothermal agents to the tumor site for the synergistic treatment of a variety of cancers. Targeting this goal, Zhai *et al.* created nanovesicles (MPV) that were composed of cell membrane coating, cisplatin (Pt) and methylene blue (MB) loaded core. The MPV produces contrast for photoacoustic tumor imaging and induces hyperthermia allowing photothermal activity and tumor invasion. The combination of localized heat, photodynamic therapy, and chemotherapy effectively killed 4T1 tumor cells, leading to tumor reduction and 97% inhibition of lung metastasis (**Figure 8**). Following intravenous administration in 4T1 tumor-bearing mice, the distribution and activation of the MPVs were tracked using photoacoustic, photothermal, and fluorescence imaging. Moreover, excellent tumor penetration and efficient lysosomal escape of the MPVs were accomplished, resulting in regression of the primary tumors and a 97.75 ± 2.01% inhibition of pulmonary metastasis without considerable toxicity. The MPV displayed selective tumor targeting and accumulation, enhanced tumor penetration, and triple combination treatment simultaneously. As a result, it revealed a promising nanomedicine for treating metastatic breast cancer [74].

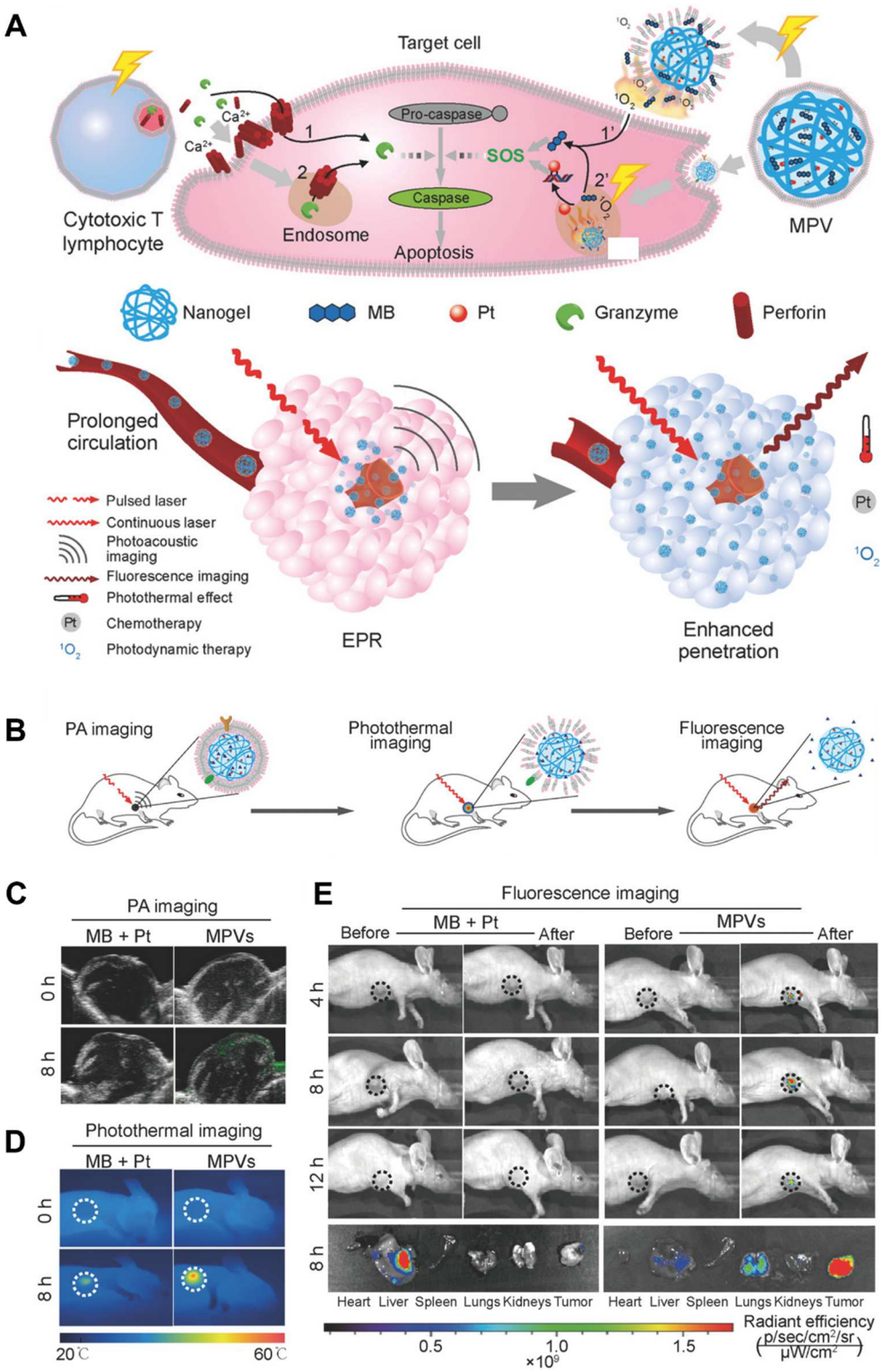

Figure 8. Combinatorial therapy of T cell-coated NPs. **A)** Illustration and mechanism of MPVs. **B)** Schematic illustration of the tracking of naive, activated, and active MPVs in 4T1 tumor-bearing mice using photoacoustic, photothermal, and fluorescence imaging. **C)** Photoacoustic imaging of the intratumoral accumulation of naive MPVs at 0 and 8 h after intravenous administration. **D)** The infrared thermographic images of mice treated with MPVs and localized irradiation (671 nm, 0.68 W cm–2, 4 min). **E)** Representative fluorescence images of MPVs treated 4T1 tumor-bearing mice and resected major organs and tumors after localized laser irradiation. Reprinted from [74] with permission from Wiley.

Chemoimmunotherapy combines and uses both traditional chemotherapy and modern immunotherapy to stop the growth, spread, and recurrence of tumors. Despite the encouraging benefits of chemoimmunotherapy in the treatment of cancer, there are still considerable challenges, including those associated with the simultaneous delivery of therapeutic molecules to target tissues and cells, which results in unpredictable drug proportions in tumor tissues. In addition, the inability of most immunotherapeutic drugs to withstand enzymatic and chemical degradation results in the loss of their biological action [75, 76]. To make a synergistic and effective combination treatment, it is crucial to design a biomimetic nanocarrier that can load and efficiently deliver these two molecules simultaneously. In this regard, innovative T-cell membrane-coated dual-responsive NPs were developed. Hyaluronic acid-disulfide bond-vitamin E succinate was produced and subsequently loaded with curcumin. For the coating, a modified T-cell membrane (phenylboronic acid-labeled T-cell membrane) was used. The coated NP was abbreviated as RCM@T. The use of the T-cell membrane not only protected drug delivery but also functioned as a programmed cell death-1 (PD-1) "antibody" to selectively bind PD-L1 of tumor cells. Following the intravenous administration, RCM@T accumulated at acidic tumor locations and exhibited a "membrane escape effect," exposing the HA residues of NPs for tumor-specific drug delivery. The NPs accumulated in the cytoplasm through CD44-mediated endocytosis and intracellularly released the loaded curcumin in the redox microenvironment. T-cell membrane debris targeted the PD-L1 of tumor cells for tumor immunotherapy, which not only directly killed tumor cells but also enhanced the CD8+ T cell level and stimulated the release of effector cytokines. Collectively, by combining stimuli-responsive drug release, chemotherapeutic agent delivery, and cell membrane-based immune checkpoint blockade immunotherapy, the designed RCM@T provided a novel technique for the rational design of anticancer nano delivery systems [77].

Overall, emerging advances in the development of T-cell membrane-cloaked NPs enable the expected revolution for more use of combinatorial therapy to overcome the challenges in developing successful new drugs and will improve the perspective of combinatorial therapy for better cancer treatment.

5. Conclusions and future perspective

Our natural lessons prompted us to present the notion of biomimetics in cancer treatment and targeted drug delivery for the first time. The dispatch of biological systems to combat their counter groups were also discovered. The idea is now being used in anti-tumor therapies in conjunction with drug delivery systems in cancer. Biomimetic immune cell-based NPs have been developed to mimic normal cells and enhance the clinical efficacy of nanodrugs by incorporating them into cellular membranes. Cell membrane-based NPs can efficiently contact and interact with numerous molecules inside the tumor microenvironment because biological membranes' functional properties and proteins are conserved during the membrane-coating process. The efficacy of bioinspired drug delivery systems, particularly those based on membrane-coating technology, is primarily determined by the cell types from which the membranes are produced, as well as the tumor-targeting tactics used. The utilization of membranes produced from immune cells, in particular, has transformed the area of targeted drug administration due to their great biocompatibility and selectivity. Although some immune cells may non-specifically aggregate in tumors, the best results are still shown in systems that allow for long-term immune cell accumulation [78]. In summary, it appears that biomimetic immune cell-based NPs for drug delivery will continue to advance for clinical use, particularly in cancer immunotherapy. Overall, membrane-coated NPs are gaining traction, but they still need further development and refinement to target tumors effectively and precisely. In conclusion, although innovative, T-cell membrane-based biomimetic NPs are still in their development. Before moving from the lab to the clinic, many obstacles must be cleared. T-cell membrane-based biomimetic NPs will continue to be the focus of a lot more creative and methodical research to support cancer diagnosis and treatment.

Authors' contributions

All authors contributed to drafting and revising of the paper and agreed to be responsible for all the aspects of this work.

Declaration of competing interest

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