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REVIEW

Light-responsive nanomedicine for cancer immunotherapy

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Abstract Immunotherapy emerged as a paradigm shift in cancer treatments, which can effectively inhibit cancer progression by activating the immune system. Remarkable clinical outcomes have been achieved through recent advances in cancer immunotherapy, including checkpoint blockades, adoptive cellular therapy, cancer vaccine, and tumor microenvironment modulation. However, extending the application of immunotherapy in cancer patients has been limited by the low response rate and side effects such as autoimmune toxicities. With great progress being made in nanotechnology, nanomedicine has been exploited to overcome biological barriers for drug delivery. Given the spatiotemporal control, light-responsive nanomedicine is of great interest in designing precise modality for cancer immunotherapy. Herein, we summarized current research utilizing light-responsive nanoplatforms to enhance checkpoint blockade immunotherapy, facilitate targeted delivery of cancer vaccines, activate immune cell functions, and modulate tumor microenvironment. The clinical translation potential of those designs is highlighted and challenges for the next breakthrough in cancer immunotherapy are discussed.

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1. Introduction

Great progress has been made in the fight against cancer over the past decades. Hailed as a revolution in the treatment of cancer, immunotherapy attempts to boost the body's immune system to destroy tumors with enhanced efficacy and fewer side effects than conventional cancer therapies, such as chemotherapy and radiotherapy[1–3]. In 2018, pioneering cancer immunotherapy studies were recognized with a Nobel Prize in Medicine or Physiology for achieving effective and long-lasting therapeutic responses for numerous patients. Meanwhile, multiple immunotherapy drugs have been approved by the US Food and Drug Administration (FDA) and used in cancer patients as first-line treatments. To date, there are more than 20 types of immunotherapy drugs in the market[4]. However, most of them were originally developed for hematological cancers and limited options are available for solid tumors[5]. Accumulating evidence has pinpointed tumor microenvironment in solid tumors as one of the major obstacles against cancer immunotherapy, posing barriers to the delivery of therapeutic agents[6].

In recent years, nanomedicine has been developed to overcome the limitations of anti-cancer drugs and regulate tumor microenvironment. By exploiting the leaky vasculature, nano-sized particles can transport cargos across biological barriers and specifically accumulate in tumor area based on the well-known enhanced permeation and retention (EPR) effect[7]. In particular, tremendous efforts have been made in developing advanced nano-platforms for immunotherapy including liposomes[8], polymeric nanoparticles[9], nanoscale metal-organic frameworks (nMOFs)[10] and cell-derived exosomes[11]. For decades it has been thought that nanomedicine can achieve tumor targeting based on the EPR effect. However, vascularization and blood flow are not homogenous across tumors, resulting in non-uniform EPR effect and leading to uneven drug distribution within the tumors[12,13]. To further enhance the targeting effect, active targeting strategies have been exploited taking advantage of the ligand−receptor interaction to increase the accumulation of nanoparticles in tumors. However, it cannot provide precise control of drug release or drug activation in most cases[14]. Therefore, efficient targeting delivery strategies with a precise control are needed.

Biomaterials with stimuli-responsiveness have been considered as one of the most promising tools for advanced drug delivery. Stimuli-responsive materials are sensitive to certain triggers, including temperature, light, electrical or magnetic fields, and chemicals, and undergo conformational and chemical changes[15]. Nano drug delivery systems made of stimuli-responsive materials are capable of releasing drugs on receiving certain signals and realising precise targeting delivery. Among the currently applied stimuli, light is a safe source for controlled drug delivery with its unparalleled advantages, such as high precision and minimal invasiveness[16,17]. The function of light-controlled drug delivery systems such as drug release can be achieved in a precise and spatiotemporal way by adjusting the irradiance, time and position of light source. Some light-controlled therapies have already been approved for clinical use. For example, photodynamic therapy (PDT) is used for the management of a variety of cancers and benign diseases by selectively destroying unwanted cells in a minimally invasive manner[15]; while photothermal therapy (PTT) is applied to convert the light energy to heat that leads to thermal burns on tumors[18]. More importantly, light-responsive nanomedicine provides unique opportunities for precise spatiotemporal control of delivery process, which is of great significance in improving the efficacy of cancer immunotherapy and minimising "off-target" delivery.

As a potential modality, light is of great interest in filling the gap in current cancer immunotherapy modalities, such as off-target effects, immunosuppressive tumor microenvironment and limited T cell filtration. Light-controlled nanosystems have been developed for the delivery of immunotherapeutic agents selectively in tumor area. Additionally, PDT or PTT-induced cell death was reported to enhance antigen presentation synergy, resulting in a systemic antitumor immune response to control residual tumor cells at the treatment site and distant metastases[19]. In this review, we provide an overview of the most widely used types of cancer immunotherapy, their mechanisms and clinical status. Four widely used immunotherapies combined with light-responsive nanomedicine will be highlighted (Fig. 1). Further, light-controlled nanoplatforms for improving the efficacy of immunotherapeutics and PDT/PTT-related immunotherapy based on nanomedicine are summarized and discussed, with particular focus on recent advanced designs in the field. Lastly, we provide insights into photoresponsive nanomedicine development for cancer immunotherapy and the challenges for their clinical translation.

2. Major types of immunotherapies for cancer

To exploit anticancer immune responses, a 7-step cancer-immunity cycle needs to be fully elucidated (Fig. 2)[20]. The cancer-immunity cycle starts with neoantigen capture (1), in which antigen-presenting cells (APCs) (such as dendritic cells) recognize the antigens created and released during oncogenesis and capture them for later processing. APCs then present the captured antigens on major histocompatibility complex class I (MHCI) and II (MHCII) molecules to naïve T cells (2), to activate effector T cell responses against such cancer-specific antigens (3). Next, the activated effector T cells (cytotoxic T cells) circulate to tumor area (4) and infiltrate into tumors (5). They then identify and bind to tumor cells *via* specific interaction between the T cell receptor and its cognate antigen (6), leading to cytotoxic effects on the target cancer cells (7). Tumor-associated neoantigens release upon cancer cell death, which then initiate the cancer-immunity cycle again. However, cancer cells often create an immunosuppressive tumor microenvironment to interfere the cancer-immunity cycle, either by 'masking' the tumor-associated antigens, or hindering the infiltration of T cells, or suppressing effector T cell activities[21].

To restore the cancer-immunity cycle in cancer patients, a number of evolutionary immunotherapy modalities have been developed, including cytokines, checkpoint blockades, immune system modulators, oncolytic virus therapy, adoptive cellular therapy and cancer vaccine. This review focuses on the most widely used types, namely, checkpoint blockades, adoptive cellular therapy, cancer vaccine, and tumor microenvironment modulation.

2.1. *Checkpoint blockades*

Checkpoint blockades have been predominantly applied in clinical practice, with cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD1) being the most potent examples of T cell immune checkpoint molecules. CTLA-4 has structural and biochemical similarities to cell surface protein cluster of differentiation 28 (CD28), but greater affinity than CD28 to its ligand

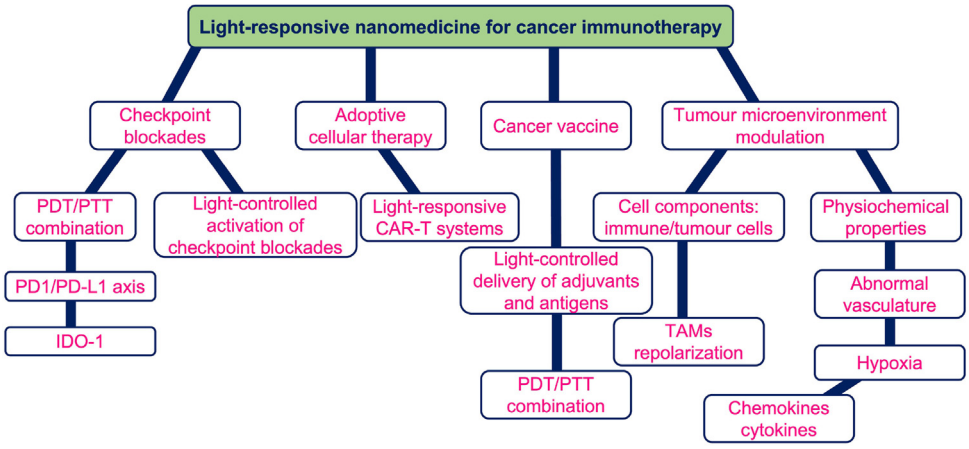

Figure 1 Light-responsive strategies for cancer immunotherapy.

B7[22]. The up-regulated CTLA-4 on activated T cells competes with CD28 for B7 ligation, and therefore inhibits further T cell activation. Inhibition of CTLA-4 on T cell surface frees B7 on APCs and restores its ligation with CD28. Therefore, T cell responses to tumor-associated neoantigens can be enhanced, leading to the priming and activation of effector T cells (Fig. 3A)[23]. Ipilimumab, a monoclonal antibody against CTLA-4, has been used in clinic for melanoma treatment since 2011[24]. Another CTLA-4 blockade tremelimumab is still seeking FDA's approval[25]. Meanwhile, antibodies against PD1 on T cells and its ligand (PD-L1) on tumor cells have been used in cancer patients with multiple formulations in the market since 2014[25]. Both PD1 and PD-L1 are highly targetable. Inhibition of the PD1/PD-L1 axis reverses the immune checkpoint and releases the brake on T cells by enhancing their effector functions and the formation of memory cells (Fig. 3B)[23]. As a result, PD1 and PD-L1 blockade can enhance immunogenic killing effects in tumors and limit metastasis[26].

Though CTLA-4 and PD1/PD-L1 blockades are the only types that are FDA-approved and currently used in clinic, the discovery of new immune checkpoint molecules continuously inspires the development of corresponding checkpoint blockades. Lymphocyte-activation gene 3 (LAG3) is one of the most promising targets. It has a similar structure to cell surface protein cluster of differentiation 4 (CD4) and can competitively bind to MHC-II, α-synuclein fibrils and lectins galectin-3[27]. LAG3

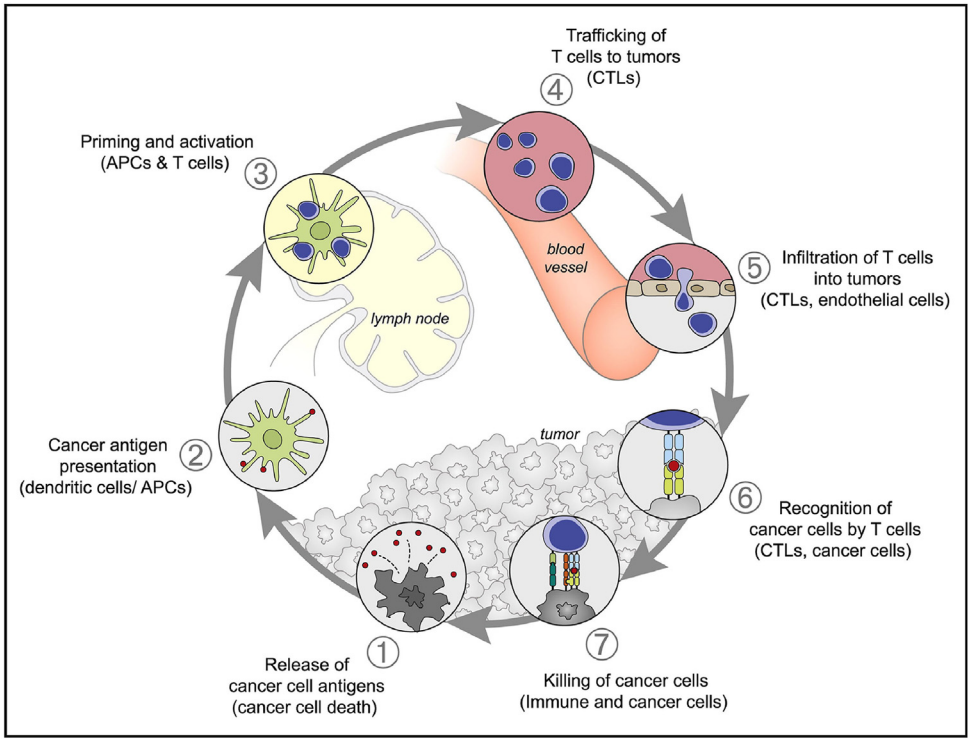

Figure 2 A schematic illustration of the seven major steps involved in the generation of an immune response against cancer. APCs, antigen-presenting cells; CTLs, cytotoxic T lymphocytes. Reprinted with permission from Ref. 20. Copyright © 2013 Elsevier.

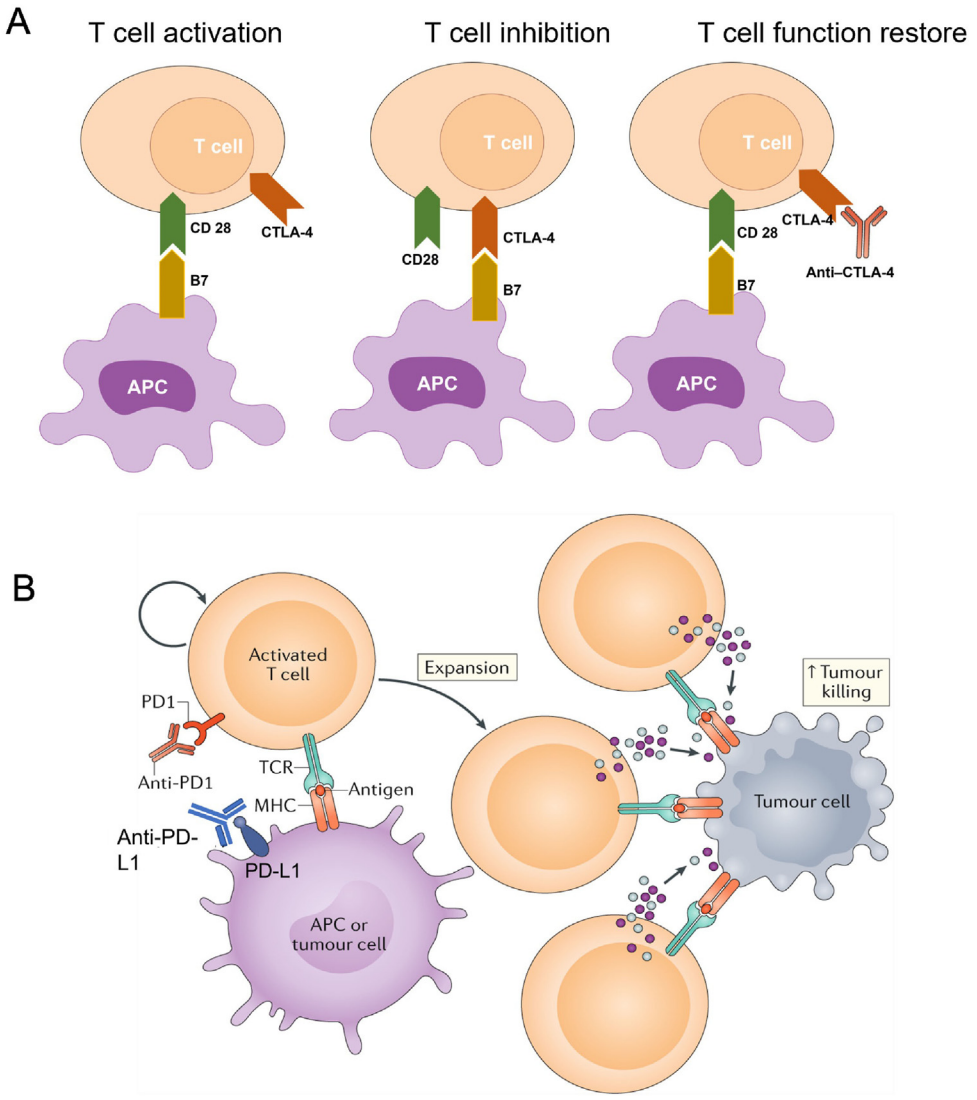

Figure 3 Mechanisms of CTLA-4 and PD1/PD-L1 blockades. (A) CTLA-4 competes with CD28 to bind to B7, inhibiting T-cell function. Anti-CTLA-4 antibodies block CTLA-4 and B7 ligation and prevent inhibition of T cell function. (B) Programmed cell death 1 (PD1) on activated T cells binds to its ligand (PD-L1) on the antigen-presenting cell (APC) or tumor cell surface to inhibit T cell activation. Blocking of the PD1/PD-L1 axis *via* anti-PD1 or anti-PD-L1 antibody prevents this inhibitory interaction and increases T cell activation and proliferation, enhancing tumor killing effect eventually. Reprinted with permission from Ref. 26. Copyright © 2020 Springer Nature Limited.

inhibits the activation of its host cells, such as activated T cells and regulatory T cells, contributing to suppressive immune responses[28]. Promising results of using LAG3 blockade alone or in combination with PD1 blockades have been demonstrated in animal models and clinical trials in recent years[29]. However, mechanisms involved in LAG3-related inhibition of immune cell activation need to be fully elucidated to promote the clinical application of LAG3 blockades.

In addition, transmembrane proteins B7-H3 and H4 have been identified as important immune suppressors. They were found to be overexpressed in various solid tumors and immune cells, and involved in suppressing T cell activation, proliferation, and cytokine secretion[30]. Antibodies targeting B7-H3 and H4, namely FPA150 and MGC018, are currently under investigation in clinical trials[31,32]. Despite the satisfactory anti-tumor results achieved, severe adverse effects, such as lymphopenia and hypertension, have been reported[33–35]. Moreover, studies focusing on innate immune checkpoint on myeloid cells have demonstrated promising clinical outcomes with mild levels of toxicity. Anti-CD47 antibody is one of the most successful examples. By blocking the interaction between CD47 on tumor cells and the inhibitory receptor SIRPα on myeloid cells (macrophages, red blood cells, etc.), anti-CD47 antibody can promote the macrophages-induced destruction of cancer cells and tumor-specific cytotoxic T cell responses[36,37]. Encouraging clinical responses have been reported in trials of combinational use of CD20 antibody rituximab and CD47−SIRPα inhibition[38].

Another immunoregulatory protein TIGIT (also called WUCAM, Vstm3, VSIG9) is a hot immunotherapy target. As a receptor of Ig superfamily, TIGIT plays an important role in regulating adaptive and innate immunity[39,40]. In solid tumors, TIGIT is co-expressed with other inhibitory receptors like PD1 on TILs and tumor antigen-specific $CD8^+$ T cells[41]. TIGIT is also highly expressed by regulatory T cells (Tregs) in peripheral blood

mononuclear cells of cancer patients and further upregulated in the tumor microenvironment. The combination of TIGIT with other immune checkpoint inhibitors represents as a promising treatment tactic[42]. In one clinical trial, dual PD-L1/TIGIT blockade (atezolizumab/tiragolumab) exhibits superior clinical outcomes in comparison with PD-L1 blockade alone for patients with PD-L1-positive non-small cell lung cancers[43].

Checkpoint blockades immunotherapy is now a clinical reality and remarkable successes have been achieved. However, blocking a central immune checkpoint may lead to severe immune-related adverse effects, such as autoimmune toxicities[44]. A major challenge lies in safely engaging these checkpoint blockades at the right time and place. Therefore, precise spatiotemporal delivery, such as light-controlled delivery, is of great need to expand the application of checkpoint blockade immunotherapy.

2.2. *Adoptive cellular therapy*

Adoptive cellular therapy by infusing autologous or allogeneic T cells into patients, is another potential alternative to modulate the immune system in cancer patients. Presently, adoptive cellular therapies can be categorized into three types, tumor-infiltrating lymphocytes (TILs), T cell receptor (TCR)-engineered T cells and chimeric antigen receptor T (CAR-T) cells. TIL therapy was initially introduced in 1986 for metastatic melanomas, using *ex vivo* expanded autologous TILs with interleukin 2 (IL-2) following transferring back into patients[45]. TIL therapy has consistently yielded durable clinical responses in patients with metastatic melanoma, but not yet in other solid tumors[46]. Furthermore, TCR-based therapy is a potent anti-tumor treatment in various cancer types, in which tumor antigen recognition is achieved by the introduction of a novel T cell receptor into T cells. Promising outcomes were shown in TCR-based therapy clinical trials, using targeting antigen NY-ESO-1 for the treatment of solid tumors, such as neuroblastoma and sarcomas[47,48]. More recently, the success of preclinical and clinical trials has brought CAR-T cell therapy into the spotlight. CAR-T cell therapy starts with harvesting T cells from patients, followed by engineering them with chimeric antigen receptors that can bypass MHC restriction and directly target tumor cells. Thereafter, the resulting CAR-T cells are infused back to the body for activation of immune response[49]. As a revolutionary paradigm, 5 CAR-T cell therapies have been approved by FDA since 2017 with many more in clinical trials[50].

Despite that CAR-T therapy has displayed good effectiveness in hematological tumor treatment, the effectiveness to treat solid tumors is still lacking due to limited infiltration of T cells[51]. The same problems occur in CAR-NK therapy, which refers to applying CAR strategy to NK cells based on the broad cytotoxicity and rapid killing ability of NK cells[52]. Tumor-associated macrophages (TAMs) can infiltrate solid tumors with a high infiltration rate and then interact with other cells within the tumor microenvironment including tumors cells and a variety of immune cells like T cells, NK cells, DCs, etc. Therefore, endeavours are made to modify macrophages with CAR against solid tumor[53]. CAR-M therapy refers to the edit of designed specific CAR gene (improve phagocytic activity and antigen presentation) into patient derived-macrophages to equip them with the capability to bind to the tumor cell surface *via* specific antigen identification, subsequently activating macrophage activity against tumor cells[54]. Currently, two clinical trials based on the CAR-M strategy have been approved by the FDA while considerations need to be addressed like fitness between CAR structure and macrophages[55], safety issues, effectiveness in human body, etc. Combination of CAR-M therapy with other immunotherapies is also a potential attempt.

Although adoptive cellular therapies have produced remarkably effective responses, limited availability of specific antigens significantly hinders the application of adoptive cellular therapies in more intractable cancer types. In addition, as the antigens explored up until now are not solely expressed by tumors, the associated toxicities can be life-threatening in some cases due to systemic cytokine release and severe immune cell cross-activation[56]. Other challenges to promote adoptive cellular therapies are the immunosuppressive microenvironment and the limited immune cell infiltration in solid tumors. Therefore, it is necessary to develop delivery technologies that can enhance the transport of engineered immune cells to target sites, to minimise the toxicities of adoptive cellular therapies while enhancing the efficacy in solid tumors.

2.3. *Cancer vaccine*

The other intriguing strategy to defeat cancers is to elicit a specific immune response against tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs) by using cancer vaccines. Most of cancer vaccines are developed based on the activation of APCs and the consequent stimulation of cytotoxic T cell-mediated immune response[57]. In theory, patients who received vaccination could mount an immune response towards tumor cells to keep them under constant restraint and eventually eliminate tumor cells, delay tumor recurrence, and prolong survival. Several types of techniques have been developed to compensate weak innate immune response against TSAs and TAAs, including dendritic cell-based vaccine[58], protein/peptide vaccines[59], and nucleic acid vaccines (DNA and RNA)[60]. Among them, nucleic acid vaccines have been particularly promising. Upon the delivery of DNA/RNA to APCs, the information they carry are then translated to induce specific antigen expression, which triggers T cell activation. To date, numerous clinical trials have demonstrated promising therapeutic results with cancer vaccines[61]. Besides vaccines for virus-related cancers (*i.e.*, HPV vaccine), two cancer vaccines have been approved by FDA[62]. Screening neoantigens that can elicit strong antitumor responses still face great challenges. Vaccine development for the neoantigens requires a considerable amount of time and financial support.

At present, limited delivery platforms are available for transporting nucleic acids across cellular and nuclear barriers. Furthermore, delivering RNA-based vaccines is particularly challenging due to their poor cellular internalisation and low stability towards nucleases. Advanced delivery systems which can protect nucleic acid vaccines from degradation and effectively transport them to target tissues and cells would greatly benefit further clinical application of nucleic acid vaccines.

2.4. *Tumor microenvironment modulation*

Tumor microenvironment is a milieu of tumor cells, immune cells, stroma cells, extracellular matrix, cytokines, and other signalling molecules. The components work individually and in combination to influence the immunogenicity of the body. Numerous studies have reported that tumor microenvironment is responsible for limited T cell filtration, reduced activity of TILs and the down-regulated expression of immune checkpoint molecules[63–65].

Therefore, modulating the immunosuppressive tumor microenvironment is essential to produce robust systemic immune responses and improve the efficacy of other immunotherapies, such as adoptive cellular therapy and checkpoint blockade.

Cytokines are important immune regulators that have pleiotropic effects in tumor microenvironment. Each cytokine controls different types of the immune cell to either support tumor growth or trigger anti-tumor responses. Cytokines, including interferon, interleukin, and granulocyte-macrophage colony-stimulating factor (GM-CSF), have been clinically used as mono-immunotherapy or combinational therapy with other treatments[66]. Interferon-γ has been approved for several types of cancer, as it plays a vital role in the maturation of dendritic cells (DCs) and activation of effector T cells[67]. Besides, interleukins promote innate and adaptive immune responses *via* the activation of $CD4^+$ T cells and $CD8^+$ T cells[66], while GM-CSF promotes the expansion and activation of myeloid cells such as DCs and macrophages.

An alternative strategy to restore the immune surveillance in tumor microenvironment is by targeting immunosuppressive cells such as TAMs and myeloid-derived suppressor cells (MDSCs). Recent efforts have been directed to the inhibition of colony-stimulating factor 1 receptor (CSF1R) and Janus kinase (JAK)-signal transducer that are expressed on TAMs and MDSCs contributing to the immunosuppressive environment[68,69]. Several inhibitors and antibodies have been developed with encouraging therapeutic effects in animal models while clinical trials in cancer patients are still ongoing[68,70,71].

Besides, the physiochemical properties such as acidity, hypoxia, abnormal vasculature, rigid extracellular matrix, and irregular enzyme level of tumor microenvironment also contribute to immunosuppressive conditions and hinder drug delivery[72]. Diverse strategies of nanomedicine have been exploited to overcome the barrier by regulating tumor microenvironment[73]. Employing light to deliver modulators is a potential modality to realize the spatiotemporal control of drug release with less off-target effect.

Although cytokines and inhibitors can effectively modulate the immunosuppressive tumor microenvironment, their side effects are not negligible in clinical use. Due to the short half-life of cytokines, repetitive doses are required for satisfactory therapeutic efficacy, which may lead to cytokine release syndrome[66]. Additionally, immune regulators such as CSF1R and JAK are involved in normal cell functioning, their inhibition could influence normal cells and lead to severe side effects[68,74]. Therefore, delivery systems that can realise precise tumor targeting with a high drug loading capacity are needed to fully validate the clinical value of tumor microenvironment modulators.

3. Light-responsive nanomedicine for immunotherapy

Although the immunotherapies described above have demonstrated promising results, challenges remain. Clinical translations of immunotherapies face multiple delivery barriers, either cellular or microenvironmental. The success of checkpoint blockades relies on their interaction with the right target proteins at desirable time. The application of adoptive cellular therapy is hindered by limited T cell infiltration in tumor microenvironment, while cytokines and cancer vaccines require systems to protect them from degradation. Further, a major challenge of cancer immunotherapy is the potential immune cell cross-activation, leading to autoimmunity and severe toxicity. Therefore, it is essential to develop strategies to realize targeted and precisely controlled cargo delivery or activation of immune systems for cancer immunotherapy.

For decades, the EPR effect has been considered as the gold standard in nanomedicine that allows nanoparticles to accumulate in tumor area following intravenous administration. However, conventional nanomedicine solely based on EPR effect is not able to overcome the heterogeneity of tumors and vasculature in clinical practice[75]. Despite endogenous stimuli can be applied to enhance the targeting ability of nanomedicine spatially based on specific condition of tumor microenvironment, such stimuli-responsive nanoplatforms lack capability to deliver drugs in a temporal fashion[76]. Strategies to realize spatiotemporal control of drug release are needed to further improve the efficacy of nanomedicine for cancer therapy.

Light surpasses in controlling biological systems in a spatiotemporal resolution by virtue of easy adjustability of irradiation conditions like time, power and site[77]. A branch of light technology applied in health and medicine can be traced back to the middle 2000s[78]. The past two decades witnessed the rapidly growing influence of light in controlling biological systems *via* synthesis and modification of photoresponsive small molecules, proteins and nucleic acids[79]. In the late 2000s, emerging research employed light technology on nanomedicine, which pioneered a new route to therapeutics, *in vitro* diagnostics, and medical devices[80]. The transfer from small molecule-based optochemical-controlled synthetic molecules to polymer-based light-responsive drug delivery systems diversified nanomedicine with intelligence and personalization. Moreover, the concept of "near-infrared (NIR) window", which refers to light between 650 and 900 nm, was brought up[81]. The light with wavelengths within the range of the NIR window stands as a desirable tool to regulate biological activities *in vivo* by virtue of higher penetration ability and less absorbance by tissue chromophores.

To exploit nanomedicine for cancer immunotherapy, light-controlled delivery nanoplatforms have been designed and demonstrated promising results with clinical application potentials. Furthermore, clinical-approved phototherapies, such as PDT and PTT, are able to precisely induce immunogenic cell death (ICD) and elicit the immune system (Fig. 4). PDT employs the application of nontoxic photosensitizers and localized external light irradiation, to generate reactive oxygen species (ROS) in tumor area. The resulting ROS can generate tumor cell destruction and produce dying tumor cell debris to send a danger signal to the innate immune system, resulting in the enhanced antigen presentation and activation of T cells[82]. PTT utilises hyperthermia induced by light to kill cancer cells. The tumor cells undergo apoptosis or necrosis and release tumor-associated antigens that can be recognized by APCs, then activate immune cells[83]. Combining phototherapy with immunotherapy has become a promising strategy for cancer treatments as it has satisfactory synergistic effects for primary and metastatic cancer treatments. In the section, we discussed four different strategies and corresponding delivery systems to advance light-responsive nanomedicine for immunotherapy (Table 1)[84–110].

3.1. *Light-responsive strategies to enhance checkpoint blockade immunotherapy*

Though checkpoint blockade immunotherapy has been used as a first-line treatment for several cancer types, patients' response varies due to tumor heterogenicity and the immunosuppressive microenvironment[111,112]. Increasing the injection dose will

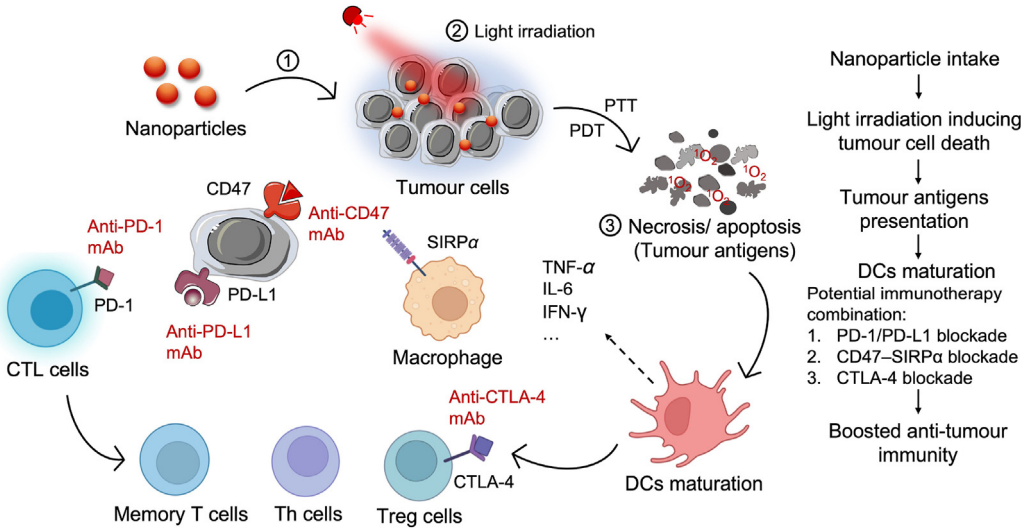

Figure 4 Schematic demonstration of PTT/PDT-induced immunogenic cell death and succeeding immune responses.

increase the risk of side effects as many of checkpoint blockades are not cancer specific. Therefore, controlled release of checkpoint blockades at the target site and eliciting antitumor immunity are desired for improving the efficacy of checkpoint blockade immunotherapy. Light-responsive nanomedicine-based strategies have been explored for reversing the immune-suppressive microenvironment to potentiate checkpoint blockade immunotherapy or delivering checkpoint agonist peptides specifically in tumor area.

Combinational use of photosensitisers and checkpoint blockades have been explored in recent years to generate synergistic cytotoxicity and immunogenicity. Peng et al.[84] designed a nanosystem to simultaneously deliver photosensitiser, PD-L1 agonist and chemotherapeutic agent. In this design, NIR dye IR820 self-assembled with chemotherapeutic docetaxel (DTX) and *N*′-bis(acryloyl)cystamine (BISS) into nanoassemblies (DTX/BISS-IR820). CF27, a PD-L1 agonist peptide with a matrix metalloproteinase (MMP)-responsive sequence, was cross-linked with BISS and further formed a nanosystem (DTX-IR820-CF27) (Fig. 5)[84]. DTX-IR820-CF27 showed significant tumor-specific release and accumulation of CF27 in tumor microenvironment to bind to PD-L1. In the meantime, DTX and IR820 underwent endocytosis and generated chemotherapy and photothermal effect upon light irradiation which further strengthened tumor cell apoptosis and necrosis. In a breast cancer mouse model, primary tumors were eliminated with systemic injection of DTX-IR820-CF27 plus light irradiation at tumor sites, while the growth of secondary tumors without light irradiation was also drastically impeded with an increase in the relative proportion of infiltrated effector T cells ($CD3^+CD8^+$ T cells). This study presented an example of the combinational use of photosensitiser, chemotherapeutic drug, and checkpoint blockade in one system, and the applicability of using NIR dye to enhance the immunotherapy efficacy of checkpoint inhibitors. Similar design has been explored in another study. Nanoparticles were formed by self-assembly of NIR dye indocyanine green (ICG), toll-like receptor (TLR)-7/8 agonist resiquimod (R848), and TLR-9 agonist CPG[85]. ICG can generate a strong photothermal effect, while CPG and R848 work as important immune stimulators. The nanoparticles were then loaded in a thermosensitive hydrogel to realise NIR light-controlled release of TLR-7/8 agonist and TLR-9 agonist. By *in situ* injection, hydrogel-treated tumor-bearing mice had the photothermal ablation, together with a strong immune response to inhibit lung metastasis and postoperative tumor recurrence.

In addition, eliciting immune response in the immunosuppressive microenvironment in solid tumors is a formidable challenge to potentiate checkpoint blockade immunotherapy. Light-responsive nanomedicine has also been used to enhance the efficacy of successively delivered checkpoint blockades. Photosensitisers have been loaded in several types of nanoparticles, such as liposomes[113], inorganic[114] and organic nanoparticles[97], to induce ICD and elevated immune response for the following injection of checkpoint blockades. Hu et al.[86] developed a drug delivery system by combining photosensitiser chlorin e6 (Ce6) with a ROS-sensitive hydrophobic core to achieve light-controlled release of chemotherapeutic doxorubicin at tumor sites. The combinational use of photosensitiser and chemotherapeutic agent induced immunogenic cell death, subsequently promoted the maturation of dendritic cells and increased T cell infiltration to tumor tissues. As a result, successive anti-PD-L1 antibody injection generated an abscopal effect in mouse models, simultaneously inhibited primary and distant tumor growth. An additional example presented a light-responsive prodrug nanosystem to potentiate a following PD-L1 blockade immunotherapy[87]. The authors developed prodrugs consisting of doxorubicin and photosensitizer (verteporfin) which were then self-assembled into nanoparticles (LT-NPs) (Fig. 6)[87]. LT-NPs accumulated in tumor area and generated immunogenic cell death upon light irradiation which led to dendritic cell recruitment, maturation, migration, and cytotoxic T cell activation. These results further amplified immune response for successive PD-L1 blockade immunotherapy. Drastically delayed tumor growth, tumor recurrence, and lung metastasis were observed in colon tumor models and metastatic lung cancer models owing to the enhanced immune response. Apart from PD1/PD-L1 blockades, other immunoregulatory molecules can be targets as well. Li's group[88] developed a NIR light-activatable cancer vaccine by attaching immunostimulatory IDO-1 inhibitor NLG919 and singlet oxygen ($^1O_2$)-responsive cleavable linker on a semiconducting polymer nanoparticle core. NIR-light excitation enabled the generation of heat and $^1O_2$ and the subsequent release

Table 1 Four different strategies and corresponding delivery systems on light-responsive nanomedicine for immunotherapy were summarized.

Strategy	Delivery system	Short description	Immunotherapeutic agent	Significance	Ref.
Light-responsive strategies to enhance checkpoint blockade immunotherapy	Self-assembled nanoparticles	820 nm light-responsive nanoparticles co-delivered a PD-L1 agonist and chemo drug docetaxel (DTX)	CF27, a PD-L1 agonist peptide	Combination of photosensitiser, chemotherapeutic and immune checkpoint blockade inhibitor	84
	Self-assembled nanoparticles	Near-infrared (NIR) light-responsive hydrogels co-delivered NIR dye, TLR-7 and TLR-9 agonist	CPG and R848, immune stimulators	Combination of photothermal therapy (PTT) with toll-like receptor agonist	85
	Self-assembled nanoparticles	NIR light-responsive nanoparticles co-delivered photosensitizer and chemo drug doxorubicin (DOX)	Anti-PD-L1 antibody	Photodynamic therapy (PDT) induced immunogenic cell death (ICD) to elevate the immune response	86
	Self-assembled nanoparticles	NIR light-responsive nanoparticles were self-assembled by a prodrug (photosensitizer verteporfin linking with doxorubicin *via* a cathepin B-cleavable peptide)	Anti-PD-L1 antibody	PDT induced ICD to elevate immune response	87
	Polymeric nanoparticles	NIR light-responsive polymeric nanoparticles generated $^1O_2$ to release tumor-associated antigens and delivered immunostimulatory agents	NLG919, IDO-1 inhibitor	Combination of IDO-1 pathway inhibition and tumor-associated antigen presentation to achieve enhanced immune responses	88
	Prodrug	Blue light responsive-prodrug selectively activated immune responses	BMS-1, inducing PD-L1 dimerization	The first photocaged prodrug for immunotherapy	89
Light-controlled modulation of immune cells	Optical dimerizer pair	Blue light-responsive CAR-T systems	CAR-T cells	Reversible light-controlled immunotherapy	90
	Silica-coated upconversion nanoparticles (UCNPs)	NIR light-responsive CAR-T systems were realized by incorporating hexagonal-shaped UCNPs	CAR-T cells	A nano-optogenetic engineering strategy with robust efficacy and potential for clinical translation	91
	PLGA nanoparticles	Simultaneous injection of PLGA nanoparticles loaded ICG and CAR-T cells	CAR-T cells	Combination of PTT with CAR-T therapy	92
Light-directed delivery of cancer vaccine	Cationic PAMAM dendrimer	UV-responsive PAMAM-based nanosystems delivered antigen ovalbumin (OVA)	Antigen OVA	Endosomal escape of OVA and elevated tumor necrosis factor α (TNF-α) secretion from macrophages	93
	PLGA nanoparticles	NIR light-responsive copper sulfide nanoparticles delivered antigen OVA	Antigen OVA	Escalated cytokines and activation of cytotoxic T cells were achieved after NIR light irradiation	94
	PheoA-PEI nanoparticles	NIR light-responsive nanoparticles co-assembled by a photosensitizer pheophorbide A grafted polyethyleneimine and OVA	Antigen OVA	Enhanced $CD8^+$ T cell proliferation and tumor inhibitory effect were found in mice injected with dendritic cells and the nanoparticles after light irradiation	95
	Self-assembled nanoparticles	Nanoparticles co-assembled by OVA and photosensitizer ICG	Antigen OVA	Maturation of DCs and elevated excretion of cytokines	96
	Polymeric nanoparticles	PLGA-ICG polymeric nanoparticles as the PTT core and coated with CMV-OMV fused membrane	Fusing melanoma cytomembrane vesicles (CMVs, antigen) and attenuated *Salmonella* outer membrane vesicles (OMVs, adjuvant)	Bacterial OMVs can stimulate immunity cytokines and melanoma CMVs can trigger antitumor immunity due to the specific antigens expressed on the membrane. The immune responses were further boosted by the PTT-induced ICD effect	97
	Photosynthetic microorganism	NIR light-responsive synthetic microorganism PCC 7942 delivered adjuvants and achieves a synergistic effect with PTT	PCC7942, adjuvants	PCC7942 served as both PTT agent and adjuvant to stimulate immune responses	98

(*continued on next page*)

Table 1 (*continued*)

Strategy	Delivery system	Short description	Immunotherapeutic agent	Significance	Ref.
	UCNPs	NIR light-responsive UCNPs delivered adjuvant oligonucleotides	CpG oligonucleotides, adjuvants	NIR-light irradiation activated adjuvant CpG, resulting in a substantially increased proportion of tumor-infiltrating T cells for improved antitumor efficacy	99
	Manganese-porphyrin metal-organic framework (MOF)	MOF modified with AS1411 aptamer to load vorinostat and photosensitizer TCPP	Manganese ions (Mn^{2+}); tumor-associated antigens	Combination of PDT-induced ICD and Mn^{2+} mediated STING pathway activation	100
	Polymeric nanoparticles	NIR light-responsive polymeric nanoparticles co-delivered immunostimulatory agents and photosensitizers	Toll-like receptor agonist; tumor-associated antigens	Combination of PDT-induced ICD and Toll-like receptor activation	101
Light-responsive strategies to modulate tumour microenvironment to enhance immunotherapy	Polydopamine nanoparticles coated with macrophage membrane	Polydopamine acted as a PTT agent and the macrophage membrane exhibited targeted ability	TMP195, TAMs repolarization agent	Combination of PTT with macrophage polarization	102
	UCNPs $NaYF_4$:Yb	Coated UCNPs with photosensitizer and tumor-associated macrophage membrane (TAMM)	TAMM	Combination of PDT with macrophage polarization	103
	Polymeric nanoparticles	Poly (styrene-*co*-maleic anhydride) (PSMA) co-assembled with polymer poly [2-methoxy-5-(2-ethylhexyloxy)-1,4-phenylenevinylene] (PPV) with photosensitivity	PSMA-composed nanoparticles, TAMs repolarization agent	Combination of PDT with macrophage polarization	104
	Liposomes	Macrophages served as carriers to load NIR light-responsive nanoparticles	Tumor-associated antigens; anti-PD-L1 antibody	Combination of PDT, chemotherapy, and macrophage polarization with PD-L1 blockade	105
	Self-assembled nanoparticles	Ce6 self-assembled with tyrosine kinase inhibitor axitinib, indoleamine 2,3-dioxygenase (IDO) inhibitor dextro-1-methyl tryptophan and human serum albumin	Axitinib, reversing immunosuppressive microenvironment by regulating the aberrant vasculature; IDO inhibitor dextro-1-methyl tryptophan	Combination of PDT with vascular endothelial growth factor receptors (VEGFR) inhibitor and IDO inhibitor	106
	Chemically modified cytokines	370 nm light-controlled galactosylceramides	Cytokines	The first example of modifying cytokines to activate T cells and immune responses	107
	Photoactivatable chemokine C−X−C motif receptor 4 (PA-CXCR4)	505 nm light-controlled T-cell infiltration	Chemokine C−X−C motif receptor 4 (PA-CXCR4)	The first example of modifying chemokines	108
	Photosynthetic microcapsules modified with UCNPs	NIR light-controlled oxygen generation	Hypoxia relief; anti-PD-1 antibody	Reversed tumor hypoxic and immunosuppressive microenvironment	109
	Iron clusters-porphyrin metal-organic framework (MOF)	NIR light-controlled oxygen generation	Hypoxia relief; anti-PD-L1 antibody; tumor-associated antigens	Reversed tumor hypoxic and immunosuppressive microenvironment	110

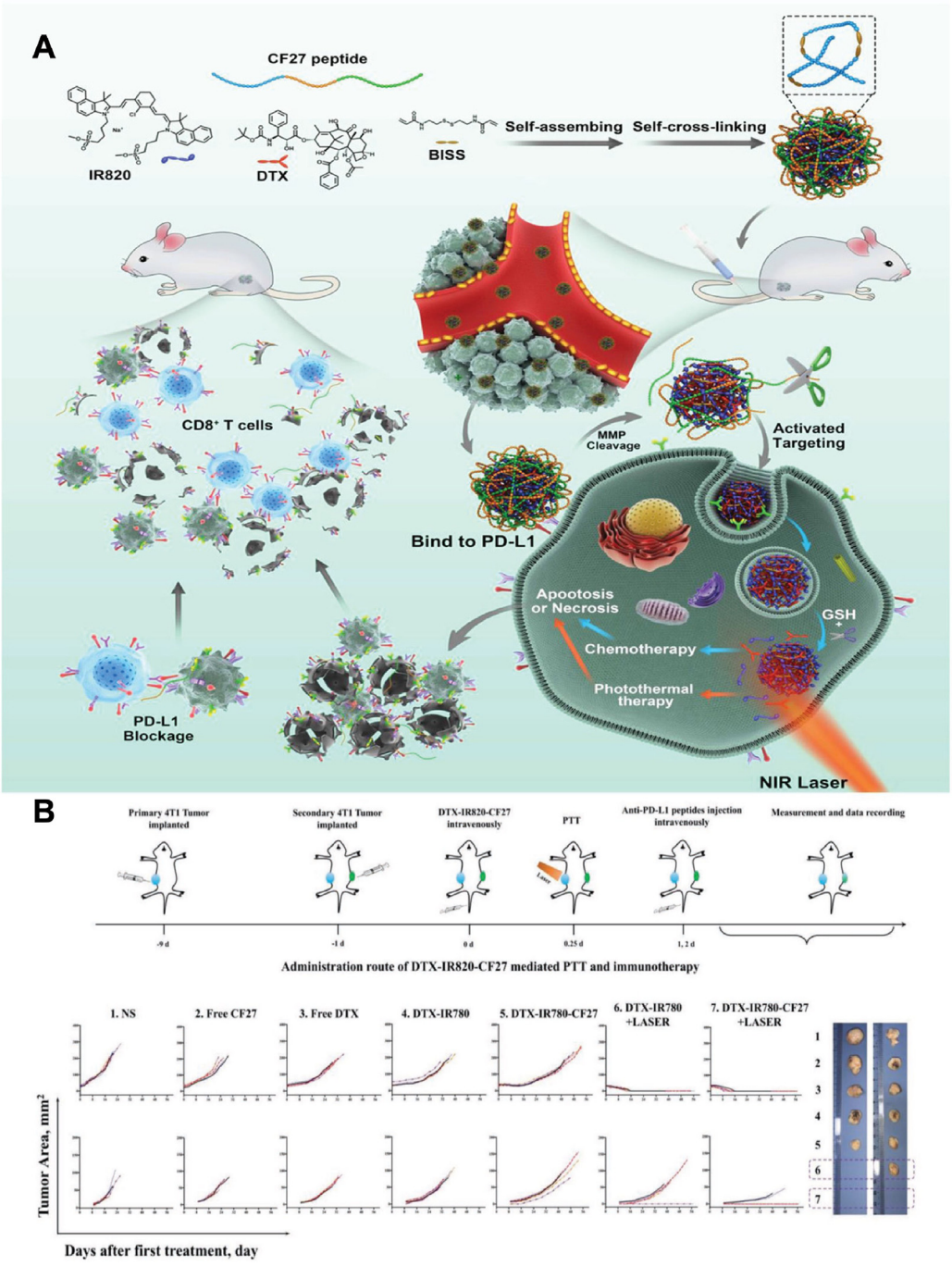

Figure 5 Illustration of self-assembly of NIR dye/drug/peptide hybrid nanosystem DTX-IR820-CF27. (A) Scheme of DTX-IR820-CF27 nanoparticles that can simultaneously deliver photosensitiser IR820, PD-L1 agonist CF27 and chemotherapeutic DTX, achieving combinatorial therapies. (B) The administration route of DTX-IR820-CF27-mediated PTT/chemotherapy/immunotherapy and anti-tumor effect in breast cancer mice model. Reprinted with permission from Ref. 84. Copyright © 2019 John Wiley and Sons.

of NLG919 and tumor-associated antigens, inducing a combined antitumor immunity.

Though light-responsive nanomedicine has been able to enhance the efficacy of checkpoint blockades, multiple injections might compromise patient compliance which could impede its clinical translation. The ideal strategy to integrate all components (photosensitisers, chemotherapeutics and checkpoint blockades) into one delivery system has not yet been reported. Existing light-responsive immunotherapeutic strategies for enhanced checkpoint blockades focused on combinational delivery of photosensitiser and checkpoint blockades. Recently, Liu et al.[89] developed a photocaging strategy that modified PD-1/PD-L1 inhibitor BMS-1 with a photo-removable molecule, (diethylamino)coumarin-4-yl] methyl (DEACM). The photocleavable prodrug showed effective PD-1/PD-L1 axis inhibition upon 420 nm light irradiation. The prodrug can be encapsulated into nanocarriers or form

nanoassemblies by virtue of its hydrophobicity. Such direct modification (*e.g.*, photocaging) of checkpoint blockades to facilitate light controlling of T cell functions remains a relatively unexplored and promising field which is worthy of further research.

Overall, several immune checkpoint blockades combined with photosensitizers and chemotherapeutics to enhance anti-tumor efficacy have been reported. However, current studies limited the use of light to trigger PDT/PTT to elevate anti-tumor immunity with immune checkpoint blockades. In the future, light-controlled precise drug delivery at the right time and place can be a direction to avoid unspecific immune system activation and resulting side effects like inflammation, autoimmune responses, etc. Precise modulation of immune checkpoint blockades by light can greatly enhance the treatment efficacy, thus reduce multiple injections and undesired side effects, which can greatly expand the application of immune checkpoint blockades for clinical applications.

3.2. *Light-controlled modulation of immune cells*

Adoptive cellular therapies such as CAR-T therapy are becoming the game-changing approach in treating cancers with promising clinical outcomes for hematologic cancers. However, personalized dosing remains the biggest challenge, as the immune response varies in individual patients and overdosing of T cell infusion can cause cytokine release syndrome and tumor lysis syndrome[115,116]. Hence, there is a great need to modulate immune cells with high precision in both space and time. Additionally, limited T infiltration in tumor microenvironment often hinders the application of adoptive cellular therapies. To this end, light-responsive delivery strategies can be utilized for the spatiotemporal control while phototherapies PDT and PTT can boost T infiltration in tumor area.

Light-switchable CAR-T cells have been developed to address the critical issue of "on-target, off-tumor" in CAR-T immunotherapy[117]. An interesting light-inducible gene activation system has been developed by combining CRY2-CIB1 (arabidopsis cryptochrome 2- cryptochrome-interacting basic-helix-loop-helix 1) dimerization with light-inducible nuclear translocation[90]. Upon blue light stimulation, the helix in the system unfolded to expose the NLS peptide which directed the translocation into the nucleus. Simultaneously, CRY2 can bind to CIB1 in the nucleus to trigger the reporter gene expression. The authors genetically encoded this system to T cells and achieved precise control with blue light in a mouse model. However, the wavelength of blue light limited its penetration depth, therefore hampering clinical translation of the reported system. Nguyen and colleagues[91] have solved this problem using upconversion nanoparticles. Firstly, CAR-T cells were engineered with photoresponsive modules in two separate domains (LiCAR T cells), respectively. Upon blue light irradiation, the two domains assembled and activated T cells to react with tumor antigen CD19 (Fig. 7A)[91]. To facilitate *in vivo* application of LiCAR T cells, a hexagonal-shaped upconversion nanoplate (β-NaYbF4:0.5% Tm@NaYF¬4 core−shell UCNPs) (Fig. 7B)[91] was injected together with LiCAR T cells to covert NIR light at 808 nm to blue light. Desirable therapeutic effects were achieved in hematologic and solid tumor mouse models with the combinational treatment. Comprehensive biosafety evaluation was carried out, LiCAR T cells treatment showed attenuated side effects including reduced B cell aplasia and cytokine storm

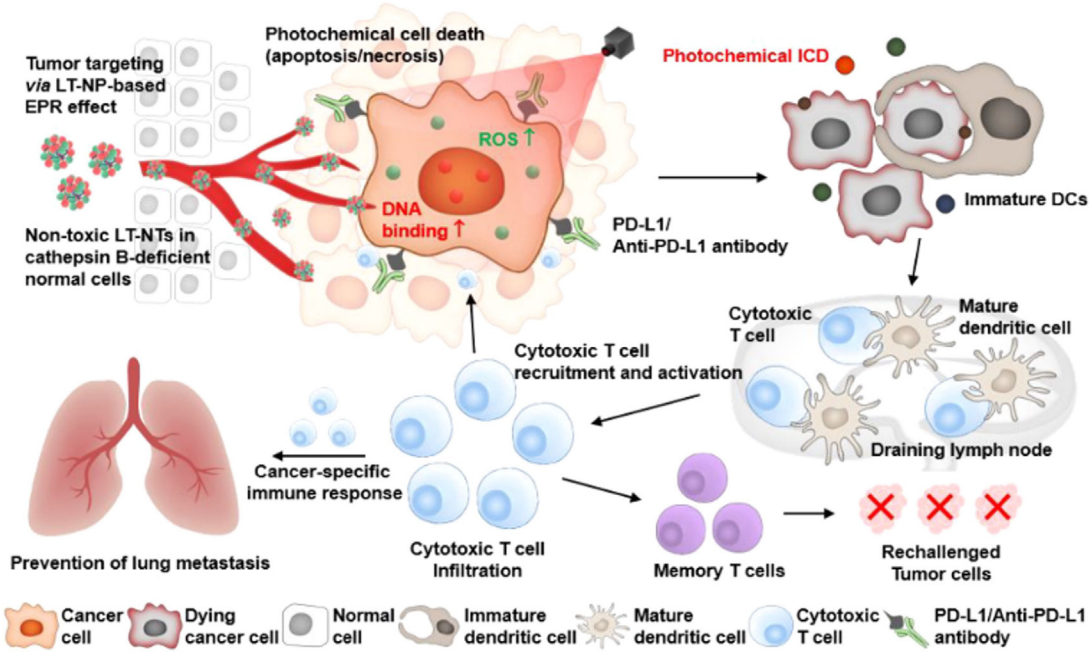

Figure 6 Schematic illustration of prodrug nanoparticles (LT-NPs) generating immunogenic cell death (ICD) at tumor sites upon light irradiation to potentiate PD-L1 checkpoint blockade cancer immunotherapy. LT-NPs accumulate in tumor area *via* the EPR effect and generate cytotoxicity and reactive oxygen species (ROS) upon light irradiation, then result in an effective ICD effect for dendritic cell (DC) recruitment, maturation, migration, and cytotoxic T cell activation. PD-L1 blockades induce a cancer-specific immune response and efficiently inhibit primary tumor progression and distant pulmonary metastatic tumors. Eventually, immunological memory established by the use of LT-NPs with PD-L1 blockade prevents tumor recurrence. Reprinted with permission from Ref. 87. Copyright © 2021 American Chemical Society.

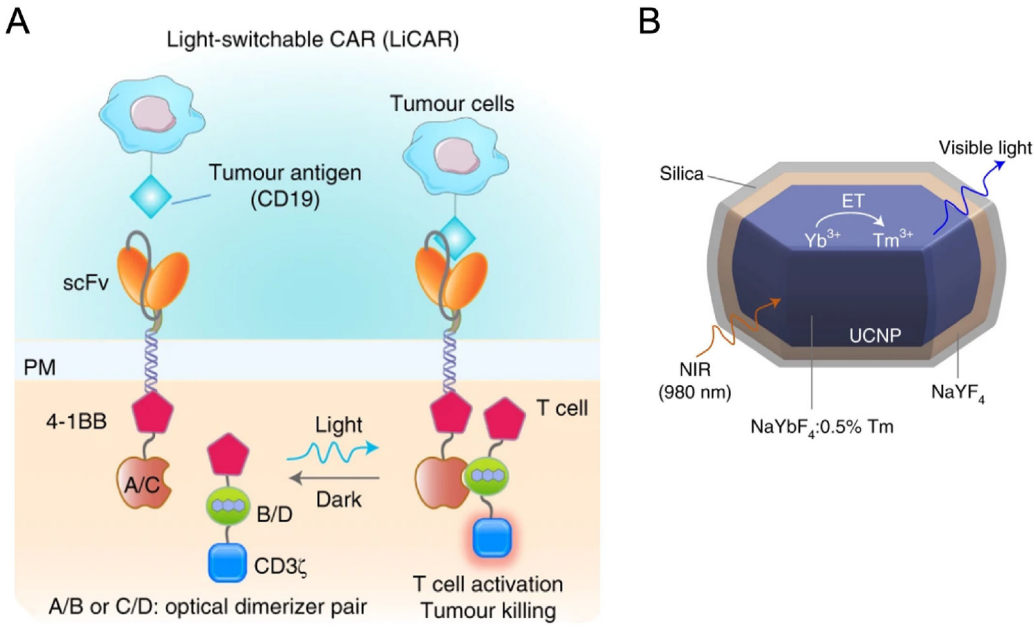

Figure 7 Graphic illustration of light-switchable CAR (LiCAR) T cells and upconversion nanoparticle. (A) Engineered CAR-T cells can only be switched on in the presence of tumor antigen (CD19) and blue light. (B) Core−shell structure of silica-coated upconversion nanoparticles which can NIR light to visible light. Reprinted with permission from Ref. 91. Copyright © 2022 Springer Nature Limited.

syndrome. This study provided a nano-optogenetic engineering strategy with robust efficacy and reduced side effects.

To tackle the challenge of limited T cell infiltration in tumor microenvironment, nanoparticles were used to deliver photosensitisers to generate hyperthermia in tumor tissues. The hyperthermia in tumor can change its compact structure, reduce interstitial fluid pressure and promote the perfusion of T cells[118]. Chen et al.[92] developed a poly (lactic-*co*-glycolic) acid (PLGA) nanoparticle loaded with photosensitiser ICG to potentiate CAR-T therapy (Fig. 8)[92]. T lymphocytes obtained from healthy donors were engineered to express the chondroitin sulfate proteoglycan-4 (CSPG4). CAR. $CSPG4^+$ T cells were then selected to exploit the overexpressed CSPG4 in melanoma. The PLGA nanoparticles were intratumorally injected into melanoma-bearing mice to induce PTT. $CSPG4^+$ T cells were intravenously injected to the mice 2 h after PTT. As a result, $CSPG4^+$ T cells was found to accumulate in tumors in PTT-treated mice due to the increased tumor perfusion and hypoxia relief induced by PTT. The PTT-CAR T cell combinational treatment significantly inhibited the tumor growth in melanoma-bearing mice with 2 out of 6 mice being completely cured. This study provided a potential platform to enhance the efficacy of CAR-T therapy in solid tumors by combining PTT and CAR-T therapy, which could inspire more combinational use of phototherapy and immunotherapy.

To conclude, light can not only induce PDT/PTT to enhance immune cell infiltration but also active CAR-T function in a spatiotemporal solution. Light-controlled CAR-T function can realize personalized dosing and minimize systemic cytokine release-associated toxicities. In this way, both two challenges can be addressed by exploiting light-responsive nanomedicine for adoptive cellular therapies. Elevated immune responses and precise drug delivery hold great promise to concurrently combat solid tumors. Future work can be focused on developing more longer-wavelength light-responsive delivery systems and applying them in adoptive cellular therapies for other cell types like CAR-NK and CAR-M therapies.

3.3. *Light-directed delivery of cancer vaccine*

Apart from T cells, APCs, including dendritic cells and tumor-associated macrophages, are playing central roles in the activation of adaptive immune response and can be targets for vaccine delivery to enhance cancer immunotherapy. Most of nanomedicine are designed to avoid opsonization and uptake by phagocytes during blood circulation which then provides sufficient accumulation at target sites *via* the EPR effect. Unlike conventional nanomedicine, uptake by APCs in circulating blood is advantageous for cancer vaccine delivery, namely extending antigen exposure to APCs[119]. However, the endosomal escape of antigens plays a key role in activation of immune responses. Apart from light-controlled cargo release strategies, photosensitisers also can disrupt the endosome and promote the escape of antigens upon light irradiation, owing to the production of ROS. Therefore, co-delivery of tumor antigens and photosensitisers by nanoparticles can be a promising strategy for cancer immunotherapy.

Cationic polymers are one of the priority options for delivering proteins, owing to their positive surface charge and excellent drug loading capacity. In one example, UV-responsive azido-terminated polypeptide was conjugated to glycosylated poly (amidoamine), introducing photo-responsiveness to the cationic polymer (Fig. 9)[93]. The synthesized polymers were then self-assembled with model antigen ovalbumin (OVA) in an aqueous solution to form antigen-loaded polymersomes. Under UV light irradiation, the polymersomes transformed into micellar aggregates at pH 7.4 and underwent complete disassembling at pH 5. As a result, an accelerated OVA release was observed in endosomal acidic pH after UV irradiation. Besides, endosomal escape of OVA and elevated tumor necrosis factor α (TNF-α) secretion from

macrophages were also observed as results upon UV light irradiation. However, the UV light-triggered cytosolic OVA release and endosome escape were only demonstrated in macrophage cell model. Though this study provided a light-responsive polymersome platform for cancer vaccine delivery, its *in vivo* applicability needs to be further investigated.

Researchers have also investigated combining metal nanoparticles with OVA in polymer nanocarriers to achieve accelerated OVA release. Copper sulfide nanoparticles were used as photosensitizers for ROS production and PLGA was used as the matrix to form nanoparticles[94]. Escalated cytokines and activation of cytotoxic T cells were achieved after NIR light irradiation. The activated immune response also inhibited distant metastatic tumor growth in a mouse model. In addition, Zhang et al.[95] developed a hydrophobic photosensitizer pheophorbide A (PheoA) grafted polyethyleneimine (PheoA-PEI) to deliver OVA. OVA was complexed with PheoA-PEI to form nanoparticles which produced ROS to promote antigen endosomal escape and subsequent cytosolic antigen release after light irradiation. In tumor-bearing mice, enhanced $CD8^+$ T cell proliferation and tumor inhibitory effect were found in mice injected with dendritic cells and the nanoparticles after irradiation with 670 nm laser at the tumor sites. Furthermore, OVA itself has been utilized as a carrier to deliver photosensitiser ICG to achieve combinational therapeutic effects. Pan and colleagues[96] have developed a multifunctional cancer vaccine by simple mixing of OVA and ICG (Fig. 10)[96]. The OVA-ICG nanovaccine has demonstrated desirable stability with an average size of 14.7 nm and a high antigen loading efficiency of 80.8%. It was observed that OVA-ICG nanovaccine promoted the maturity of an immature dendritic cell line, DC2.4 cells, characterized by elevated secretion of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), and increased expression of dendritic cell maturation markers, MHC-II, CD 80, and CD 83. Melanoma-bearing mice were intratumorally injected with PBS, ICG, and OVA−ICG nanovaccine, separately, followed by 808 nm laser irradiation to trigger PTT after injection. Owing to the fluorescence of ICG, the nanovaccine can be easily detected *in vivo*, providing a sensitive tracking of dendritic cells. Significant fluorescence enhancement in tumor regions was observed after injecting OVA−ICG nanovaccine. Besides, OVA-ICG nanovaccine and laser irradiation-treated group demonstrated significantly delayed tumor growth, in comparison with other groups. Tumor prevention was observed in mice immunized with OVA-ICG nanovaccine with light irradiation in tumor rechallenging experiment, together with increased $CD8^+$ cytotoxic T cells in tumors and elevated level of the anti-OVA immunoglobulin G (IgG) in serum. This study presented a robust nanovaccine with scaling-up potential which demonstrated the enhanced therapeutic efficacy by combining PTT and immunotherapy.

More interestingly, biomimetic platforms have also been exploited in the delivery of light-responsive cancer vaccine. Chen et al.[97] designed a tumor-specific antigenic nanoplatform with self-adjuvants activities by fusing melanoma cytomembrane vesicles (CMVs) and attenuated Salmonella outer membrane vesicles (OMVs) (Fig. 11)[97]. Bacterial OMVs provide the system with a rigid structure and ability to stimulate immunity cytokines, while melanoma CMVs can trigger antitumor immunity due to the specific antigens expressed on the membrane. The authors used a well-researched polymeric nanoparticle PLGA-ICG as the PTT core, and then coated with CMV-OMV fused membrane (PI@EPV). PI@EPV was found to have ability to stimulate dendritic cell maturation and T cell proliferation, which was further boosted by laser irradiation due to the PTT-induced ICD effect. In comparison with monovesicle-camouflaged formulations, PI@EPV demonstrated superiority in preventing tumorigenesis in mice challenged with B16F10 melanoma tumors, with 78.57% of tumor suppression rate. Moreover, the PI@EPV vaccination showed no noticeable tumor suppression in mice challenged with 4T1 breast cancer cells, indicating the specificity of anti-tumor immunity of melanoma cell vesicle-derived vaccine. Additionally, increased tumor specific cytotoxic T lymphocytes ($CD3^+$ $CD8^+$ CD107a) in spleens and enhanced induction of effector memory T cells ($CD3^+$ $CD8^+$ $CD44^+$ $CD62L^-$) were found in mice vaccinated with PI@EPV. Furthermore, PI@EPV plus laser irradiation also demonstrated great photothermal-immunotherapy synergy, with 80% of the treated mice becoming tumor free and reaching 60 d survival.

In another study, a photosynthetic microorganism PCC 7942 was utilized as photosensitiser and drug delivery platform[98]. Under light irradiation at 660 nm, PCC 7942 released pathogen-associated molecular patterns to act as adjuvants, which then activated dendritic cells and promoted the proliferation of anti-tumor CTLs. At the meantime, heat was generated by PCC 7942 to induce PTT effect. As a result, local injection of PCC 7942 in 4T1 tumors enhanced local tumor killing and antitumor immune response in tumor-bearing mice. This study has proved that microorganism is a promising light-controlled platform for cancer vaccine delivery. Nevertheless, comprehensive biosafety evaluation is needed prior to its clinical translation. A NIR light-controlled drug delivery system to boost immune response was developed by Chu and co-workers[99] *via* linking a UV light-responsive CpG oligonucleotides (ONDs) adjuvant with UCNPs. NIR-light irradiation can liberate ONDs from the nanoparticles, resulting in enhanced immune responses to combat solid tumors, since a substantially increased proportion of tumor-infiltrating T cells were observed in tumor microenvironment from *in vivo* experiment.

Apart from delivering antigens and adjuvants, ROS and heat-induced ICD served as internal antigens, which can be combined with other immunotherapies. Recently, Zhao and co-workers[100] designed an intracellular self-assembly-driven nucleus-targeted photo-immune stimulator. The system comprised of vorinostat (SAHA)-loaded manganese-porphyrin metal-organic framework (Mn(III)-TCPP MOF) modified with AS1411 aptamer. Intracellular glutathione-controlled release of AS1411 can self-assemble with photosensitizer TCPP[120], which further facilitated nucleus-targeted delivery of TCPP. The released manganese ions (Mn^{2+}) further enhanced the cytosolic DNA/cyclic GMP-AMP synthase-stimulator of interferon gene (STING) pathway-mediated innate immunity. The encapsulated SAHA can induce chromatin decompaction, synergistically promoting TCPP-mediated PDT. PDT-induced immunogenic cell death led to the co-activation of robust adaptive and innate anti-tumor immunity. In another research, a charge-reversal enhanced nucleus-targeting drug delivery system to improve immunotherapy was fabricated by Fang et al.[101] NIR light-responsive nanoparticles were utilized to co-deliver Toll-like receptor (TLR2) agonist Poly (I:C)[121] and photosensitizer chlorin e6 (Ce6). Light irradiation can not only trigger PDT-induced ICD but also turn the surface charge of nanoparticles from positive to negative, which led to the dissociation of the nanoparticles. Poly (I:C) release can cooperatively function with ICD to boost anti-tumor immunity and inhibit tumor growth as a result.

Light-responsive cancer vaccines are still at the early stage of development and current research are mainly focused on protein-

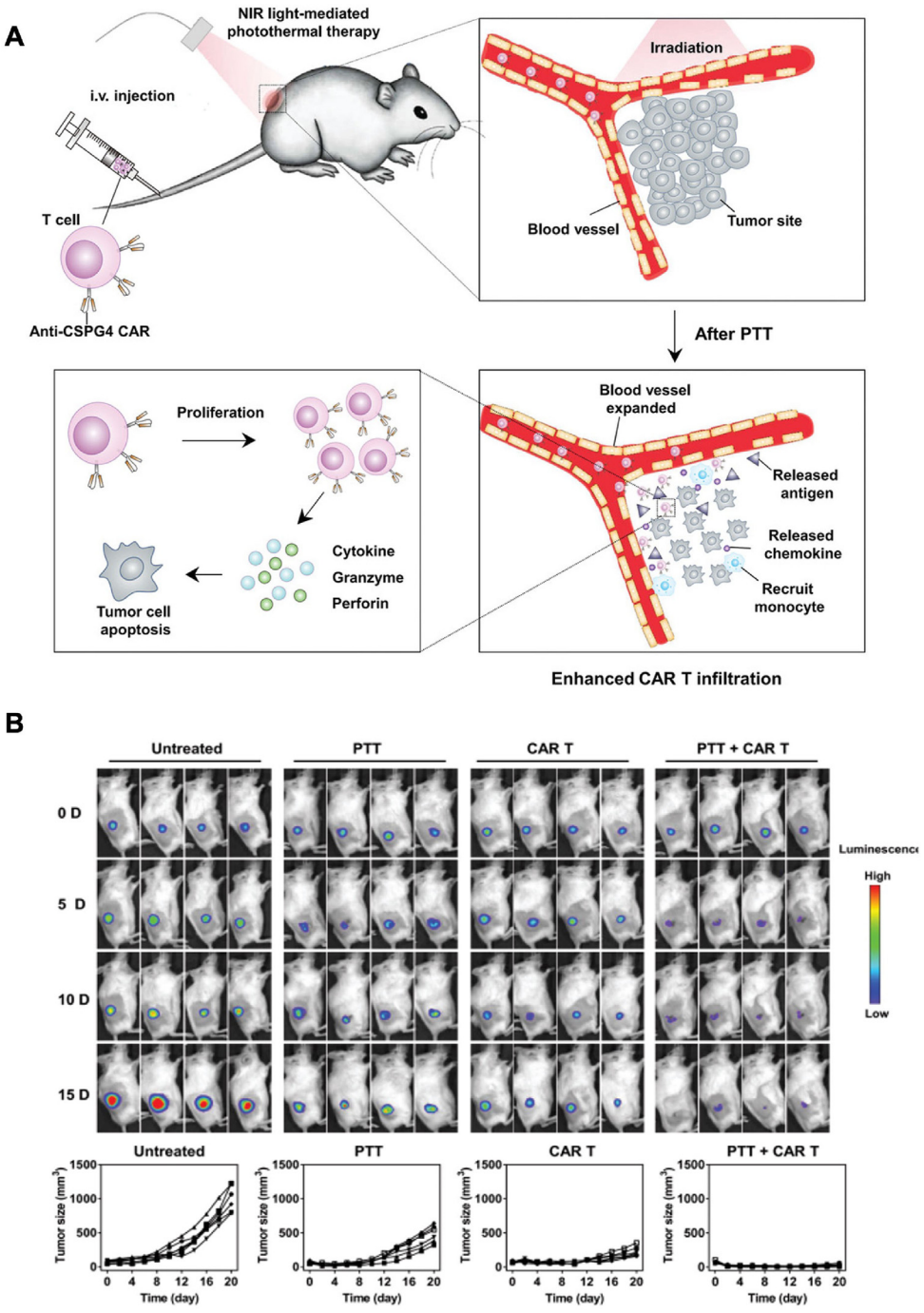

Figure 8 Example study of utilizing PTT to potentiate CAR-T therapy. (A) Schematic illustration of the PTT induced by nanomedicine and promoting successive CAR-T cell infiltration in the tumor and cytokine release. (B) Representative images and tumor growth kinetics of tumor-bearing mice with different treatments, namely PTT, CAR-T and their combinational therapy. Reprinted with permission from Ref. 92. Copyright © 2019 John Wiley and Sons.

based antigen delivery. More advanced light-responsive delivery systems to facilitate nucleus targeting are needed for the development of RNA/DNA vaccination. Detailed *in vitro* and *in vivo* studies are necessary to demonstrate their clinical potential. Moreover, most of studies focus on co-deliver tumor antigens and photosensitizers to achieve synergistic anti-tumor effects. The heat or ROS generated by photosensitizers can destroy the endosome and facilitate the escape of antigens upon light illumination. More novel light-responsive delivery strategies can be exploited to co-deliver antigens, photosensitizers along with adjuvants to realize boosted immunity with maximum treatment efficacy.

3.4. Light-responsive strategies to modulate tumor microenvironment to enhance immunotherapy

Immunotherapy has undergone rapid development in recent years with well-established modalities being clinically used daily, including checkpoint blockades and CAR-T cell therapies.

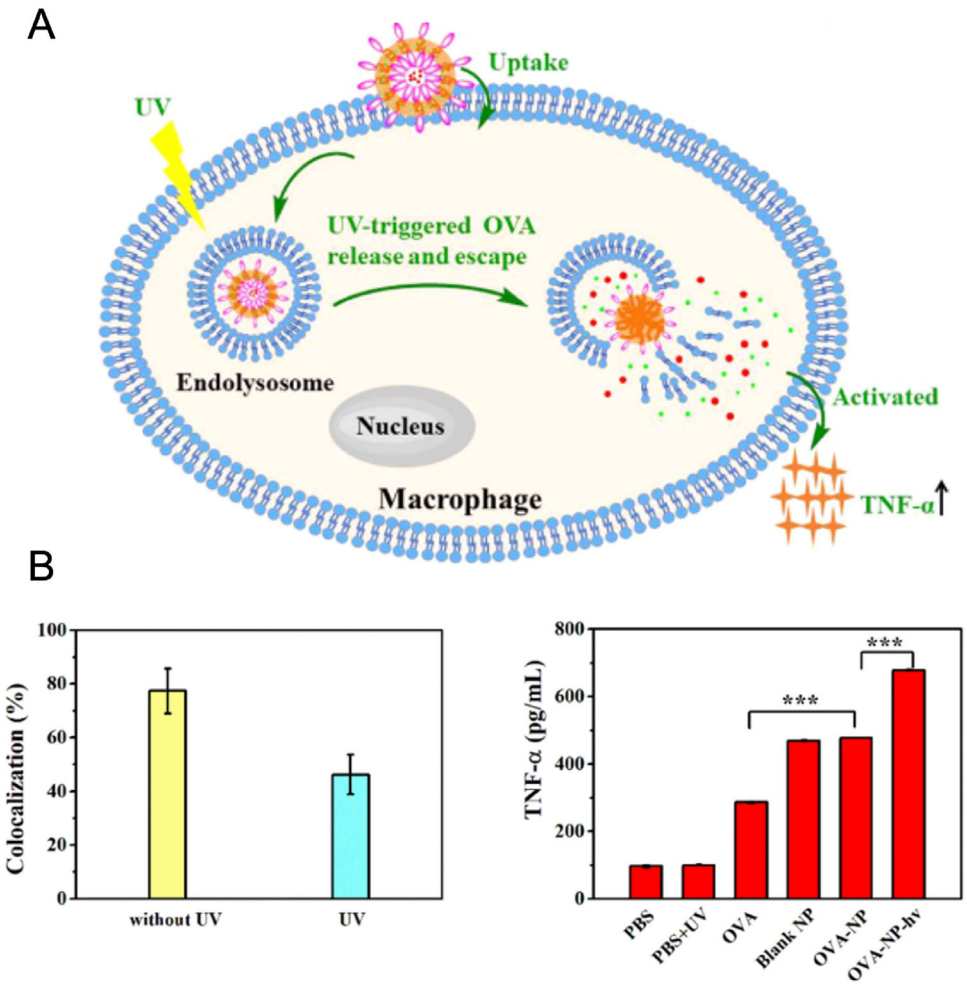

Figure 9 (A) Cellular uptake of OVA-loaded light-responsive polymersomes. UV light triggers OVA release and escape from endosomes, resulting in macrophage activation and TNF-α secretion. (B) Co-localization of OVA-loaded polymersomes and endolysosomes in macrophages and TNF-α secretion with/without UV light irradiation. OVA, antigen ovalbumin; TNF-α, tumor necrosis factor α. Reprinted with permission from Ref. 93. Copyright © 2020 American Chemical Society.

However, the number of patients who showed resistance to immunotherapies is not negligible. Scientists have paid much attention to the immunosuppressive microenvironment surrounding tumors and identified the factors that contribute to the hampered immunity in cancer patients. A variety of strategies aiming to enhance patients' response to immunotherapies are based on alterations of the complex immunosuppressive tumor microenvironment like regulating functions of cells within TME including immune cells and tumor cells, or modulating physiochemical properties including hypoxia, acidity, high levels of ROS, dense extracellular matrix, and abnormal vasculature. Light-responsive nanomedicine is particularly promising in the modulation of tumor microenvironment, due to their properties of specific targeting, spatiotemporally controlled drug release and desirable drug loading capacity.

Macrophages, one of the major cell types in the tumor microenvironment, can be divided into M1 macrophages with antitumor functions, and M2 macrophages that promote tumor progression[122]. In the immunosuppressive microenvironment, M2 macrophages are the dominant phenotype associated with poor clinical outcomes in several cancer types[123]. As TAMs consist of M2 macrophages and a small population of M1 macrophages, repolarizing the TAMs to immune-activating phenotype is with copious potential[124,125]. A variety of strategies have been developed to repolarize TAMs, including using cytokines, microRNAs and phototherapies[122]. PDT and PTT can produce ROS under light irradiation to induce ICD, release damage-associated molecular patterns (DAMPs), and polarize macrophages from the immunosuppressive M2 phenotype to the antitumor M1 phenotype[126–128].

Biomimetic nanomedicine, such as cell membrane or extracellular vesicle-coated nanoparticles, have been extensively investigated to target macrophages and release therapeutics for repolarization. Yue et al.[102] developed a polydopamine nanoparticle loaded with the TAMs repolarization agent TMP195. The nanoparticles were then coated with macrophage membrane (P/T@MM NPs) Polydopamine is a photothermal transduction agent, which can effectively convert NIR light to heat and induce ICD and the secretion of inflammatory cytokines. The macrophage membrane on P/T@MM NPs surface provides excellent targeting ability to the TAMs, which are enriched in the post-PTT tumor microenvironment. As a result, in a breast tumor model, P/T@MM NPs exhibited preferential accumulation in tumor area

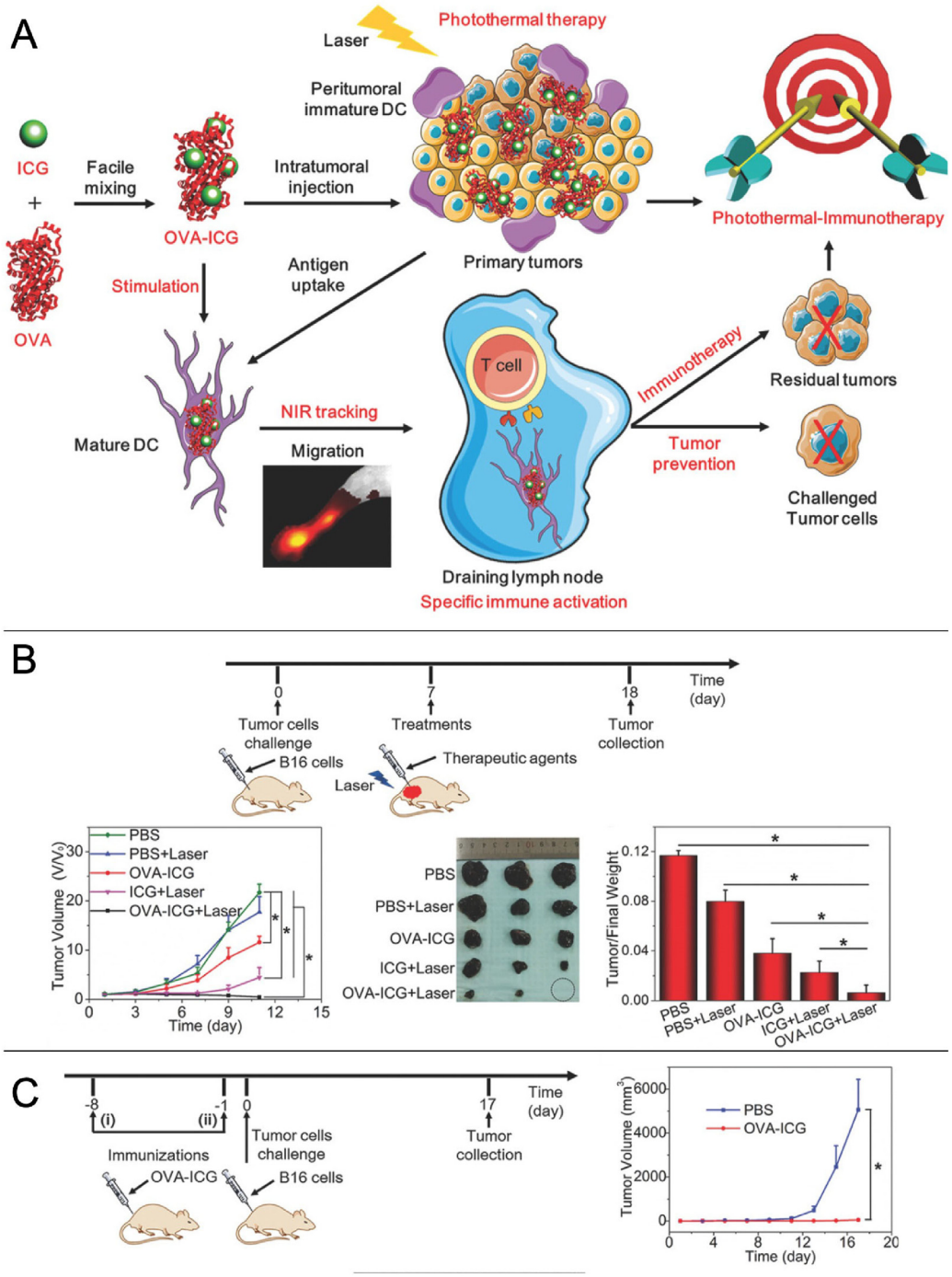

Figure 10 Nanovaccine fabricated with OVA and photosensitiser ICG to achieve photothermal immunotherapy against tumor. (A) Graphic illustration of the fabrication of OVA and ICG to form nanovaccine and the anti-tumor mechanism. (B) Protocol of *in vivo* anti-tumor experiments and tumor growth monitoring after different treatments. (C) Tumor prevention assay design and tumor growth curves of the mice treated with PBS or OVA−ICG. OVA, ovalbumin; ICG, indocyanine green. Reprinted with permission from Ref. 96. Copyright © 2019 John Wiley and Sons.

and significantly elevated the level of M1-like TAMs ($CD80^+$ in $F4/80^+$ cells) after PTT. Additionally, after PTT, tumor-infiltrating immune cells, including $CD3^+$ $CD8^+$ CTLs, were significantly increased while the immunosuppressive cells such as MDSCs and Tregs dramatically decreased. TAMs repolarization and alterations in tumor microenvironment eventually led to a tumor-elimination rate of 60%. Similar design has been exploited in another study by coating upconversion nanoparticles conjugated with photosensitizer with tumor-associated macrophage membrane (TAMM) derived from the primary tumor (NPR@TAMMs) (Fig. 12)[103]. The upconversion nanoparticles NaYF4:Yb,Er@NaYF4 conjugated with photosensitiser Rose Bengal were able to respond to NIR light at 980 nm facilitating treatment for deep-seated tumors. TAMM on the surface endows the system with unique antigen-

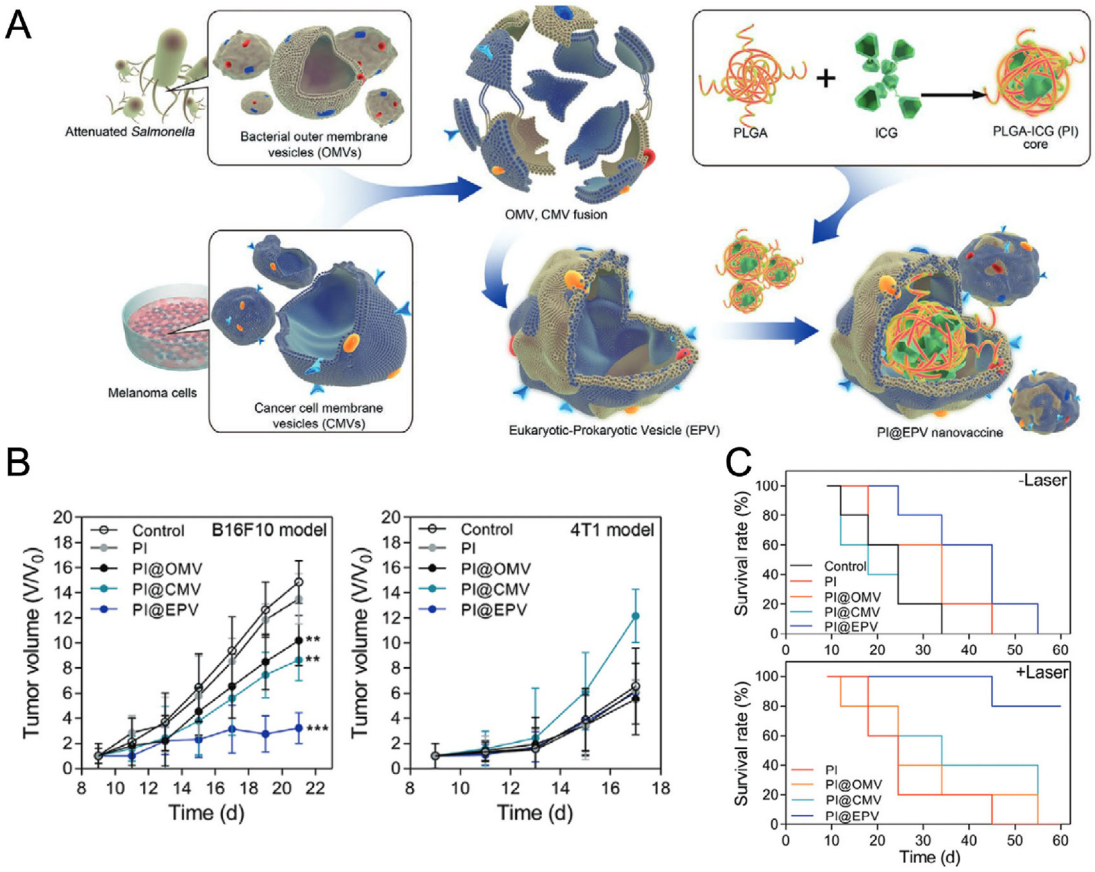

Figure 11 Tumor-specific biomimetic nanovaccine with PTT inducer in the core. (A) Preparation of eukaryotic−prokaryotic membrane-coated polymeric ICG nanoparticle, PI@EPV. (B) Tumor growth curves of B16F10 tumors and 4T1 tumors with different treatments. (C) Survival rate of tumor-bearing mice after nanovaccine injection with or without laser irradiation to trigger PTT. Reprinted with permission from Ref. 97. Copyright © 2019 John Wiley and Sons.

homing affinity and immune compatibility. Notably, TAMM can bind with CSF1 which is a key regulator of macrophage differentiation. By combining PDT and TAMs repolarization, NPR@TAMMs demonstrated superior tumor inhibition efficacy and antitumor immunity efficiency in an orthotopic mouse model with primary and distant breast tumors.

Furthermore, polymeric nanoparticles have also been utilized to inhibit tumor growth by repolarizing TAMs into the tumoricidal M1 phenotype[104]. The polymeric nanoparticles (PPV-PSMA-NPs) were co-assembled by poly (styrene-*co*-maleic anhydride) (PSMA) and conjugated polymer poly [2-methoxy-5-(2-ethylhexyloxy)-1,4-phenylenevinylene] (PPV) with photosensitivity. *In vitro* results showed that PPV-PSMA-NPs were co-localized with lysosomal tracker inside macrophages (RAW 264.7) for 3 days, allowing modulations to alter the biological function of macrophages. Macrophage repolarization was then elucidated by immunofluorescence staining of tumor slices from the nanoparticles-treated tumor-bearing mice. Up-regulation of M1-related markers CD80, inducible nitric oxide synthase (iNOS) and inflammatory factor TNFα were observed, along with down-regulated M2 markers CD206 and CD163. PDT triggered by light irradiation was able to accelerate tumor cell death by ROS generation in cell models, but not yet tested in animal models. Besides, white light was used in this study which raises concerns about possible phototoxicity. Furthermore, light-responsive nanoparticles have been exploited to activate neutrophils[129] and natural killer cells[130], therefore potentiating antitumor immune response.

An engineered macrophage that can load nanoparticles to enhance tumor tropism capacity was developed by Huang and co-workers[105] to achieve enhanced chemo/photo/immunotherapy. Oxaliplatin prodrug and photosensitizer Zinc phthalocyanine are designed as NIR light-responsive drug vectors and concurrently loaded in the lipid bilayer. The drug encapsulated polarized macrophages to the anti-tumor M1 phenotype, providing macrophages the ability to exert anti-tumor effects themselves. The combination of PD-L1 blockade with PDT/chemotherapy displayed desired anti-tumor efficacy in primary and bone metastatic breast cancer.

Other than immunosuppressive cells, the aberrant vasculature with dysfunctional blood flow is another major reason for the immunosuppressive environment. Zhou et al.[106] designed a photosensitizer-based nanoplatform to achieve enhanced photodynamic immunotherapy by promoting vascular normalization in tumor microenvironment (Fig. 13)[106]. The nanoplatform (CAM NP) was self-assembled by photosensitizer Ce6, tyrosine kinase inhibitor axitinib and indoleamine 2,3-dioxygenase (IDO) inhibitor dextro-1-methyl tryptophan with the help of human serum albumin. Axitinib can inhibit vascular endothelial growth factor receptors (VEGFR), thus promoting the normalization of blood vessels[131]. On the other hand, IDO inhibitors can suppress the conversion of tryptophan to kynurenine, thereby enhancing the

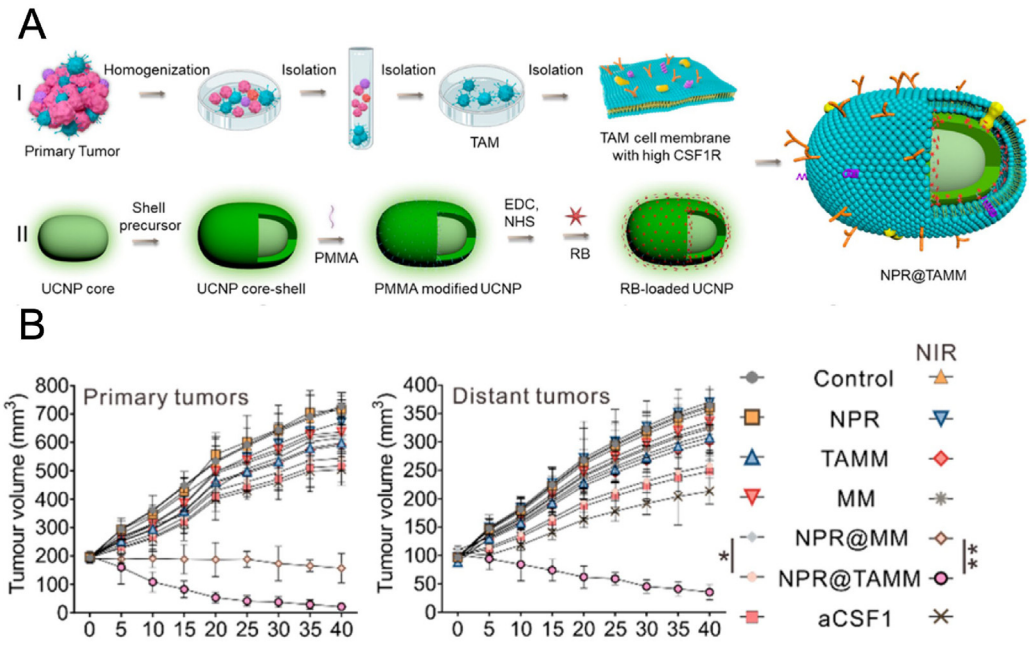

Figure 12 Tumor-associated macrophage membrane (TAMM)-coated upconversion nanoparticles NPR@TAMMs for enhanced photodynamic immunotherapy. (A) Preparation of upconversion nanoparticle conjugated with photosensitiser rose bengal (RB) (I), and coated with cell membrane extracted from primary tumor-associated macrophages (TAMs) (II). (B) Primary and distant tumors were significantly suppressed by combining PDT and TAMs repolarization using NPR@TAMMs. Reprinted with permission from Ref. 103. Copyright © 2021, American Chemical Society.

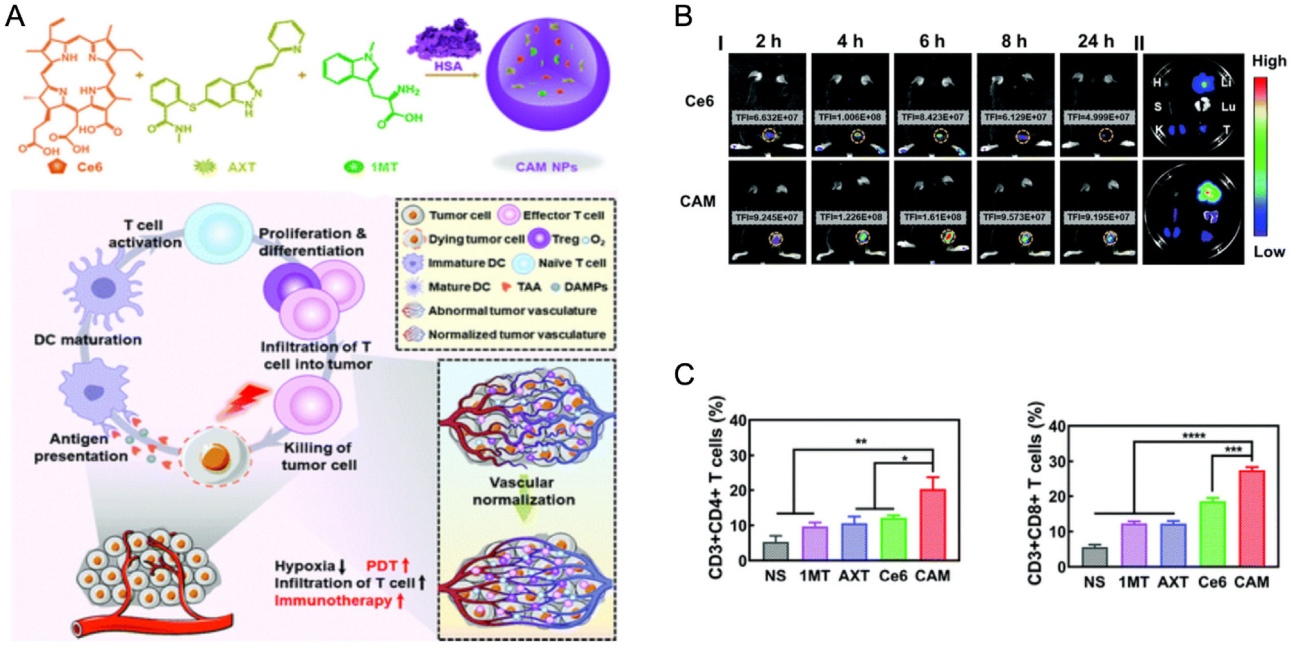

Figure 13 Photosensitizer-based nanoplatform to achieve enhanced photodynamic immunotherapy. (A) Graphic illustration of the fabrication of the nanoplatform CAM NP and mechanisms of enhanced PDT and anti-tumor immune responses. (B) Tumor targeting effect of CAM NPs based on biodistribution compared to free Ce6. (C) Increased T cell infiltration in tumors treated with CAM NPs, in comparison with free drug-treated groups. Reprinted with permission from Ref. 106. Copyright © The Royal Society of Chemistry 2021.

immune response[132]. CAM NPs exhibited excellent *in vitro* cytotoxicity on melanoma cell line B16F10 after light irradiation and increased apoptosis rate (63.4%) with peripheral blood mononuclear cells incubation. *In vivo* evaluation elucidated that CAM NPs could accumulate in tumor area and demonstrated significant inhibition of tumor growth with the aid of laser irradiation. Furthermore, in comparison to the control group, the blood vessel density in CAM NPs treated tumors was significantly increased based on anti-CD31 immunohistochemistry (IHC) staining. A remarkably higher proportion of CTLs and reduced

population immunosuppressive TAMs were observed in both primary and abscopal tumors, in comparison with those in other groups (blank, Ce6 and single inhibitor-treated groups). Thereby, modulation of the tumor microenvironment was achieved by normalization of tumor vessels and IDO inhibition, resulting in enhanced immune response and amplified PDT effect. In addition, light-responsive strategies have been used in selective activation of cytokines in the tumor microenvironment with high spatiotemporal precision. Upon irradiation, chemically modified cytokines undergo changes in conformation or polarity, resulting in a difference in binding affinity to the target receptor and reducing off-target effects. Photoswitchable galactosylceramides have been developed to activate natural killer T cells under 370 nm light, to produce immunomodulatory cytokines such as IFN-γ[107]. Moreover, photoactivatable chemokine C−X−C motif receptor 4 (PA-CXCR4) has been developed to transmit intracellular signals in response to 505 nm light[108]. Increased T-cell infiltration in tumors has been observed in melanoma-bearing mice, resulting in enhanced immune responses and optimal outcomes in the later adoptive cellular therapy. However, the combinational use of nanomedicine with photoswitchable cytokines remains unexplored and yet with potential in modulation of tumor microenvironment.

Besides modulating abnormal vasculature, tumor immunosuppressive environment can be reversed by creating a hyperoxic tumor microenvironment. A photosynthetic microcapsule was developed by encapsulating cyanobacteria and upconverting nanoparticles in alginate microcapsules[109]. The microcapsules can convert laser light into red-wavelength radiation, which triggers stable cyanobacterial photosynthesis, increasing the oxygen level in the tumor. The developed system was applied to combine with anti-PD-1 therapy. The improved anti-tumor efficacy was confirmed in orthotopic breast cancer mouse model and transplanted hepatocarcinoma in rabbit model. In another research, a nanoscale metal−organic framework, Fe-TBP made of Fe_3O clusters and porphyrin ligands was prepared to overcome tumor hypoxia[110]. Upon light irradiation, a cascade reaction in which intracellular H_2O_2 was decomposed by the Fe_3O clusters to produce oxygen through a Fenton-like reaction whereas the generated oxygen was converted to cytotoxic singlet oxygen ($^1O_2$) by photoexcited porphyrins. The efficacy of PDT can be greatly enhanced by generated oxygen. Furthermore, PDT-induced anti-tumor immunity concurrently worked with anti-PD-L1 immune checkpoint blockade, resulting in effective suppressed growth of both primary and distant tumors.

Light-responsive nanomedicine surpasses in its ability to modulate tumor microenvironment by virtue of its characteristics of precisely controlled drug release and specific targeting. Existing examples focus on repolarizing tumor-associated macrophages and normalizing tumor microenvironment. More advanced light-responsive drug delivery system can be developed to regulate the functions of other types of immune cells, fibroblasts and etc., which also play a crucial role in tumor microenvironment.

4. Challenges and future directions

Cancer immunotherapy research has begun to bear fruit only in recent years, principally in the form of checkpoint blockades, CAR-T cell therapies and cancer vaccines, while new approaches, such as modulation of tumor microenvironment, are being developed rapidly. With the same momentum, a growing number of advanced nanomedicines for cancer immunotherapy are being investigated in pre-clinical and clinical stages. Given the ease of spatiotemporal control, light-responsive nanomedicine has attracted increasing attention in research on cancer immunotherapy. In the review, the combination of light-responsive nanomedicine with four types of widely used immunotherapies was illustrated with representative examples. The mechanism, virtues and limitations of each modality were discussed as well.

Despite the potential achievements summarized in this review, light-responsive nanomedicine for immunotherapy is still at its early stage with preclinical studies. More endeavours are still needed to tackle the unresolved issues to advance its clinical translation potential. Further progresses can be expected particularly in the following aspects: (1) Comprehensive evaluation of biosafety studies. Comprehensive biosafety studies are needed to characterize the toxicity profiles of nanomedicine in cancer immunotherapy. Light-responsive nanomedicine has been demonstrated to have greater selectivity and higher efficacy in activating adoptive immune response, but it is unclear whether the autoimmune side effects will be increased. (2) Mass production and manufacturing cost. Nanomedicine and cancer immunotherapy are generally more expensive than other existing treatments even in the optimistic setting. For example, in CAR-T therapy cell generation and administration processes can cost $373,000−475,000[133]. Introducing light-responsiveness may lead to an increase in complexity and duration for manufacturing. Therefore, simple formulation design with scaling-up capability will greatly accelerate the clinical translation of light-responsive nanomedicine in cancer immunotherapy. (3) Development of advanced light source. A homogeneous illumination from light source is a key factor for the success of light-responsive nanomedicine. In addition, the penetration of light *in vivo* is also a major concern to realize desired treatment efficacy. Despite that the light within the NIR window displays relatively better tissue penetration, the precise light delivery at the diseased regimen remains a current challenge. One study has applied optical fibres in treating esophageal carcinoma *via* introducing optical fibres through the biopsy channel of the endoscope to improve light delivery precision and overcome the limitation of delivery distance[134]. For tumors deep in the human body such as liver cancer, portable and insertable micro-LEDs with feasibility to match with targeting tissues serve as a potential modality to overcome the limited penetration of light source.

Furthermore, a variety of strategies can be exploited to improve the treatment efficacy of light-responsive nanomedicine for immunotherapy. Firstly, four types of immunotherapies can work cooperatively to achieve boosted immunity. Combination of different immunotherapies represents as a bellwether for clinical use in the future. Secondly, the internal stimuli, such as enzymes, redox, hypoxia and pH, can be employed with light irradiation for dual-responsive drug delivery to further improve precise targeting and reduce off-target drug release[135].

Light-responsive nanomedicine for cancer immunotherapy is at the cutting edge of cancer therapy. The precise and controllable nature of light-responsive nanomedicine fits the need for cancer immunotherapy. With continuous advancements in light-responsive nanotechnology and increasing knowledge of cancer immunology and biology, it is anticipated that light-responsive nanomedicine will move from the laboratory to the clinic.

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Author contributions

Weirong Kang and Weiping Wang conceptualized and designed this article. Weirong Kang and Yuwei Liu wrote and revised the manuscript. Weiping Wang revised the manuscript. All authors have read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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