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Nanotechnology Synergised Immunoengineering for Cancer

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Abstract

Novel strategies modulating the immune system yielded enhanced anticancer responses and improved cancer survival. Nevertheless, the success rate of immunotherapy in cancer treatment has been below expectation(s) due to unpredictable efficacy and off-target effects from systemic dosing of immunotherapeutic. As a result, there is an unmet clinical need for improving conventional immunotherapy. Nanotechnology offers several new strategies, multimodality, and multiplex biological targeting advantage to overcome many of these challenges. These efforts enable programming the pharmacodynamics, pharmacokinetics, delivery of immunomodulatory agents/co-delivery of compounds to prime at the tumor sites for improved therapeutic benefits. This review provides an overview of the design and clinical principles of biomaterials driven nanotechnology and their potential use in personalized nanomedicines, vaccines, localized tumor modulation, and delivery strategies for cancer immunotherapy. In this review, we also summarize the latest highlights and recent advances in combinatorial therapies avail in the treatment of cold and complicated tumors. It also presents key steps and parameters implemented for clinical success. Finally, we analyse, discuss, and provide clinical perspectives on the integrated opportunities of nanotechnology and immunology to achieve synergistic and durable responses in cancer treatment.

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1. Introduction

The conventional therapies, such as surgery, radiation, and chemotherapies or their combination, have shown significant improvements in cancer treatment. Surgery is feasible only in removal of primary and solid tumors. [1] However, it is often difficult to detect tumors in the early stages.[2] While chemotherapy and radiation treatments are often recommended but encountered higher relapse.[3] Thus, research has been focused on immunotherapies in which the human body's own defense mechanism acts against cancer cells. Cancer immunotherapy is considered a paradigm shift in cancer treatments.[4] The immune system is primarily responsible for protecting humans from foreign particles and microorganisms (bacteria, viruses, and organisms) in the human body. The effective function of immune system is coordinated by two cellular compartments, i.e., "innate" and "adaptive" immune system[5]. The innate immune system involves phagocytes (macrophages and dendritic cells) and granulocytes (neutrophils, eosinophils, basophils, and mast cells), while adaptive immune response is governed by T-lymphocytes and B-lymphocytes. The innate immune system provides the first line of defense by distinguishing widespread molecular recognitions on pathogens; thus, phagocytes and granulocytes are instantly stimulated and deployed to the sites of inflammation, infection, or tissue damage. In addition, lectin and other associated pathways are considered as complementary components of the innate immune system. Whereas, adaptive immune system recognizes pathogens *via* specific antigen presence. This immune component is also referred as "memory" to the immune response, i.e., it can rapidly recollect specific immune responsivity to molecule or antigens that are present on pathogen that had seen in the past. In general, immunotherapy is used to treat a disease either by inhibiting or enhancing the immune system. Cancer immunotherapy functions by producing the immune response and train the immune cells to search and destroy the cancer cells. The discovery of immune checkpoint inhibitors by James Allison and Tauku Honjo (the 2018 Noble laureates) reestablished the belief in immunotherapy for the treatment of cancer[6, 7]. Currently, immunotherapy is one of the clinically proven treatment options for many cancers to enhance the immune system by employing cytokines, immune checkpoint inhibitors, engineered T cells, monoclonal antibodies, and cancer vaccines.[8]

1.1. Cytokines

Cytokines are a group of proteins and major regulators of innate and adaptive immunity. Cytokines display significant role in boosting the immune system. Interferon (IFN), interleukins (IL), and Granulocyte-macrophage colony-stimulating factor (GM-CSF) are widely employed cytokines in cancer immunotherapy [9]. In response to microbial infection, immune cells produce interferons that are responsible for the maturation of other immune cells like natural killers (NK), macrophages, dendritic cells, and lymphocytes [10-12], The interferon also responsible for the inhibition of angiogenesis in the tumor, while interleukins

help in stimulating CD4+ and CD8+ T-cells [12-14]. GM-CSF aids in the homeostasis of T-cells, which is critical for its survival, also supports the differentiation of dendritic cells to promote antigen presentation. GM-CSF, as well as granulocyte colony-stimulating factor (GCSF), are also used for maintaining the number of granulocytes after chemotherapy and radiotherapy [15]. Cytokines were first time introduced for immunotherapy with the approval of IFN. Currently, 3 recombinant cytokines have been approved for immunotherapy, and several more are in pipeline [16] (Table 1). However, high dosages of cytokines are required due to shorter half-life that leads to vascular leakage and cytokine release syndrome. Also, it might cause immune attack on the healthy tissue [9, 17]. Towards it, IL-15 and IL-21 have been found to be advantageous in comparison to IL-2 [18, 19]. Current treatment strategies include usage of cytokines in combination to other therapies like chemotherapy and checkpoint inhibitors for reducing the dosage-related adverse effects [11].

1.2. Checkpoint inhibitors

Checkpoint inhibition is a new approach in cancer immunotherapy and demonstrating clinical benefits. The immune checkpoint inhibitors are capable of maintaining healthy environment and protect the tissue from self-immune attack [20, 21]. These inhibitors release biological damper of the immune system; thus, immune cells can efficiently recognize and attack tumor cells. Therefore, such therapy is called immune checkpoint blockade (ICB). For example, during the inflammation, T cells get activated and start expressing the programmed cell death protein 1 (PD-1) to recognize the abnormal and cancerous cells. The cancerous cells evade the immune response by overexpressing the programmed death-ligand 1 (PD-L1) for binding to PD-1 and render T cells inactive [22, 23]. Thus, the blocking of this PD-1 and PD-L1 interaction with the help of checkpoint inhibitors (like monoclonal antibodies, mAbs) facilitates the death of cancer cells by preventing the inactivation of T cells (Fig. 1). Another checkpoint inhibitor is cytotoxic T lymphocyte antigen 4 (CTLA-4), a co-inhibitory molecule to regulate the extent of T cells activation. The ligands of CTLA-4 are CD80 and CD86, which inactivate the response of T cells [24]. It is also under investigation as some of the CTLA-4 blocking antibodies can also deplete the T cells population [25-27]. Currently, five checkpoint inhibitors for the PD-1/PD-L1 and one CTLA-4 are available for cancer treatment (Table 1). More than 700 clinical trials are underway to test the efficacy of several checkpoint inhibitors alone or in combining them with other cancer therapies [28].

Although checkpoint inhibitors have tremendous potential, it has been found to cause side-effects in different organs. Also, many patients have been found unresponsive to checkpoint inhibitors [29-32]. Thus, there is a need for the study of factors responsible for showing the responsiveness to the checkpoint inhibitors. It could be the low number of infiltrated T cells, adaptive resistance, low expression of checkpoints, deregulation of checkpoint inhibitors as well as tumor microenvironment capabilities of immune suppression [33, 34].

1.3. Engineered T cells

In this type of immunotherapy, the T cells are derived from the patient(s) and engineered to express the chimeric antigen receptors (CARs) that are specific to the particular type of antigen present on the cancer cells. These engineered T cells are re-administered to the same

patients [35] (Fig. 1). Unlike other types of immunotherapy, it is a one-time treatment, and engineered T cells can retain their activity for more than a decade [36, 37]. Many patients have got complete remission from cancer. However, the long-term effect of this treatment is still under observation [38, 39]. The chimeric antigen receptor T (CAR T) cells initially target the CD19 that are present on the B cells' leukemia and lymphomas. At present, two CAR T-cell based therapy (tisagenlecleucel and axicabtagene ciloleucel) have been approved for acute lymphoblastic leukemia and large B cells lymphoma, respectively [40, 41] (Table 1). The success of CAR T-cell therapy has encouraged the development of different CAR T-cells to target multiple antigens towards developing generalized cancer therapy [35, 42].

Although CAR T-cell therapy is a most promising therapy, limitations, such as expensiveness, time-consuming, complexity of the process, neurotoxicity, and cytokine release syndrome, are commonly encountered [43-45], The penetration incompetence of engineered T cells into the core of the solid tumor is another drawback of the CAR T-cell therapy [29, 46].

CAR T-cell therapy is also successful in Epidermal growth factor receptor variant III (EGFRvIII) expressing glioblastoma [47]. T cell receptor-transduced T cells (TCR T) have come up instead of CART cells. Unlike the CART cells, TCR-T cells are major histocompatibility complexes (MHCs) specific and are highly matched to the patients' immune profile [48]49]. Engineered T-cell therapy is seeking novel pathways for improving its therapeutic efficacy [50].

In addition, several agonist antibodies bind to the receptors of T cells, can stimulate and enhance the growth of T cells having higher specificity for cancer cells [51]. The most common costimulatory receptors are CD28 and tumor necrosis factor (TNF) family like glucocorticoidinduced TNFR related protein (GITR), OX40, 4-1BB, or CD137 [52, 53], The phosphoinositide-3-kinase–protein kinase B (PI3K-PKB), c-Jun amino-terminal kinases (JNK), and nuclear factor-kappa B (NF-κB) pathways are commonly used for the activation of T cells [54, 55]. The United States (US) Food and Drug Administration (FDA) has approved a recombinant fully human anti-OX40 monoclonal antibody (IBI101) for the clinical trials [56]. Also, utomilumab and urelumab, which target the 4-1BB (CD137), are in phase II clinical trials[57, 58]. Current studies are investigating to reduce dose-dependent toxicity by improving the administration strategy. For example, in lungs metastatic model, the agonist antibodies to 4-1BB show more efficacy with fewer side-effects if delivered in conjugation to liposomes [59].

1.4.   Cancer vaccines

Dendritic cells (DCs) vaccine therapies are the most commonly used vaccines for the treatment of cancer [60]. DCs are taken out from the patient and engineered for the expression of specific antigen to activate the T cells against cancer cells [61] (Fig. 1). In 2010, PROVENGE® (sipuleucel-T, Dendreon Pharmaceuticals, LLC), a dendritic cell-based vaccine, has been approved for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer [62]. There are many cancer vaccines that have good safety profiles; however, got failed in the clinical trials due to poor efficacy [63] (Table 1). Thus, if a subset of dendritic cells presenting a high level of

antigen could be identified and directly given to the lymph node, which may improve the efficacy of cancer vaccines.

DNA and RNA-based vaccines are an alternative to conventional vaccines, wherein exogenous nucleic acid is injected into the target cells. The antigen-presenting cells (APCs) uptake the nucleic acid and express the antigen. These antigens are presented to T cells to activate them against the given tumor type [64] (Fig. 1). The nucleic acid-based antigens may not require knowledge about the immunogenic epitopes and human leukocytes antigen (HLA) type. The nucleic acid-based antigens are also helpful in prolonging the antigen presentation in comparison to other types of vaccines. However, nucleic acid delivery barriers and immunogenicity have been the major hurdle in clinical implementation [65]. To address such clinical issues, mRNA-based vaccines have been developed to directly express the antigens. Even after having several advantages over the DNA based vaccines, mRNA is sensitive to nuclease driven degradation and has poor internalization into the cells [64, 66, 67]. Thus, there is a critical need for an efficient transfection or delivery carrier for improved intracellular delivery [68].

The neoantigens based cancer vaccines are also under development stage. It boosts the immune system(s) using the tumor-specific antigen called the neoantigens, which only present on the cancer cells arise due to somatic DNA alteration; thus, off-target effects are almost eliminated. These vaccines have encompassed number of neoantigens that are beneficial for the treatment of heterogeneous cancers[69, 70].

1.5. Cancer pathology/progress due to immune system:

There is a great debate from decades whether immune system checks the cancer progression or promotes it. It is established that although specific immune responses like immunosurveillance and immunoediting are required for checking the progression of cancer, the unresolved immune response like inflammation can promote the progression of cancer as the chronic inflammatory diseases are more associated with the risk of cancer and anti-inflammatory drugs reduce the risk of cancer [71]. There are many paths followed by the infiltrated innate immune cells that lead to the promotion of cancer like angiogenesis, free radical damage, adaptive immune suppression, tissue remodeling, and growth factors production. Although the innate immune response is critical for initiating the adaptive immune response, the innate inflammatory response might inhibit the activation of the adaptive immune response [72, 73]. For example, CCL22, chemokine produced by tumor-derived macrophage, enhance the infiltration of Tregs to the tumor. Also, MDSC inhibit the development of specific tumor immune responses. The effector cells like CD4+, CD8+ T cells, and cytokines like IFN-γ are anti-tumor while the MDSC, TAM, and cytokines produced like TNF, IL-6, IL-23, IL-β are pro-tumorigenic. Also, there are few other types of immune cells whose role still remains elusive, like Th17, CD25+, Foxp3+ regulatory T cells, and the cytokines like TGF-β.

In the early stages of tumors, TAM infiltrate in response to inflammation and releases pro-inflammatory chemokines and cytokines like CXCL10 and CXCL19 to attract as well as promote the development and differentiation of NK, Th1, and Th17 cells [72]. The GM-CSF and INF-γ direct towards the M1 phenotype of TAM, whereas IRF5 expression helps in

maintaining the M1 markers, lymphocyte production, and response of Th1/Th17 by upregulating the TNF-α, IL-23, IL-12p40, and IL-12p35. In the advanced tumor condition, M1 phenotype changes to M2 type, which favors the Th2 differentiation and recruitment. The release of the different types of cytokines and chemokines like CCL24, CCL22, and CCL17 favoring the development of Tregs. Also, M2 supports the remodeling, tissue repair, and angiogenesis with the help of VEGF or EGF. Overall, these M2 types get proinflammatory with the release of cytokines and chemokines like IL-6, IL-12, IL-23, and TNF-α, which promote the anti-cancer immunity with the production of IL-10 and TGF-β. The molecular mechanism controlling the regulation of TAM is largely unknown. Its elucidation will help in finding out the more effective therapies and determining the inflammation associated progression of cancer.

The MDSC favor the inflammation and exerts suppressive effects to the T cells via the reactive oxygen species, nitric oxide, and secretion of TGF-β, which also lead the Treg induction [74], Also, it produces IL6 in high levels, and its expansion in the presence of VEGF factor is also reported. Usually, MDSC differentiates after migration, but in the tumor area in presence of cytokines, factors, and other chemokines, it remains undifferentiated to immature myeloid cells and causes the immunity suppression of tumor via different ways. IL6 is another factor that promotes the proliferation of cancer cells, along with inhibiting the apoptosis mechanism via the Stat3 [75]. It could also affect the differentiation of T cell subsets which further gets mighty in presence of other cytokines like TGF-β. Also, it has been found to play role in carcinogen driven liver cancer and act as angiogenic factor like TNF, which itself is the primary inflammatory mediator of NF-κB. IL-β polymorphism is linked to gastric cancer, and its role in the activation of NF-κB is also established [76]. The Stat3 and NF-κB appear to be working in positive feedback loop during the interaction of cancer cells and inflammatory cells, which helps in the cancer progression [72]. Like in the Src oncogene model, the induction of inflammation was helpful for the activation of Stat3 via NF-κB and IL-6 [77].

1.6. Drawbacks of conventional immunotherapy and implications of nanotechnology in immunotherapy

Although several checkpoint inhibitors have been approved by the FDA, still, several challenges need to be addressed before the widespread commercialization [78]. One of the hurdles is the limited response, i.e., only 10-30% of patients respond to immunotherapy, particularly to checkpoint inhibitors due to their cold tumors, which is characterized by low number of T cells in the tumor microenvironment, less number of PD-1, PD-L1, CTLA-4 expression, immunosuppressive microenvironment, and other factors. Towards this, there have been efforts on the administration of the combination of different checkpoint inhibitors like anti-PD-1, anti-CTLA-4, etc. However, adverse immune responses have been observed with the seriousness of grade 3 and 4, i.e., renal, hepatic, and gastrointestinal disorders. Additionally, there are prospects of generation of self-antigen reactive T cells, but damages to healthy tissue [79]. There has been research on neoantigen driven personalized immunotherapy [80]. The combination of different cellular therapies like tumor-specific T cells and APCs with the checkpoint inhibitors reflected the promising outcome. However,

engineering of T cells and tumor antigen-specific dendritic cells has been very expensive, labor-intensive, and afflicted with lot of variations and quality issues [43-45,81].

There are number of nanomaterial platforms focus on efficient delivery and addressing the challenges of immunotherapy [82]. (Fig. 2) Nanomaterials or nanoparticles (NPs) can help in the efficient delivery of the therapeutic agent(s) to the tumor(s) and accumulation in tumor(s) *via* enhanced permeability and retention (EPR) or active targeting mechanism. Such mechanisms not only reduce side-effects of therapeutic agents but also protect from degradation and quick systemic elimination. Further, release kinetics, as well as other physicochemical properties of nanomaterials, can be easily tuned as per the patient's profile [83]. However, the potential of nanotechnology in clinical trials is still underway for controlled delivery of cytokines, adjuvants, antigens, and other immunological moieties [59, 84-86]. Also, there have been efforts on combining conventional therapies like chemotherapy, radiotherapy, hyperthermia, and others with immunotherapy towards converting the cold tumors into hot tumors and observing the abscopal effect for the treatment of disseminated metastatic sites [87-90].

Herein, we summarize the current development of immunotherapy in reference to nanomaterials and combinatorial therapy approaches. It includes the immunological functionalization of NPs, advantages of combinatorial therapy, usage of scaffold in the localized release of adjuvant, antigen, intervention towards the maturation of dendritic cells, and activation of the T cells. The nanotechnology combination helps in accelerating the specificity, sensitivity, and improving safety profile of the immuno-therapeutic agents (Fig. 2). This review aimed to demonstrate NPs mediated immuno-theranostics for widening therapeutic and imaging window in cancer treatments.

2. Nanotechnology Approaches in Cancer Immunotherapy

Despite positive outcomes with conventional cancer immunotherapies, some inherent issues are noticed. These concerns include but not limited to convoluted tumor cell population, heterogeneity, desmoplasia, and their tumor microenvironment. All these limits the entry of therapeutic agents into tumors for their effective actions. To tackle these unsolved issues, nanotechnology-based cancer immunotherapy can be a viable option towards smooth translation to clinical applications. (Table 2) Currently, there are more than 80 FDA-approved therapeutic nanoparticle-based medicinal agents available for clinical use. Most of these NPs are found to be highly biocompatible for improved, targeted, and sustained delivery applications. They have potential to be tuned for different degrees of tissue penetration, distribution, pharmaco-kinetic, and pharmaco-dynamic profiles. Nanotechnology also helps in improving the stability, bioavailability, half-life of therapeutic molecule(s). Thus, this section is devoted to present novel principles, opportunities, and advances of nanotechnology in cancer immunotherapy.

2.1. Nanoparticles-based cancer vaccines

The NPs can reach the lymphatic system (lymphatic vessels and lymphoid organs) and elicit the efficient activation of the immune response. Nanotechnology is extensively applied for developing targeted DC vaccines. The goal of NPs based vaccine is to enhance the delivery

of antigen (Fig. 3) to DC for the activation of T cells, as well as sustained release of antigen(s) along with high biocompatibility. These vaccines are also being used for eliminating malignancies and prevent tumor relapse after post-surgery[91]. DepoVax, a liposome-based DC vaccine, is in Phase I clinical trial for prostate, breast, and ovarian cancer. The DepoVax is a blend of several tumor-specific epitopes like TNF-α converting enzyme (TACE), topoisomerase II α, epithelial discoidin domain receptor I (EDDR1), B cell receptor-specific protein 31 (CDM), and γ catenin. This mixture of epitopes and adjuvants can be manipulated as per the requirement of specific tumor and activation of immune cells[92] (Table 3). Similarly, iron and zinc-based nanoshells were applied to deliver the gene of interest to DC and for simultaneous imaging purposes[93]. An up-conversion NPs formulation conjugated with polymers [polyethylene glycol (PEG) and polyethylene imine (PEI)] has been used for delivering the ovalbumin (OVA, a model antigen) to DC and to track the DC migrations in *in vivo* conditions[94, 95]. This antigen nanocomplex system efficiently activated the CD8+ cytotoxic T cell population. Further, Cruz *et al.*,[96] showed the importance of antigen interactions with DC using the PEG-coated poly(lactic-*co*-glycolic acid) (PLGA) NPs[97]. This PLGA NPs formulation was loaded with OVA and Toll-like receptor (TLR) ligand and conjugated with CD40, CD11c, and DEC-205 monoclonal antibodies for effective DC targeting. This approach led to the production of IL-2 and results in robust immune response in comparison to non-targeted cancer vaccines. Further, the subcutaneously injected vaccine targeted to CD40 of DC helped in proliferating the growth and enhanced response of CD8+ T cells.

The combination of antigen and immunoadjuvant delivery using biodegradable nanocarriers elicit more potent and robust immune response.[98] In comparison to the liposomes, polymeric NPs have the advantage for sustained release of therapeutic antigen and adjuvants, which can induce the long-term memory of T-cell phenotype[99]. However, it was suggested that the short-lived vaccine depots overture the sequestration of T cells as well as dysfunction and deletion at the vaccination site [100, 101]. Such vaccine depots not only overcome the persistent antigen delivery limitations but also provide improved therapeutic benefits.

Nucleic acid vaccines have several advantages over epitope and adjuvant-based vaccines. However, the delivery of nucleic acids has been a major challenge [102, 103]. A set of recent studies demonstrated that DC has been engineered *ex vivo* with mRNA encapsulation and then supplemented back to the patient[103] for rational design of mRNA vaccines. Systemic delivery, targeting, and protection of nucleic acid from degradation were achieved using a complexation based liposomal formulation with neoantigen coding mRNA[104]. This mRNA-liposome complex can facilitate the cytosolic delivery of mRNA in the mouse tumor model to induce potent effector and memory T cell response. Such RNA based vaccine(s) can produce antigen and peptide, thus helping the development of broad-spectrum antitumor vaccines.

2.2. Manipulation of T cells

T cells act as executor in the immune response cascade. However, infiltration of T cells into tumor(s) is a major hurdle in immunotherapy. Also, activation and proliferation of T cells

are often affected by several signaling pathways. A well-known example of such pathways is PD-1/PD-L1 interaction. Therefore, cutting off PD-1/PD-L1 interaction and engineering of T cells are successful approaches. However, harnessing the full potential of T cells driven therapy is still lacking. Thus, the usage of nano- and microbiomaterials has been adopted as follows[105] (Table 3).

2.2.1.   Proliferation and reprogramming—Although CAR T-cell therapy has shown promising results, there are only few centers worldwide that can implement such advanced therapy. Moreover, the financial hurdle (approx. 0.5 million USD for single infusion) restricts the widespread implementation [106]. Thus, in an attempt to simplify the adoptive T therapy, Smith *et al.* [107] have developed the *in situ* gene delivery technology. In this T cell programming approach, gene encoding the leukemia-specific 194-1BBz CAR were complexed with poly(β-amino ester)-based polymeric NPs (size 150 nm and zeta potential −7.8 mV). This NPs system was attached with anti-CD3e f(ab')2 fragment-modified polyglutamic acid and peptides containing the microtubule-associated sequence and nuclear localization signals for targeting the T cells and nuclear homing (Fig. 4a). In *in vitro* studies, 4% of T cells were found to be CAR+ within 30 h of incubation, which is quite efficient. Further, intravenous administration of targeted polymeric nanocomplex was capable of entering the T lymphocytes and effectively reaching out to the spleen, bone marrow, and lymph nodes, while the non-targeted nanocomplex didn't show the efficient accumulation in T lymphocytes and ended up in the liver. Similarly, polymeric NPs loaded with both CAR transgene and plasmids encoding iPB7 transpose showed better insertion of CAR gene in the genome of T cells [108]. The percentage of CAR+ T cells reached 5.8%, with an increase in efficacy of 70% and extended survival of mice to 58 more days in comparison to control.

The effector T cells are sensitive to the immunosuppressive environment of the tumor. Although cytokines help in augmenting the efficacy of effector T cells, severe side effects may be encountered with bolus injections. To overcome such uninvited events, Stephan *et al.*, [109] developed the multilamellar lipid NPs composed of superagonist IL-15SA and IL-21 and functionalized with maleimide group to react to the thiol of T cells. This engineering precisely allowed binding with T cells (100 liposomes on the surface of T cells) and did not affect the function, proliferation, transmission, and tumor homing capabilities of T cells. The liposome conjugated T cells showed the persistent immune response and amplified homing to lymph nodes and spleen, whereas unmodified T cells gradually cleared from systemic circulation. The disadvantage is the dilution of pharamcyte (i.e., attached liposome) with the division of T cells. Thus, the same group also developed the *in vivo* targeting of T cells with the engineered liposomes to avoid one-time injection limitation [110]. Herein, either the F(ab')2 fragment attached liposomes were directed to the Thy1.1 antigen present on the T cell surface or IL-2 engineered on Fc fragment. This approach allows more than 90% T cells to bind with the liposome upon a single injection with no serious toxicities, indicating its clinical feasibility (Fig. 5a-h).

A smart cytokine releasing nanocarrier can significantly activate higher number of T cells [111]. This reduction sensitive cross-linked nanogel comprised of cytokines (IL-15SA) and decorated with anti-CD45 antibody promotes effective release of payload to the T cells surface. Schmid *et al.* [112] have developed the SD208 [an effective inhibitor of

transforming growth factor (TGF-β) kinase, which is responsible for the proliferation and activation of CD8+ T cells] loaded PLGA NPs. These NPs were tagged with anti-CD8 antibody using the fragments of F(ab')2 *via* maleimide/thiol click chemistry. Up to 90% T cells showed efficient binding with targeted PLGA NPs, and less than 20% of these bound NPs were internalized. Flow cytometry analyses confirmed that 90-100% of immune cells were attached to the targeted NPs after 1 h of injection. Moreover, it has been found that the SD-208 loaded and PD-1 targeted NPs showed the efficient activation of CD8+ T cells and enhanced production of IFN-γ and granzyme-B. Further, the R848 (agonist of TLR7/8) loaded, and PD-1 targeted PLGA NPs were prepared for stimulating the infiltration of CD8+ T cells in the core of MC38 tumor. The mice treated with R848 loaded and PD-1 targeted NPs showed extended survival in comparison to control mice.

2.2.2. Delivery of immune checkpoint inhibitors—Checkpoint inhibitors are the crucial bases for the current developments in immunotherapy [113], Many immune checkpoint blockers (ICBs) have shown the complete regression of tumor(s) in small cohorts of patients[78]. However, along with the low response rate, the adverse effects are also associated with ICB therapy, which is life-threatening [79]. Thus, to minimize the off-targets and increase the efficacy, several different delivery methods have been adopted as following [114].

An ICB antibody conjugated to an extracellular matrix (ECM)–super-affinity peptide (derived from placenta growth factor–2, PIGF-2$_{123-144}$) was engineered [115]. The unmodified antibodies rapidly leaked out from the tumor environment to the blood vessels, while peptide modified anti-CTLA-4 and anti-PD-L1 antibodies showed less off-target effects. The antitumor response was augmented with the enhanced infiltration of CD4+ and CD8+ T cells in the tumor environment of B16F10 melanoma. The local treatment of the primary tumor also inhibited the development of metastatic sites. The superior efficacy of the peptide modified ICB antibodies was further confirmed in both chemically induced and xenograft (MMTV-PyMT) tumors developed in genetically engineered Tyr:Cre-ER$^+$/LSL-Braf^{V600E}/Pten$^{fl/fl}$ mice. Also, the memory effect against the MMTV-PyMT tumor was noticed in peptide modified ICB antibodies treated mice (Fig. 4b). Along with peptides, platelets have also been exploited for delivering immune checkpoint inhibitors. The anti-PD-L1 conjugated platelets using the maleimide based bifunctional linker was established without compromising the efficacy of antibody and function of platelets [116]. The anti-PD-L1 antibody functionalized platelets showed enhanced circulation (> 34 h) and accumulation at the surgical site in comparison to the bare anti-PD-L1 antibody (< 10 h). The modified antibody showed effective inhibition of tumor recurrence after the removal of the primary tumor. The treatment was associated with the high infiltration of CD4+ and CD8+ T cells in comparison to the controls (PBS, free anti-PD-L1 antibody, and platelets). Additionally, the platelets attached anti-PD-L1 antibody inhibited the metastasis of the lung and prolonged the survival of treated mice. The efficacy was also observed in the triple-negative breast cancer model, wherein the recurrence was delayed significantly. These data show that the platelets conjugated anti-PD-L1 antibody is effective in inhibiting the tumor recurrence after surgery as well as treating the metastatic sites.

The biodegradable polyester-based microparticles have been used for high loading capacity and long-term release profile. Seyednejad and Ghassemi teams efficiently fabricated anti-CTLA-4 antibody containing poly(lactic-*co*-hydroxymethyl glycolic acid) (PLHMGA) microparticles [117, 118]. The localized and sustained release profile of the anti-CTLA-4 antibody was evidenced for up to 20 days with minor systemic toxicity. In an *in vivo* MC-38 tumor-bearing mice study, it was confirmed that antibody was less in the blood, which illustrates the localized retention at the tumor site[119]. A DNA-based NPs system has also been applied for the successful delivery of anti-PD-1 antibodies to the resectioned sites [120]. This construction is quite efficient for subsequent release of anti-PD-1 due to the presence of guanine residues (CpG) and sites for the restriction endonuclease Cfo I (HhaI) enzyme. The localized applications of anti-PD-1 loaded DNA NPs were effective in inhibiting metastasis in the lungs after the removal of the primary tumor.

2.3. Modulation of the tumor microenvironment

The immunosuppressive environment of the tumor is a major hurdle for immunotherapy. The immunosuppressive effects can be exerted both directly or indirectly with the help of regulatory T cells (T_{regs}), tumor cells, myeloid suppressor cells, tumor-associated macrophages, and several soluble immunosuppressive factors. Thus, to improve the efficacy of immunotherapy, the inhibition of these cells and factors is critically required. For example, PEI functionalization of siRNA helps in better uptake by the ovarian cancer cells and leads to more than 50% inhibition of PD-L1 [121]. Similarly, siRNA encapsulated in protamine and hyaluronic acid (HA)-functionalized liposome knocked down the overexpressed CD47 in a very effective manner [122], A nanolipo gel formulation comprised of liposomes, polymers, SB505124 (TGF-β inhibitor), and IL-2 (immunomodulant) [123] has proven to promote both innate and adaptive immune response by the activation of CD8+ T cells and NK cells. This gel formulation also extended the survival time of mice melanoma models. T_{regs} are also primarily responsible for the immunosuppressive environment. However, the inhibition of these cells often leads to autoimmune diseases. Thus, it is highly crucial to achieve selective targeting of the T_{regs} present in the tumor environment. Selective depletion of such T_{regs} in the tumor microenvironment was achieved by the near infraredphotoimmunotherapy (NIR-PIT) [124]. In this approach, IR700 molecules were conjugated to the F(ab')2 fragments that target the CD25. After systemic administration in mice, these molecules reach the tumor(s), which were shined for 30 min. This process leads to the 85% selective depletion of CD4+CD25+Foxp3+ T_{regs}. This approach also leads to the activation and infiltration of CD8+ T cells, APCs, and NK cells for the complete regression of the tumor (Fig. 6).

2.3.1. Suppressive immune cells—The tumor-associated macrophages (TAM) are a major population in the tumor, and its phenotype (usually M2 type) responsible for the proliferation, metastasis, and drug resistance of tumor cells. Thus, reversing the M2 phenotype to M1 type, i.e., antitumor type, has been accomplished using several strategies [125, 126]. Towards this, an FDA approved iron oxide NPs (ferumoxytol) formulation can be applied, which also has good safety profile [127]. Ferumoxytol treatment exhibited the upregulation of TNF-α and CD86 markers in the macrophages, which represent the M1 phenotype, while the downregulation of CD206 and IL-10 represents the M2 phenotype. The

ferumoxytol treated tumor (bilateral tumor model) was found to have increased concentration of CD80+ cells and evidence of the depletion of TAM. This therapy was effective in the treatment of liver and lung metastatic models of mice. Although ferumoxytol is approved for iron-deficient anemia, its high concentration usage should be further evaluated for the treatment of cancer [128, 129].

NPs are preferably endocytosed by macrophages [130]. The R848 inhibitor of TLR7/8 is highly effective in changing the murine macrophage to M1 phenotype. A succinyl-β-cyclodextrin cross-linked with L-lysine nanoparticle formulation proved to be effective in delivering the R848 to the TAM of MC38 tumors with the help of EPR effect [131]. This R848 nanoparticle formulation can efficiently reach tumors and accumulates in TAM, which resulting in increased expression of IL-12 (represents the M1 phenotype). This treatment approach helped in prolonged survival and long-term inhibition of the tumor growth and enhanced the efficacy of the anti-PD-1 antibody.

Another major population of leukocytes relates to immune-oncology is neutrophils, which are responsible for the innate immune response. The programming of neutrophils is effective for eliciting antitumor immunity [132]. A nucleic acid devoid cowpea mosaic virus can enhance the production of IL-1β, IL-12p40, CCL3 (MIPl-α), IL-6, and TNF-α, which represent the stimulation of primary macrophage or bone marrow-derived dendritic cells (BMDCs). The intranasal delivery significantly increased the concentration of CD11b+Ly6G + neutrophils in healthy mice and capable of inhibiting the metastasis of lung in the 4T1 tumor rechallenge model (immunogenic comparator: lipopolysaccharide, poly (I:C), and STING agonist).

2.3.2.   Soluble suppressive factors—Soluble factors such as indoleamine 2,3-dioxygenase (IDO) and TGF-β also play an important role in immunosuppression. Transforming growth factor-beta (TGF-β) is a multifunctional cytokine and helps in inhibiting the activity of cytotoxic T lymphocytes (CTLs), NK cells, as well as the proliferation of T_{regs} [133]. The TGF-β inhibitor (SB525334) was successfully delivered using liposomes [134]. These liposomes were targeted to both internalization receptor (CD90) and noninternalization receptor (CD45). Anti-CD90 targeted liposomes were more effective than anti-CD45 targeted liposomes in *in vivo* studies. This may be due to the fact that anti-CD45 targeted liposomes undesirably up taken by the peripheral macrophages, B-cells, and dendritic cells. Another nanoparticle formulation (~ 120 nm) based on methacrylated β-cyclodextrin and PEGpolylactide diacrylate revealed efficient delivery of SB505 and IL-2 to inhibit TGF-β as well as the proliferation of T cells [123]. This dual (SB505 and IL-2) formulation showed greater efficacy in subcutaneous B16 melanoma mice model than free and single component loaded NPs. This was evidenced with the increase in CD8+ T cells and NK cells in the tumor microenvironment. siRNA delivery using 30 nm liposome-protamine-HA NP formulation is also promising to inhibit the effect of TGF-β [135]. The intravenous delivery of siRNA nanocomplex was found to inhibit ~50% expression of TGF-β in the late-stage tumors, thus increased the efficacy of the vaccine. Delivery of methyl-2-cyano-3,12- dioxooleana-1,9(11)-dien-28-oate through 120 nm PEG-PLGA NPs has also been reported to significantly decrease T_{regs} population [136].

3.   Combination therapy

The conversion of the cold tumors to the hot tumors is difficult to achieve using conventional immunotherapy due to strong immunosuppressive environment [137]. The CAR T-cell therapy has been approved for the hematological related malignancies, but its application for the treatment of solid tumors is a challenge [138]. The treatment of primary tumor with the help of conventional treatments like chemotherapy, radiotherapy, photodynamic therapy, etc. lead to immunogenic cell death of cancer cells. The dying cancer cells express the specific antigen or damage-associated molecular patterns (DAMP) on the surface, thus help in activating the adaptive as well as innate immune response [139, 140]. It's also used for developing the *in situ* vaccination for the broad repertoire of cancer antigens [141]. The current limitations of immunotherapy are being taken care of by the synergistic combination of it with conventional therapies like chemotherapy, photothermal, photodynamic, and radiotherapy using nanomaterials, as following (Fig. 7).

3.1.   Chemo-immunotherapy

Chemotherapy has been the standard treatment for cancer management. There is a high interest in combining it with immunotherapy. In phase III clinical trial, albumin NPs assisted delivery of paclitaxel along with the PD-1/PD-L1 immune checkpoint inhibitor helped in progression-free long survival of non-small cell lung and triple-negative breast cancer patients [84-86, 142]. Similarly, the phase III clinical trial of chemoimmunotherapy is underway in urothelial cancer patients [143, 144]. It was noticed that the non-small cell lung cancer patients responded poorly to the alone PD-1/PD-L1 checkpoint inhibitors therapy by expressing low PD-L1. However, on the combination of chemotherapy, the response enhanced multifold[89]. Although a segment of patients also showed the adverse effect on the treatment of chemoimmunotherapy, which ranged from moderate to life-threatening. It leads to the discontinuation of treatment by 10-20% of patients [85, 86, 142, 145]. Thus, further interpretation of the off-target toxicity needs to be explored along with the focus on targeted and localized approaches. There are several chemotherapeutic drugs (mitoxantrone, doxorubicin, oxaliplatin, etc.) that can kill the cancer cells in immunogenic fashion and elicit the systemic immune response during cell death [139, 140]. During the immunogenic cell death, soluble factors like CX-chemokine ligand 10 (CXCL 10), high-mobility group box 1 (HMGB1), calreticulin (CRT), and ATP are released. These signals the dendritic cells to phagocytose the dying tumor cells and present antigen to facilitate the infiltration of T cells. In contrast to cancer vaccines which rely on tumor antigen, the chemotherapeutic driven immunogenic cell death leads to the immune response against multiple antigens. Therefore, targeted delivery of chemotherapeutics to the tumors needs to be promoted by choosing targeted nanocarriers (liposome, polymeric NPs, drug-polymer conjugates, etc.) to avoid the off-target effects and promoting the therapeutic index [146] (Table 3).

The combination of immune checkpoint inhibitors with the targeted chemotherapeutic NPs has shown promising results in preclinical studies. For example, doxorubicin (DOX) loaded nanodisc comprised of synthetic high-density lipoprotein exhibits higher blood circulation time and accumulation of DOX in tumor(s) [141]. It was experienced that the combination

of anti-PD-1 immune checkpoint inhibitor with DOX loaded nanodisc lead to the seven-fold increase in the IFNγ$^+$CD8$^+$T cells and leads to complete regression of CT26 tumors (Fig. 8).

The combination of chemotherapeutics with immune adjuvants also helps in increasing immunity. DOX loaded dendrimers entrapping CpG (TLR9 agonist) and targeted against the prostate-specific membrane antigen helped in potent immune response in 22RV1 tumor-bearing mice [147]. Paclitaxel (PTX), another potent chemotherapeutic drug, shows good combination with the immunotherapy by inducing the maturation of TLR4 mediated dendritic cells and infiltration of CD8+ T cells [148, 149]. The polyglutamic acid microparticles carrying the PTX and imiquimod (TLR7 agonist) lead to the robust localized and systemic immune response, which inhibited distant metastatic sites in B16F10 tumor-bearing mice [150]. The combinatorial delivery of paclitaxel and the detoxified bacterial lipopolysaccharide (LPS, a TLR4 agonist) exhibits to increase the number of T-helper cells [151]. Similarly, the sequential delivery of PTX, CpG, and siRNA against the IL-10 with the help of PLGA NPs can prolong the survival of B16F10-OVA melanoma tumor-bearing mice [152].

Furthermore, the combination of mitoxantrone, CpG, and the immune checkpoint inhibitor has been explored for the tumor vaccination to check the recurrence [153]. It was found that 78% of tumor-bearing mice showed complete remission. The co-delivery of DOX and CpG using PLGA NPs boosts the activation of dendritic cells and T cell response, which was further amplified when the CTLA-4 and or anti-OX40 (immune checkpoint inhibitors) was co-administered [154]. A nanogel formulation comprised of chitosan was loaded with PTX and IL-2, and also coated with the erythrocyte membrane for enhanced blood circulation [155]. This construct facilitated more exposure of CRT to the dendritic cells and thus increased response of CD8+ T cells in comparison to alone PTX or IL-2 in B16F10 tumor-bearing mice. Similarly, the combination of DOX and IFNy has been used for extending the survival of B16F10 melanoma mice [156]. Further, mesoporous silica NPs have been used for the co-delivery of DOX, IL-2, and all-trans-retinoic acid (ATRA, a potent immunomodulator and increases the infiltration of CD8+ T cells as well as NK cells) for chemoimmunotherapy of B16F10 tumor-bearing mice [157].

3.2. Photothermal-immunotherapy

Photothermal therapy (PTT) is a type of hyperthermia wherein the photon is converted to heat with the help of photothermal agents [158]. The release of tumor antigens and other immune stimulator molecules after photothermal ablation induces the cascading immune response. For example, the gold nanoshells based photothermal therapy has been reported to induce the expression of pro-inflammatory cytokines [IL6, IL-1, IL12p70, TNF-α, GCSF, GM-CSF, macrophage colony-stimulating factor (MCSF)], chemokines [CC-chemokine ligand (CCL2, CCL4), and chemokine (C-X-C motif) ligand 1 (CXCL1)] and maturation of dendritic cells in the lymph nodes [159]. However, the suboptimal immune activation, myeloid-derived suppressive cells, and other factors cause difficulty in the treatment of metastatic sites in photothermal monotherapy [159]. Further, it was noticed that if the temperature during the PTT raised above the 45 °C, then the immune response decreases due to adverse effects on the cytokines, chemokines, vasculature of the tumor, and immunogenic

death of the cancer cells[160]. Thus, for the ablation of the big tumor and the suboptimal activation of immune response is a limitation, which results in relapse due to left-out cancer cells. Literature suggests that combining the PTT with the immune-modulating agents can ablate the big tumors and as well as metastatic sites [161, 162] (Table 4). For example, the chitosan-coated and CpG loaded copper sulfide NPs not only ablated the primary tumor with the help of PTT but also activate the plasmacytoid dendritic cells for the elimination of distant metastatic sites and untreated tumor [163]. Similarly, the combination of checkpoint inhibitors (anti-CTLA-4) and PTT with single-walled carbon nanotube demonstrate reversion of the immune suppression by the infiltration of T_{regs} to the tumor [88]. In another study, the combination of anti-PD-L1 with the gold nanostar helped in increasing the infiltration of T and B cells and decreasing the myeloid-derived suppressor cells (MDSC), thus helped in eliminating the distant tumor along with the primary one [164]. The synergistic effect of photothermal therapy with chemotherapy has been demonstrated in various xenograft and syngeneic tumor models[165]. The polydopamine coated spiky gold NPs with the subtherapeutic concentration of DOX and PTT can assist in the elimination of distant secondary tumor with the help of systemic immune response, i.e., abscopal effect [166].

3.2.1. PTT-Immunoadjuvant therapy

The combination of PTT with immunoadjuvant is emerging as a promising field in cancer treatment. Hollow copper sulfide crystals (CuS, photothermal agent) with the immunoadjuvants oligodeoxynucleotides containing the cytosine-guanine (CpG) motifs efficiently release the IFN-α by the plasmacytoid dendritic cells (pDCs) in tumors [163]. The myeloid dendritic cells (mDCs) cross primed the T cells to the antigen-specific CD8+ T cells, hence triggered the adaptive immunity. Additionally, the level of IFN-γ was found higher, which not only inhibited the growth of primary tumor but also the secondary tumor in EMT6 tumor model. Besides inorganic crystals, gold NPs are also a potential photothermal agent due to its biocompatibility, ease of synthesis, and targeting capability [167-170]. The simple chemistry of functionalization with the protein, oligonucleotides, and other molecules gives several folds advantage over other types of photothermal agent [171, 172]. The CpG with thiol groups can be conjugated instantaneously to the surface of gold NPs for synergistic photothermal and immunotherapy [169]. The efficiency and absorbance wavelength of gold NPs can be controlled by varying the synthesis parameters [173]. The laser irradiation leads to the ablation of the primary tumor as well as generation of heatshock protein 70 (HSP70), which elicited the immune response and resulted in the reduction of distant tumor with 80% survival rate in C57BL/6 tumor model. Gold nanostars and iron hexacyanoferrate dye known as Prussian blue, have also been used for the synergistic application of photothermal and immunotherapy [174, 175]. Further, indocyanine green (ICG) is an FDA approved imaging and photothermal agent [176, 177]. It can be encapsulated inside the carrier due to small molecule size. The ICG and OVA can be formulated in ambient conditions [178]. The OVA-ICG nanovaccine enhanced the secretion of IL-6 and TNF-α, indicating the positive immune response. In the prophylactic model, the nanovaccine was injected before the transplantation of B16 melanoma cells for developing the immunogenic memory.

3.2.2.   PTT-ICB Therapy—The alternative photothermal combination strategy is the usage of immune checkpoint inhibitors. PD-L1 receptors are upregulated in the cancer cells [164]. The gold NPs were injected in the C57BL/6 mice implanted with MB49 bladder cancer cells. It facilitated the photothermal induction for promoting anti-PD-L1 therapy. This synergistic therapeutic outcome is 40% more compared to anti-PD-L1 monotherapy. Similarly, hydrogel incorporating the tumor penetrating peptide with the ICG and JQ1 (inhibitor of PD-L1) promotes matured DC (~62%) and proinflammatory cytokines abundance in tumors [179]. The antibody against the CTLA-4 has also been exploited for photo-immunotherapy. It helps in the downregulation of T_{regs} in the draining lymph nodes [160, 180]. The PEGylated single-wall carbon nanotubes (SWCNT) can increase temperature up to 53 °C when irradiated with 808 nm laser [88]. While concurrent administration of anti-CTLA-4 antibody with these NPs helped in the downregulation of T_{regs}, thus increased the ratio of CD4+ and CD8+ T cells to the Tregs. In the case of photo-immunotherapy, 57% of the mice survived for 50 days, while in surgery, only 25% survived. An ICG, imiquimod (R837), and TLR-7 agonist combined encapsulation in PLGA nanoparticle formulation resulted in sustained release of R837 and TLR-7 increased the maturation of dendritic cells as well as the secretion of proinflammatory cytokines [181]. A pronounced inhibition of secondary tumors was achieved along with the increase in effector T memory cells (CD3+, CD62L+, and CD44+) in comparison to the control.

3.2.3.   Considerations in hyperthermia—Hyperthermia generated in the temperature range 39-45 °C supports the DAMP, particularly HSPs, for the immune stimulation [182, 183]. The milder rise in temperature promoted the expression of HSPs as cell response to physiological changes; however, higher temperature hampered the HSPs expression and led to necrosis [170, 184]. Further, the modest temperature facilitated more infiltration of APCs and T cells due to enhancement in the interstitial and lymphatic blood flow [185]. The research in understanding the thermal dose for optimum immuno-stimulation is still in infancy[183], Li *et al.* [186] have significantly improved photo-immunotherapy of IR-7, and unmethylated CpG loaded liposomes in the CT26 colon cancer bi-flank model. Similarly, SWCNT and glucosamine polymer, *N*-dihydro-galacto-chitosan as immunoadjuvant based formulation induced a strong immune response with the enhanced infiltration of CD8+ T cells and increase in the secretion of IFN-γ and IL-2 in the spleen in EMT6 tumor model of BALB/c mice [163, 187]. Also, the OVA based nanovehicle delivered the ICG and antigen against the B16 melanoma cancer cells, and the hyperthermia temperature achieved was more than 60 °C [178].

3.3.   Photodynamic therapy-immunotherapy

Besides PTT, photodynamic therapy (PDT) has also shown great promise in immunotherapy. The mechanism is similar to PTT (i.e., generation of DAMP). The tumor-specific antigen and DAMP are presented by APCs, which helps in the maturation of DC, cross-priming of T cells, and developing the immunologic memory. A long immunological memory with the help of bis (amino) silicon (IV) phthalocyanine (BAM-SiPc) mediated PDT in CT26 BALB/c mice model helped in the eradication of 70% tumor in the test group [188]. The 5-5-(4-N, N-diacetoxylphenyl-10, 15, 20-tetraphenylporphyrin) (DTPP) mediated therapy, which was evidenced with the increase in the ratio of CD4+/CD8+, percentage of NK cells,

IL-1 and IFN-γ levels along with lymphocytes congregation at the site[189]. Burley *et al.* [190] have developed the affibody ($Z_{EGFR:03115}$) to the phthalocyanine dye IR700DX for the treatment of brain tumor. Another report demonstrated higher stimulation of macrophages along with the increase in HSP70 on the PDT treatment of SCC VII mouse model [191].

The development of 2nd and 3rd generation photosensitizers has given the global reorganization to PDT for the treatment of cancer [192]. Gollnick and Henderson used PDT as a prophylactic vaccine for the first time[193]. In contrast to conventional treatments, herein, tumor is taken out and treated with PDT, the lysate formed is injected into the same patient (autologous) or different patient (allogenic) [192, 194, 195]. Yu *et al.* [196] used it for developing vaccination using graphene-based PDT. 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-alpha coated with graphene, and HK peptide (high affinity for the αvβ6 integrin receptor which is highly expressed in the tumor) exhibited an enhanced generation of singlet oxygens and maturation of DCs (increase in the expression of CD40 and CD70 in the lymph nodes). Further, the ratio of CD8+ to CD4+ improved along with the higher level of IFN-γ showed the activation of antitumor immunity. In addition, this approach efficiently eliminated residual cells, inhibited the metastasis and relapse (Fig. 8). Though several groups have used PDT solely for the induction of antitumor immune response, there are other groups also wherein the combinatorial approach has been used for inducing the persistent and stronger immune response. (Table 4)

3.3.1. PDT-Immunoadjuvant therapy

Calreticulin (CRT, a well-known DAMP in apoptotic cells) is located in the endoplasmic reticulum. Under stress conditions, it translocate to the cell membrane and signals for the phagocytosis, i.e., 'eat me.' The immunogenic property of CRT replaces the immunoadjuvants like OVA and CpG [196]. CRT driven generation of antitumor immune response was observed upon PDT [197]. Synthetic long peptides (SLP) have shown therapeutic benefits and currently being researched for cancer vaccination [198]. For example, SLP with PDT offers enhanced CD8+ T cells infiltration and elimination of distant metastatic sites [87]. This combination vaccination aided in the treatment of 30 % more inhibition of tumor growth of mice (20 % for SLP and 0 % for the PDT and control. Another nanoscale coordination polymer (NCP) loaded with pyrolipid and oxaliplatin lead to CRT overexpressed on the surface of the cells and helped in the migration of DCs [199]. This treatment shows higher levels of IFN-γ, IL-6, and TNF-α, which helped in the inhibition of tumor growth in two animal models.

3.3.2. PDT-ICB therapy

PDT-ICB is another type of combinatorial therapy wherein immune checkpoints are blocked along with the PDT. A pH-sensitive micelleplex multifunctional nanoplatform was encapsulated with RNAi (for silencing the PD-L1 expression) and pheophorbide (PDT agent) [200]. This unique micelle formulation produces 5.6-fold higher reactive oxygen species generation and creates immune response due to the HSP70, NF-κB expression, and infiltrating CD8+ T cells. The monotherapy of PD-L1 and PDT leads to the inhibition of 65% and 73% tumor growth, respectively. In contrast, the combinatorial approach leads to the complete elimination of the tumor. The combination of PD-L1 with PDT and its pH triggered release significantly reduces the T_{regs} level and increase in CD8+ T cell population [201]. In both studies, effector memory T cells were

noticed for rendering long-term immunization. Similarly, PDT in combination with anti-PD-L1 therapy inhibited the lung metastasis along with the complete elimination of primary tumor [202], Xu *et al.*, [203] synthesized the upconversion NPs using 20% Yb and 2% Er-doped $NaYF_4$ with PEG and loaded with immunoadjuvant R837 and chlorin e6 (photosensitizer). The antigen released due to PDT was amplified with the help of immunoadjuvant R837, which further activated the DC and release of cytokines like IL-12p40 and other molecules like TNF-α and IFN-γ.

The usage of IDO enzyme inhibitors has gained popularity along with the other checkpoint inhibitors [204]. A nanoconstruct of photosensitizer protoporphyrin IX (PpIX) to the caspase responsive peptide was linked with IDO enzyme inhibitor 1-methyltryptophan (1MT) *via* the PEG and palmitic acid [205]. The regression of CT26 tumor was noticed after the intravenous injection of PpIX-1MT NPs due to immunogenic cell death and expression of CRT on the cell surface. Further, the ratio of CD8+ against CD4+ increased in spleen and sera. Another report indicated synergistic actions of PDT and IDO enzyme inhibitors in primary and secondary tumor sites of CT26 and MC38 [206].

3.4. Radio-immunotherapy

Radiation therapy is used for the treatment of more than 50% of cancer patients. Cancer cells are vulnerable to radiotherapy because their DNA repair mechanism is impaired in comparison to healthy cells. Radiation also causes immunogenic cell death, which enhances the expression of radiation-responsive DNA damage repair proteins. This process can increase the infiltration of CD8+ T cells and activate the dendritic cells with the help of pro-inflammatory cytokines, type I interferon, cytosolic sensor, stimulator of interferon genes mediated DNA detection, IL-1β, CXCL16, and TNF-α [207, 208]. These complimentary events induce the abscopal effect and help in the inhibition of secondary distant metastatic sites [209]. It has been experienced that low dosage of radiotherapy preferably causes the expansion and recruitment of less radiosensitive immunosuppressive cells like T_{reg} than other lymphocytes [210]. Also, it increases the expression of immune inhibitory proteins like PD-L1 and TGF-β [211]. Thus, there is a need for combining radiotherapy with immunotherapy for the optimum and desired action of immune cells showing significant abscopal effect.

The combination of radiotherapy with the cowpea mosaic virus has been noticed to convert the ID8 cold tumor to hot tumor [212]. In addition, the combination of radiotherapy with the checkpoint inhibitors has augmented the immune response even in poorly immunogenic tumors such as triple-negative 4T1 and TUBO spontaneous mammary tumors [213, 214]. Triple combinatorial therapy (radiotherapy with anti-CTLA-4 and anti-PD-L1 antibodies) further improved efficacy due to synergistic and non-redundant mechanisms of their action [211]. Radiotherapy has been combined with the CpG for the treatment of cutaneous T cell lymphoma and low-grade B cell lymphoma in phase I and II patients. This combination therapy has 36% response rate [215]. Inorganic NPs have been found very effective in reducing the dosage of radiotherapy, thus side effects to neighboring healthy cells. Nanomaterials are being researched out dynamically towards increasing the therapeutic index of radio-immunotherapy. For example, NPs having the ability to scavenge the free

radicals and renders anti-oxidative properties are very effective in increasing the safety profile of radio-immunotherapy. The NPs, like gadolinium and hafnium, have already entered the clinical trial. Along with enhancing the radio-sensitization and radioprotection capability, they have also been noticed to improve the abscopal effect [216].

3.5. Gene-immunotherapy

Although the RNA based therapeutics are promising, it has been moderated due to instability, sensibility for degradation, poor delivery, and uptake problems. Thus, the NPs assisted delivery techniques had come to picture to address these limitations [217] (Table 4). For example, the efficient siRNA driven silencing of the PD-1/PD-L1 pathway has been achieved via the folic acid functionalized PEI NPs [121]. These NPs sensitized the ovarian epithelial cell and improved the antigen mediated cytotoxicity of CD4+ and CD8+ T cells. Other RNA nanotherapy was effective in silencing the other immunosuppressors like signal transducer and activator of transcription 3 (STAT3), IDO, suppressor of cytokine signaling 1 (SOCS1), etc., which are upregulated in the tumor microenvironment [218]. An *ex-situ* IDO silencing of dendritic cells was achieved using siRNA and injecting back into the patients, lead to more infiltration of CD8+ T cells, along with the decrease in the number of T_{regs} [219]. The liposomes have been loaded with IDO siRNA and conjugated with mannose for specifically targeting the dendritic cells in the lymph nodes [220, 221]. This regimen assists in decreasing the apoptosis of CD4+ and CD8+ T-cells and the maturation and function of dendritic cells. Similarly, another nanoconstruct comprised of the conjugation of STAT3 silencing siRNA with CpG was improved in TLR9 mediated uptake, thus the inhibition of myeloid-derived suppressor cells in murine prostate cancer model [222]. siRNA against SOCS1 delivered using PLGA NPs enhanced the antigen-specific CD8+ T cells, and expression of proinflammatory cytokines includes IL-2, IL-6, IL-12, and TNF in comparison to naked siRNA [82]. Another HA-functionalized liposomal formulation with TGFβ siRNA, CpG, as well as tyrosinase-related protein 2 (TRP2) peptide further increased the infiltration of CD8+ T cells in the B16F10 tumor model [135].

The application of photodynamic therapy after the PD-L1 siRNA delivery by cationic micelles improved the robust immune response [200]. Also, the combination of radiotherapy with PD-L1 siRNA micelles has helped in the elimination of the residual cells [223]. The complete regression of lung adenocarcinoma in xenograft mice tumor model was obtained when the gold NPs tagged with the M2 macrophage-specific targeting peptide (M2pep) and siRNA against vascular endothelial growth factor [224]. Alternatively, the lipid protamine NPs encoding the trap for the IL-10 and CXCL12 promotes the reversing of immunosuppression in the orthotopic 4T1 breast and KPC pancreatic tumor model of mice [225]. The combination of oxaliplatin enhanced the infiltration of CD4+ and CD8+ T cells, along with reducing the expression of PD-L1 in multiple tumor models like B16F10, CT26-FL3, and 4T1 tumor model. The plasmid encoding the IL-2 and IL-12 has been delivered successfully using liposome [226]. The combination of radiotherapy boosted the infiltration of CD8+ T cells, NK, and macrophages in head and neck squamous cell carcinoma. Moreover, the combination of IFNγ-inducible protein 10 gene and adoptive T cell therapy helped in the inhibition of the growth of tumors in melanoma and hepatocellular carcinoma model of mice [227].

In contrast to peptide and DNA, mRNA can be encoded for the stimulation of pattern recognition receptors and co-delivery of encoded antigens and danger signals. The combination of mRNA and chemotherapeutics against immune checkpoints has been found to act synergistically [228]. For example, the combination of protamine-mRNA and anti-CTLA-4 antibodies leads to the enhanced infiltration of cytotoxic T cells and NK cells [229]. The mannose tagged liposomes were proposed to target the dendritic cells for delivering the mRNA encoding the Mucin 1 (MUC1, tumor antigen) for eliciting the immune response in TNBC 4T1 tumor model [230]. The immune response was further enhanced when combined with the anti-CTLA-4 antibody. All the above literature suggests the versatility of gene therapy and its potential combination with the other cancer treatment modalities.

3.6. Combination Therapy: Sequential or Simultaneous

There are number of clinical trials focused on harnessing the advantage of combination therapies like experiencing high efficacy, fewer side-effects, and reducing the chances of resistance development. Although biological system is complex, and the interaction between several components decides whether the alone, sequential, or simultaneous intervention could lead to the best result. For example, the simultaneous application of chemotherapy and hormonal therapy didn't have any significant improvement in the overall survival of breast cancer patient. However, in the case of prostate cancer, the combination of androgen ablation and taxane-based chemotherapy had more significant effect than the sequential administration in LNCaP and Shionogi tumor model [231]. It reflects the importance of dosing regimen and timing of combination therapy, as many times simultaneous delivery may often be difficult for the co-delivery as well as induce adverse side effects, like in chemotherapy, side effects are severe, and combination of drugs may further extend and aggravate it. Also, the combination of drugs may limit the maximum therapeutic effect of individual drugs. Herein, the importance of sequential delivery might be realized than the simultaneous one to reduce the drug-drug interaction and side-effects along with the easing of delivery and increasing the drug access to the targets [232].

The benefits of combined therapy like hyperthermia plus radiotherapy can be harnessed more if the changes in the delivery of treatment are rationalized. In the in vitro and animal studies, it has been found that if hyperthermia is given simultaneously instead of sequentially (conventional), the sensitization to radiotherapy is increased even at a lesser dosage. The mild hyperthermia (~41 °C) for 60 min produced more heat-induced radiosensitization during the simultaneous treatment than hyperthermia (> 42 °C) given during sequential treatment [232]. In contrast, the sequential combination of paclitaxel and carboplatin and later radiotherapy has been found to have more advantageous than the simultaneous combination of cisplatin and radiotherapy in high-risk cervical cancer patients [233]. In another study of breast cancer, the simultaneous application of radiotherapy and tamoxifen didn't show any disadvantage in any of the in vitro studies; it also improved the survival of the patient. However, lung and subcutaneous breast fibrosis was found to increases in the later years [234].

4.   Localized Immunotherapy

The systemic delivery of immunomodulators has been experienced to develop cytokine release syndrome and cause abnormal liver function. Thus, in many therapeutic decisions, the local and sustained release systems are required to reduce the off-target effects. Mineral oil has been used for the sustained and localized delivery of anti-CD40 antibodies in the immunotherapy clinical trial [235]. In comparison to systemic injection of antibodies, the localized injection of this formulation lowered the dosage of antibodies in generating the systemic immune response and activating the T cells [236]. However, this system also causes inflammation and swelling at the injection site[237]. This led to the usage of biodegradable polymeric based nano- and microparticles. The PLHMGA microparticles exhibited sustained delivery of anti-CD40 and anti-CTLA-4 antibodies [119]. PLHMGA protects antibodies from rapid biodegradation and provides a better-sustained release (over 30 days) compared to PLGA. The earlier systems include mineral oils and polymeric microspheres for sustained and controlled release. However, by the time, more advanced systems have emerged as follows.

4.1.   Implantable scaffold

Most of the implanted immune cells can die upon the transplantation and involve a lot of modifications during *ex-situ* engineering. The polymeric scaffold used for drug delivery can be extended for the release of bioactive molecules, recruiting, and proliferation of the dendritic cells [238, 239] (Table 5). The antigens loaded in these scaffolds could activate and recruit the dendritic cells for efficient antigen presentation. PLGA is a widely used scaffold material that efficiently encapsulates GM-CSF for the recruitment and proliferation of the dendritic cells [240]. In contrast to bolus injection, the scaffold helped in the release of antigens and stimulation of dendritic cells over the 2 weeks study [241]. In general, intravenously injected T cells marginally reach tumor while the localized delivery suffers immunosuppression. The implantation scaffold-based approach can solve this issue [242]. Porous alginate-based scaffolds allow T cell entrapment and release in the cavity of post-operated tumors or nearby to the inoperable tumors [243] (Fig. 10). The collagen mimicking peptides were conjugated to alginate scaffold for the efficient migration (8-folds) and enhancing the viability of T cells (22-folds). This approach has also been applied for the sustained release of immunostimulatory molecules[244]. Further, the lysate of lung carcinoma, rat glioma, and others have been loaded on the scaffold towards improving the antigen presentation profile[245, 246].

4.2.   Injectable scaffolds

The scaffold-based immunotherapy often requires surgical implantation. Therefore, injectable scaffolds comprised of gelatin, mesoporous silica rods, alginate hydrogel, etc., have shown alternative approach for immunotherapy application [247-249]. The high aspect ratio mesoporous silica rods have been administered *in vivo* to form the porous structure for the recruitment and activation of immune cells [250] (Fig. 10). Mesoporous silica is extensively used for the drug delivery application due to high surface area and biocompatibility[251]. On the administration of the silica rods, it self-assembled into porous structure to localize the immune cells and release the loaded GM-CSF,

oligodeoxynucleotides containing CpG motifs (CpG-ODNs), and antigens [239]. Further, the nanomaterials can be modified with the PEI, which stimulates the secretion of pro-inflammatory cytokines, thus helps in increasing the immunogenicity of the neoantigens to target the heterogeneous tumor clones [251, 252].

4.3. Injectable hydrogels

The in-situ injectable hydrogels are being used for delivering the combined immunotherapy and chemotherapy agents. It's beneficial for patients having poor immunogenic tumors or show side effects to the immune therapies [253]. Hydrogel based technology shows delivering the immunotherapy in a minimally invasive way [242]. A poly(vinyl alcohol) based nanogel enables sequential release of gemcitabine and anti-PD-L1 antibody to elicit antitumor immunity [254]. An injectable thermohydrogel composed of chitosan, phosphate buffer, and sodium hydrogen carbonate has been used to release T cells [255]. The 50 to 500 µm pore size hydrogel showed the optimum T cell proliferation and migration. This system promotes the production of Th1 cytokine (INFN-γ).

4.4. Transdermal delivery

The transdermal delivery has been proposed for sustained release and reducing the required dose of mAbs [256]. Microneedle technology is an advanced form of transdermal delivery which can reach the immune cell-rich epidermis and release the content [256, 257] (Fig. 10). Microneedles produced from HA, pH-sensitive polymers, and immune checkpoint inhibitors enhanced survival of the melanoma mouse model (40 days vs. 30 days alone anti-PD-1 antibodies) [256]. The loading of 1-methyl-DL-tryptophan (1-MT, an inhibitor of IDO) and anti-PD-1 in NPs embedded microneedles efficiently increased the survival rate of melanoma mice to 70% in comparison to controls [256].

5. Nano-Immunoimaging

The nano-immunoimaging is a representation of imaging, immunology, and nanotechnology. This novel tool enables to probe the unanswered questions of immunology, including visualizing the immunodynamics in a spatially and temporally controlled manner, insights of the immune cell biology, cell trafficking, and monitoring the therapeutic index (Fig. 11). For nano-immunoimaging, the cognate ability of imaging at optimal *in vivo* concentration without disturbing the immunological signaling is desirable (Table 6).

5.1. Magnetic resonance imaging

Iron oxide NPs, primarily super paramagnetic iron oxide NPs (SPIONs) are the first example of immunoimaging agents that are used to label the immune cells and can be imaged under magnetic resonance imaging (MRI) [258]. The macrophages actively uptake the SPIONs due to high endocytic capabilities [259]. It was reported that SPIONs containing macrophages (~500 cells) could be tracked *in vivo*. Such non-invasive imaging of macrophages recruited to the lesion site and understanding the role of macrophages in the stroke associated neuroinflammation [260]. Besides macrophages, DC and NK can also be labeled with the SPIONs for immunoimaging. Effective labeling with biocompatible SPIONs was achieved by the coating of iron oxide NPs with the poly(aspartic acid)-*b-*

poly(ε-caprolactone) for DC imaging [261]. These SPIONs were found to have no effect on the viability, proliferation, and differentiation capacity of DC. SPIONs provide excellent contrast in MRI and whole-body DC cell tracking; for example, after injection of labeled DC cells in the footpad, it was observed draining to the lymph nodes. The labeling of autologous dendritic cells with iron oxide and imaging with MRI helps not only tracking the inter and intranodal movement of dendritic cells but ensure its accurate delivery to the lymph node of melanoma patients. NK cells usually have low phagocytic capabilities; thus, transfecting agents like Protamine® or Lipofectin® are used for the labeling of SPIONs [262]. The SPIONs labeled NK cells have been used for the liver cancer model, wherein the increase of NK cells in the liver determined by MRI was also found to be correlated with the histology studies. The loading of SPIONs is further facilitated with the usage of the external magnetic field [263]. The NK-92MI cells were loaded with the Cy5.5 labeled SPIONs can be applied to track real-time infiltration of NK cells to the tumor with the help of the external magnet. Besides innate immune cells, adaptive immune cells like CD8+ cytotoxic T lymphocytes can also efficiently labeled with SPIONs using cell penetrating TAT peptide [264]. It increased the detection efficiency to 2 cells/voxel in *in vitro* studies and 3 cells/voxel *in vivo* studies.

Magnetic nano-immunoimaging has been explored for *in vivo* labeling. For this purpose, the dextran-coated SPIONs were injected intravenously (~ 56 mg per kg), which were preferentially uptaken by the macrophages [265]. The SPIONs were found in higher numbers in the atherosclerotic plaques having higher inflammation. A positive contrast image of the plaque can be achieved after 24 h injection of NPs in MRI [266]. Such imaging techniques not only provide qualitative images but the degree of inflammation. HA (target CD44 receptors on the macrophages) functionalized SPIONs were 4 times more uptaken than the non-functionalized SPIONs and can be imaged atherosclerotic plaques more efficiently [267]. This targeted SPION formulation can decrease the dosage of the imaging agent required for imaging. Another SPION formulation that was functionalized with Annexin V facilitates superior interaction with the phosphatidylserine expresses on the surface of dying macrophages and other cells in atherosclerotic plaques [268]. Such labeling also helped in reducing the dosage of SPIONs to more than 200-folds. Similarly, nano-immunoimaging is also helpful in the early determination of the rejection of the allograft and rejection induced apoptosis of mesenchymal stem cells by attaching the peptides showing the Tight up' feature in the presence of caspase-3 (apoptosis marker) to SPIONs [269].

During the inflammation and metastasis, the E-selectin gets upregulated and recognizes the tetrasaccharide sialyl LewisX (sLeX) expressed on the leukocytes [270]. The sLeX-SPIONs reflected less attenuated MRI signal in hepatic mice than the uncoated SPIONs[271]. The ultrasmall SPIONs has been used for the labeling of exosomes for understanding the activation of T cell with MHCII bearing exosomes released from B-lymphocytes [272].

Magneto-motive ultrasound imaging (MM-US) is another imaging modality for immunoimaging[273]. Wherein a strong, focused magnetic field is applied to generate motion in tissue with the help of SPIONs, and then signals are measured using ultrasound transducers. After the injection of SPIONs, the motion of macrophages was readily noticed in the liver. These techniques have strong selectivity potential in tracking applications

without the usage of radioactive materials. The limitations of the SPIONs are inherent inflammation, oxidative stress, and toxicity to the cells. The high chance of false-positive results if the labeled cells die and release the SPIONs, which could be taken up by the other cells[274].

5.2. Optical imaging

The benefits of optical imaging are the ability to even detect single cells with higher sensitivity, specificity, and higher temporal and spatial resolution [275]. There are instances wherein it has been used complementary to MRI and CT imaging for whole-body scanning and understanding the interaction of nanomaterials with the cell's biology [276]. However, the limitations of optical imaging are the depth of imaging, which is usually trade-off with spatial resolution and background autofluorescence. Thus, the usage of NPs has come up to address these limitations. The high-resolution optical imaging includes fluorescence, bioluminescence, scattering, and absorbance based imaging[277]. Quantum dots are fluorescent nanomaterials, which are extensively used for optical immune imaging due to their size-tunable emission and robust fluorescence stability[278, 279]. To overcome the problem of shallow penetration of UV light, lanthanide-based upconversion nanoparticles (UCNPs) have been explored for the imaging of immune cells with low background [280]. They can fluoresce on the irradiation of near-infrared light (high penetration depth, 600-900 nm) due to the reverse stokes process. There are also reports of coating UCNPs with polyethyleneimine and oligo-arginine to facilitate its uptake by DCs on the incubation [281]. On the hypodermic injection of UCNPs to the footpad of the mice, it reached to the draining lymph nodes, which was determined with the help of luminescence imaging.

Optical coherence tomography is widely used for studying the movement and function of immune cells inside the tumor [282]. Towards this, TAM has been labeled with the gold nanorods as an optical scattering contrast agent. It helped in better and deeper imaging in the complex, hypoxic, and necrotic environment of the tumor. Optical imagining is also being used for tracking the multifunctional NPs in the course of immunotherapy. For example, multifunctional NPs were incorporated with GFP/Luc for tracking the activity and location inside the body [107].

5.3. Nuclear imaging

The usage of radioactive materials has given insights from the decades on finding the distribution and interaction of immune cells [283]. Recent advancement shows that NPs being surface decorated with radioactive isotopes like ^{89}Zr, ^{124}I, ^{64}Cu *via* chelation chemistry or encapsulation for the positron emission tomography (PET) and single-photon emission computed tomography (SPECT) [284]. There are reports of labeling the TAM with the radioactive modified NPs for assessing the therapeutic response and stratifying the patients in the clinical trials. For example, polyglucose NPs were modified with the ^{64}Cu, which helped in the quantification of TAM inside the tumor. It was observed that more than 700% strong radioactive signals were obtained in the TAM rich tumor than from the TAM deficient tumors [285] (Fig. 12a-f).

The high contrast of nuclear imaging has also helped in monitoring the CAR-T cell therapy. For example, gold NPs modified with $^{64}Cu^{2+}$ were used to track the CAR-T cells. The PET/CT imaging also ensured that CAR-T cells reach and remain at the intended site to avoid the side effects[286]. In comparison to other imaging modalities, radioactive material is also required in very less amount, thus an intangible chance of affecting the native functions of the cells or interactions, which has also been one of the reasons that nuclear imaging is rapidly being explored in the clinical trials.

5.4. Multimodal imaging

Multimodal imaging represents the combination of two or more imaging modalities, such as optical and acoustic in photoacoustic, and other combinations of different conventional imaging modalities. In photoacoustic imaging, ultrasound imaging is combined with optical imaging, wherein the multi-centimeter depth with micrometer resolution is achievable [287]. It gives the advantage of spatial contrast of optical imaging while understanding the anatomical and penetration depth of ultrasound imaging [288]. For example, human cytokine-induced killer (CIK) cells were loaded with the silica modified gold nanorods, which along with the photothermal therapy to gastric cancer, also helped in photoacoustic imaging of the subcutaneous gastric cancer after 4 h of injection [289] (Fig. 12g-h). It killed the MGC803 cancer cells, along with modulation of immune response due to the upregulation of cytokines and interferons.

To further harness the potential of magnetic and optical imaging modalities, peptides have also been used for decorating the SPIONs. For example, peptide (CDSDSDITWDQLWDLMK) has been attached to fluorescent SPIONs *via* the N-terminus cysteine to binds with the E selectin which facilitates the enhanced optical imaging of activated endothelium in mouse tumor model [290].

7.   Challenges and opportunities

7.1.   Challenges

The delivery of the required concentration of NPs to the specific site is one of the major limitations in cancer immunotherapy. The fabrication of NPs with due consideration on the shape, size, and pharmacokinetics can make the delivery of NPs more efficient with fewer side effects. However, challenges like a homogenous synthesis of NPs on a large scale and its interaction with immune cells inside the body need further investigation[291, 292]. It has been experienced that only less than 5% of the administered NPs reach the tumor due to the heterogeneous nature of the tumor, ECM, pharmacokinetics, and many other factors[291, 293]. In most of the studies, mouse tumor models have been used as pre-clinical models, which has been noted to differ significantly from the human in terms of heterogeneity, tumor growth, blood vessel diameter, and many more parameters. The safety of nanomaterials is another complication in immunotherapy. There are several biomaterials which are commonly used and have their own advantage and disadvantages (Table 7). Thus, the interaction between the nanomaterials and immune cells should be thoroughly evaluated. For example, it has been noticed that different sizes of NPs induced different types of immune response, e.g., ~40 nm particles induced the IFN-γ response while ~100 nm particles

activated the CD4+ T cells and IL-4 secretion [294].The intrinsic immune regulating activities of nanomaterials is important to understand, which can significantly affect the physicochemical properties. For example, PEI (cationic polymer) known for gene delivery, has been reported to have self-adjuvant properties and affect the immunological response *via* TLR5 pathway [295]. Similarly, cationic liposomes are known to stimulate the APCs for expressing the costimulatory molecules like CD80 and CD86, while zwitterionic or anionic lipid shows no response towards DC.

The load of mutations differs from cancer to cancer as well as between patients. It demands the approach of bioinformatics for finding the top neoantigen in a cancer type. However, the physicochemical and biological property of the neoantigen also needs to be considered as it affects the delivery to the draining lymph nodes, thus efficacy and immunogenicity of the vaccines. Additionally, the expeditious screening of patients reactive to neoantigen needs to be researched out. Towards achieving the broad T cell response, the competitive binding of neoantigen with MHC needs to be considered. Competitiveness and combination with the other antigens in the codelivery system need to be explored [296, 297].

The manufacturing process needs to be streamlined and cost-effective for the successful adoption of immunotherapy. It is another critical parameter to produce good manufacturing practice (GMP) grade vaccines which majorly critical in clinical trials or evaluation of particles. For example, the neoantigen-encoding mRNA vaccines take around 160 days to include the determination of neoantigen, production of mRNA, vaccine manufacturing, and product release [298]. Similarly, the neoantigen peptide vaccine takes around 18 weeks from the determination of neoantigen to vaccine production [299]. The cost of immunotherapy comprised of individual costs of biopsy of the tumor, bioinformatics, mRNA and DNA sequencing, current GMP manufactured biologics, carrier for the cells and drugs, and skilled personnel for delivering the tailored dosage. Thus, the requirement of a simplified approach and clear-cut manufacturing are highly sought.

The varying stability and physicochemical property of peptides, plasmids, biomaterials, and other components of immunotherapy demand the standardized formulation, analytical method, and sterilization protocol for quick product release [81]. The dosage and safety profiles of nanotherapeutics need to be established, as faster kinetic and potent therapeutics might require a lower dosage and vice versa.

7.2. Opportunities

The nature-derived NPs, like albumin NPs, protein nanocages, virus-like particles, exosomes, etc., have proven their place in clinical applications. In comparison to synthetic NPs, nature-derived NPs have advantages such as good biocompatibility, facile production, and immunotherapy boosting characteristics[300]. In contrast to conventional vaccines, albumin, and lipid conjugates having multiple sites, found to be more effective in eliciting the T cell response [301]. The coating of NPs with the cell membrane is another exciting field toward the NPs driven natural vaccines. These advancements help in maintaining the complex antigenic information, thus increase in the therapeutic efficacy in a very specific manner [302, 303]. High-density lipoprotein NPs have low immunogenicity and high stability in the blood and can deliver both the antigens and immunoadjuvant together[304].

Similarly, there are many reports which indicate that natural NPs themselves can elicit the augmented immune response and can work as cancer vaccines. For example, virus-like particles (VLPs) have been experienced to induce both cellular and humoral immune response. The VLPs based prophylactic vaccination (Gardasil or Cervarix) has been used for the treatment of HPV caused cervical cancer [305]. The cowpea mosaic virus in the form of NPs has been found to manipulate the tumor microenvironment and reduce immunosuppression[132].

Exosomes are 40-100 nm endogenous NPs with the properties of cell membrane. They often express the MHC-1 and 2, along with heat shock proteins, help in eliciting the immune response of T helper cells [306]. The key exosome markers like Alix, CD63, CD9, and TSG101 have been noticed to induce cellular immunity and activate the NK cells [306]. Exosomes are known to contain several antigens, which help in inducing specific immunity [307]. The role of exosomes has been determined in the immunosuppression and pro-metastatic preparation of the tumor.[385]Tumor-derived exosomes (TEX) can also induce antitumor immunity due to the antigen present on their surface [308]. It has been found that TEX causes the apoptosis of pancreatic cancer cells via PI3K/Akt/GSK-3β pathways and Notch signaling [309]. The exosomes driven activation of innate immunity with the help of IgG and NK activity has been reported along with adaptive immunity [310].

The usage of exosomes for presenting the antigen or delivering the chemotherapeutic or RNAi to the specific site has been very hopeful [311, 312]. It has been noticed that the dendritic cells derived exosomes (DEX) can work on boosting humoral and cellular immunity. The MHC complex, CD86, and adhesion molecules include MFG-E8, and ICAM-1 activate the CD8+, CD4+ T cell response [313]. DEX has been used in the cell-free vaccination of mice [312]. DEX activates innate immunity *via* NKG2D-dependent NK cell and IL-15Rα assisted cell proliferation [314]. Thus, it has been used for the inhibition of melanoma, and the results of early preclinical trials have been promising [315]. However, the challenges like suppression of host immune response and number of activated T cells on the usage of DEX as tumor vaccines need to be further investigated.

The nanomedicines are usually evaluated on the basis of parameters like the ability to target tumor cells and vasculature, active and passive drug delivery, high stability, slower body clearance, high tumor uptake, high drug loading efficiency, and release profile. Out of the several next-generation nanomedicines (e.g., liposomes, micelles, polymeric, and metal NPs), liposomes appear to be suitable for tuning to all the above parameters.

Since 1995 or earlier, FDA has approved several nanomedicines based on micelle, metallic, protein, nanocrystal, liposome, and polymeric materials. During 2001-2005, the approval of nanomedicine was at the peak with nanocrystals holding the highest percentage. However, after 2005, there was a decline in the FDA approval rate and an increase in the nanomedicines clinical trials. Currently, ~ 77 products are in clinical trials, and most of them are in phase 1/2 clinical trials. Further, it was noticed that 40% of the clinical trials listed in clinicaltrials.gov started in 2014 and 2015.

8. Conclusion and Future Direction

Although nanotechnology driven immunotherapy is still in the nascent stage, it holds great potential towards increasing the efficacy and safety profile of cancer treatment. The approaches discussed in this review article may help in facilitating opportunities that can be applied to increase the efficacy of combined therapies, designing biomaterials, and fabrication of multifunctional NPs towards the treatment of aggressive and complicated cold tumors. The outcome of clinical trials is also reflecting the potential of nanotechnology synergized immunotherapy; however, reproducibility, manufacturing feasibility, and undefined toxicity of the nanomaterials should be carefully considered before commercialization.

Acknowledgments

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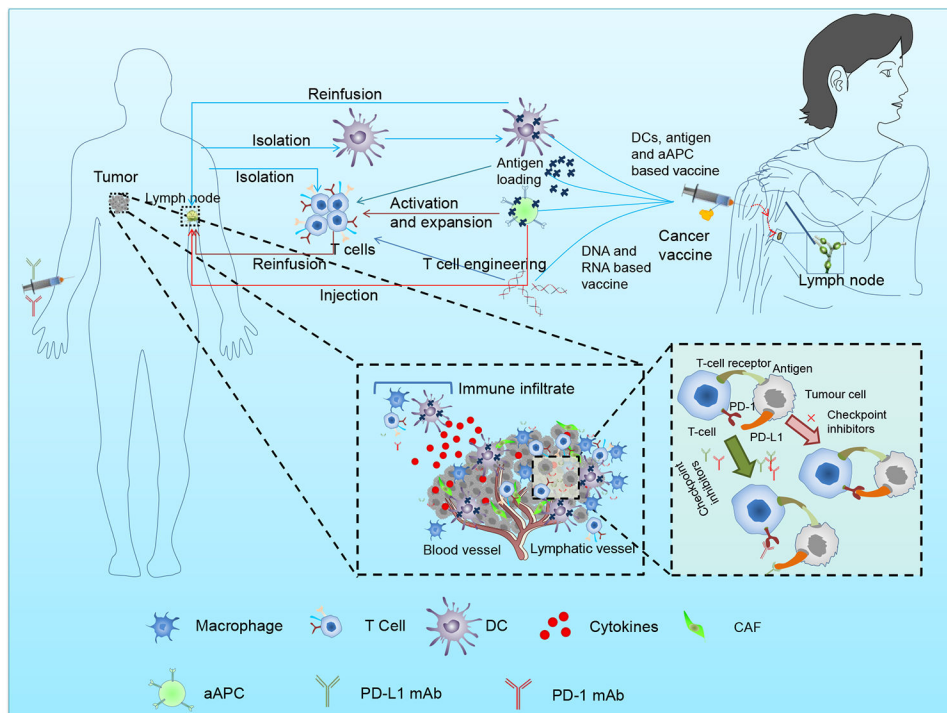
Fig. 1. Manipulation of T cells, infiltration of immune cells in tumor microenvironment, checkpoint inhibitor, and approaches followed in vaccine development.
Manipulation of T cells includes antigen representation by DC and artificial antigen presenting systems (aAPC), and nucleic acid transfer. The immune cells (macrophages, T cells, dendritic cells) infiltrate in the tumor microenvironment. The approaches for vaccine development include the injection of engineered dendritic cells, antigen, and aAPC.
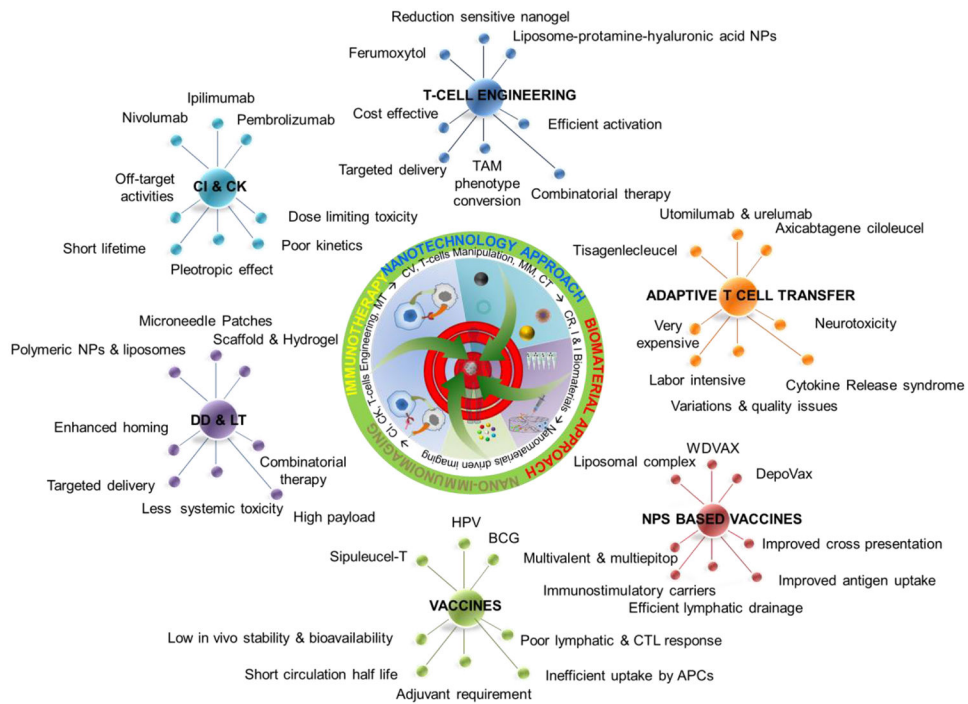
Fig. 2. Developmental Pathway and Interconnectivity of Immunotherapy and Nanotechnology:
The top 3 spikes show the current advancements, while the bottom spikes show the advantages and disadvantages of nano-immunotherapy and convention immunotherapy, respectively. Integration of nanotechnology, material science, and nano-immunoimaging towards reinforcing cancer immunotherapy. The area of pie sector represents the percentage of current development. Abbreviation: checkpoint inhibitor (CI), cytokines (CK), drug delivery (DD), localized therapy (LT), microenvironment tunning (MT), cancer vaccines (CV), microenivornment modulation (MM), combination therapy (CT), controlled release (CR), implantable and injectable biomaterials (I&I Biomaterials).
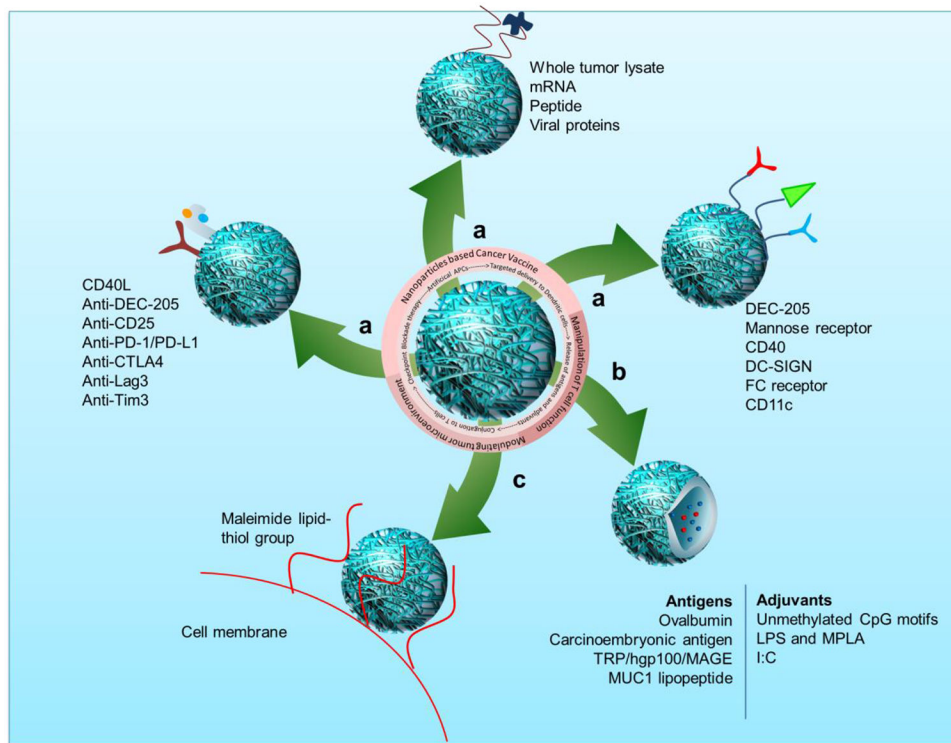
Fig. 3. Role of nanoparticles in the different areas of cancer immunotherapy.
Nanoparticles are helpful in **a)** targeted delivery of antigens to dendritic cells, **b)** controlled and triggered release of antigen and adjuvants to the tumor. **c)** Conjugation to the T cells for long-term activation and increasing the efficiency of checkpoint blockade therapy.
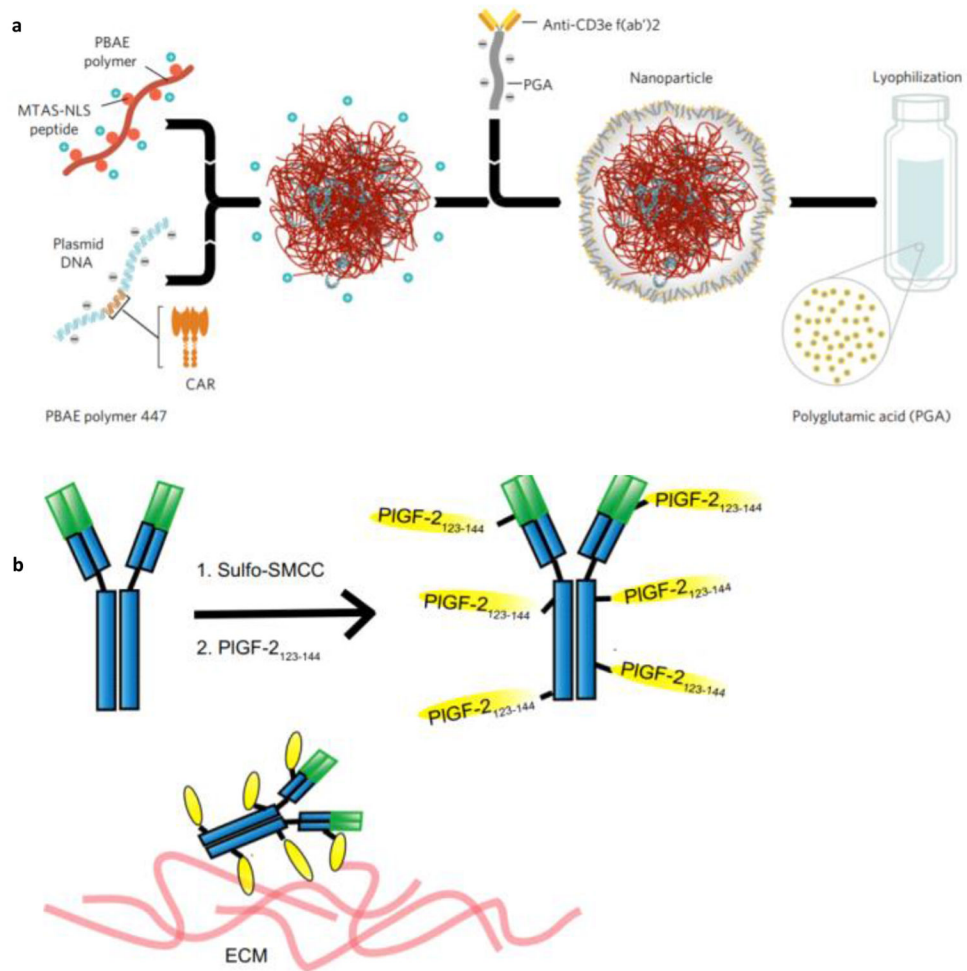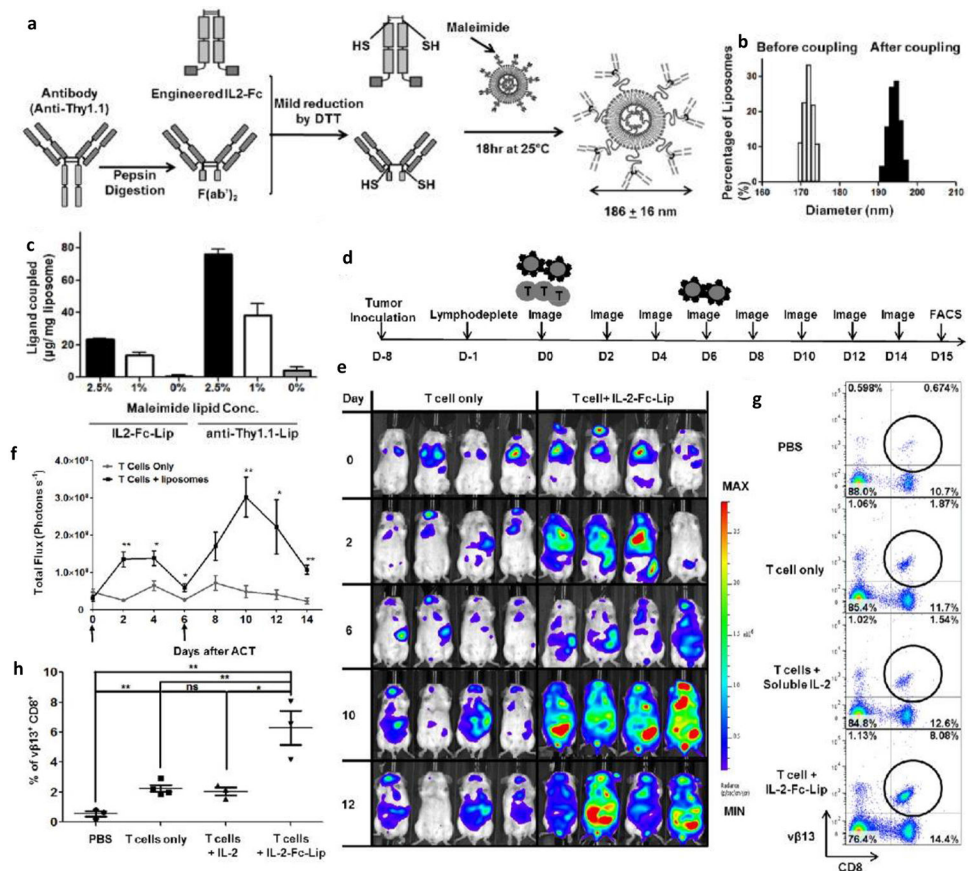
Fig. 4.
a) Schematic showing the fabrication of the anti-CD3e f(ab′)2 fragments attached poly(β-amino ester) nanoparticles. **b)** Schematic showing the conjugation of PlGF-2 peptide to IgG antibody for improving the binding to ECM proteins. Adopted with permission from reference [107] (a) and [115] (b)

Fig. 5.
a) Schematic showing the preparation of immunoliposomes. **b)** Size distribution of immunoliposomes before and after coupling with T cells. **c)** Quantification of ligand (IL2 or anti-Thy1.1) to the liposomes containing different concentration of maleimide. **d)** Timeline representing the study regimen. **e)** Representative bioluminescent images of mice over different time periods. **f)** Quantitative analysis of whole-body imaging. **g)** Flow cytometric analysis after the adaptive transfer of the tumor-specific (vβ13 TCR+) T cells. **h)** Quantitative analysis of tumor-specific (vβ13 TCR+) T cells in the inguinal lymph nodes. Adopted with permission from reference [110].
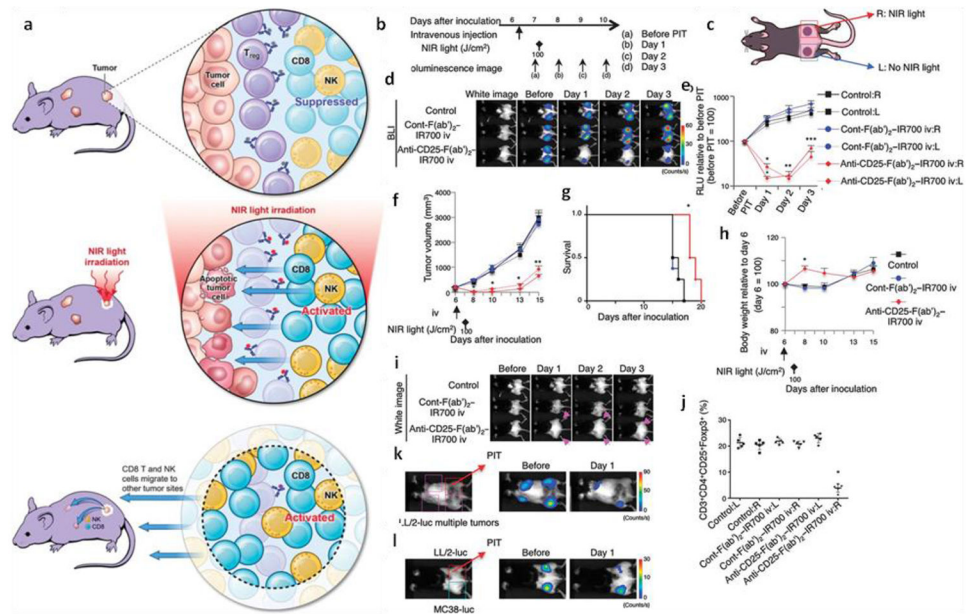
Fig. 6.

a) Schematic representation of the induced immunotherapy after NIR-PIT. **b)** General regimen adopted for the NIR-PIT. **c)** Biflanked tumor model: right tumor was treated with NIR light and anti-CD25-F(ab′)2–IR700 or (ab′)2–IR700 driven phototherapy, while the left tumor was left untreated. **d)** Representative bioluminescence images showing the changes after the localized NIR-PIT. **e)** Reduction in the relative light units (RLU) of the right tumor after NIR-PIT as well as in the left non-irradiated tumor. **f)** Reduction in size of the tumor after the CD25 treated right tumor as well as non-irradiated one. **g)** Prolonged survival of mice after NIR-PIT. **h)** Change in weight after the NIR-PIT, **i)** Edema due to NIR-PIT at both tumors after CD25 targeted NIR-PIT, **j)** Depletion of CD4+CD25+Foxp3+ Tregs in the right tumor but not in the left untreated. **k)** Regression of multiple LL/2-luc tumors after the localized CD25 targeted NIR-PIT at the right tumor. **l)** Negligible effect on the MC38-luc tumor after NIR-PIT on the LL/2-luc tumors of the right side. Adopted with permission from reference [124].
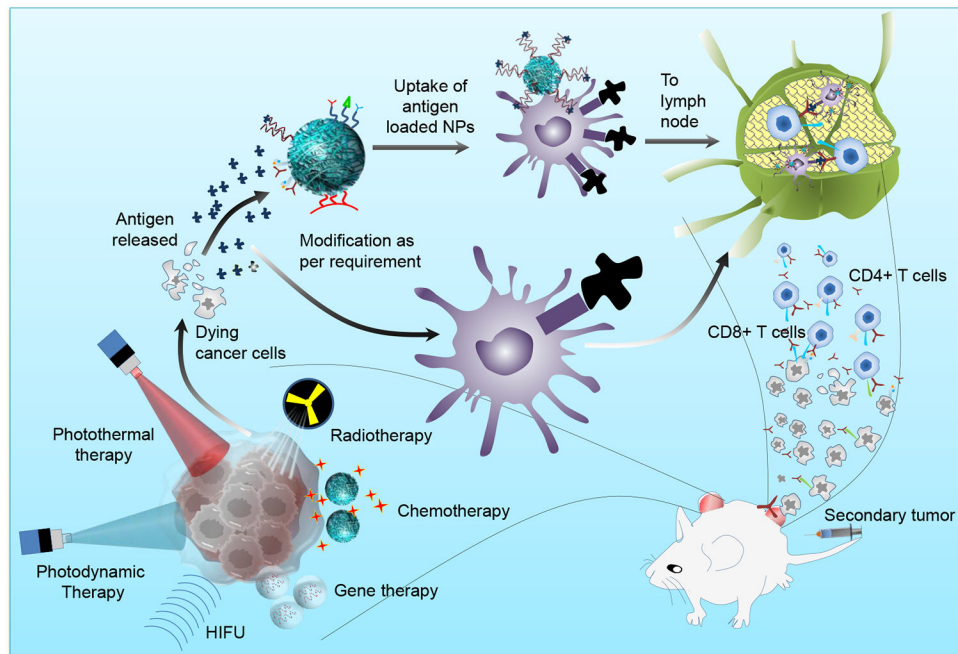
Fig. 7. Synergistic effect of conventional therapies and immunotherapy in reference to nanoparticles functionalization.

Chemotherapy, photothermal, photodynamic, radiotherapy, and gene therapy cause immunogenic cell death, and nanoparticle functionalization leads to robust activation of the immune response, which is helpful in observing the abscopal effect.
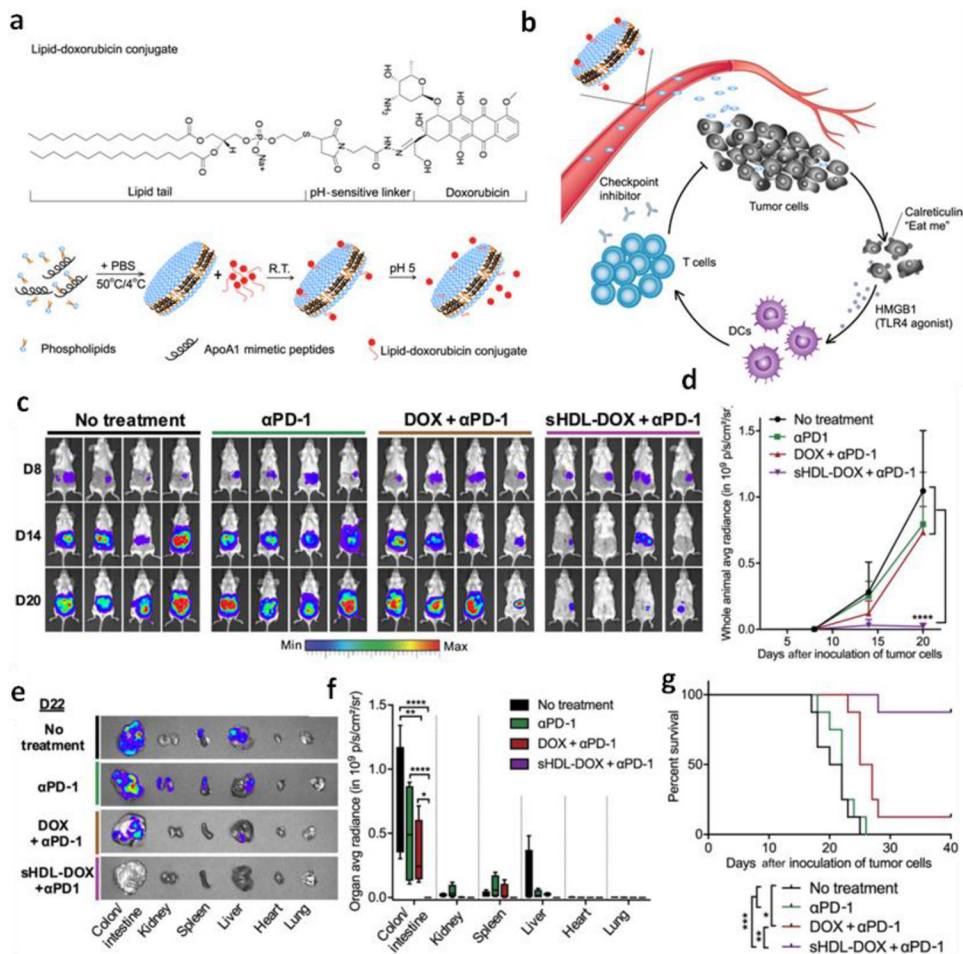
Fig. 8.
a) Schematic of sHDL-DOX synthesis for the chemo-immunotherapy. **b)** Schematic showing the intratumoral delivery of DOX due to ultra-small nature of sHDL, and also triggering ICD and danger signals like HMGB1 and calreticulin. **c)** Representative bioluminescence images of mice during the course of study. **d)** Quantification of the signals. **e)** Imaging of the major organs harvested. **f)** Quantification of signals from each organ harvested. **g)** Survival graph of mice. Adopted from reference [141] which is distributed under a Creative Commons Attribution Noncommercial License 4.0 (CC BY-NC).
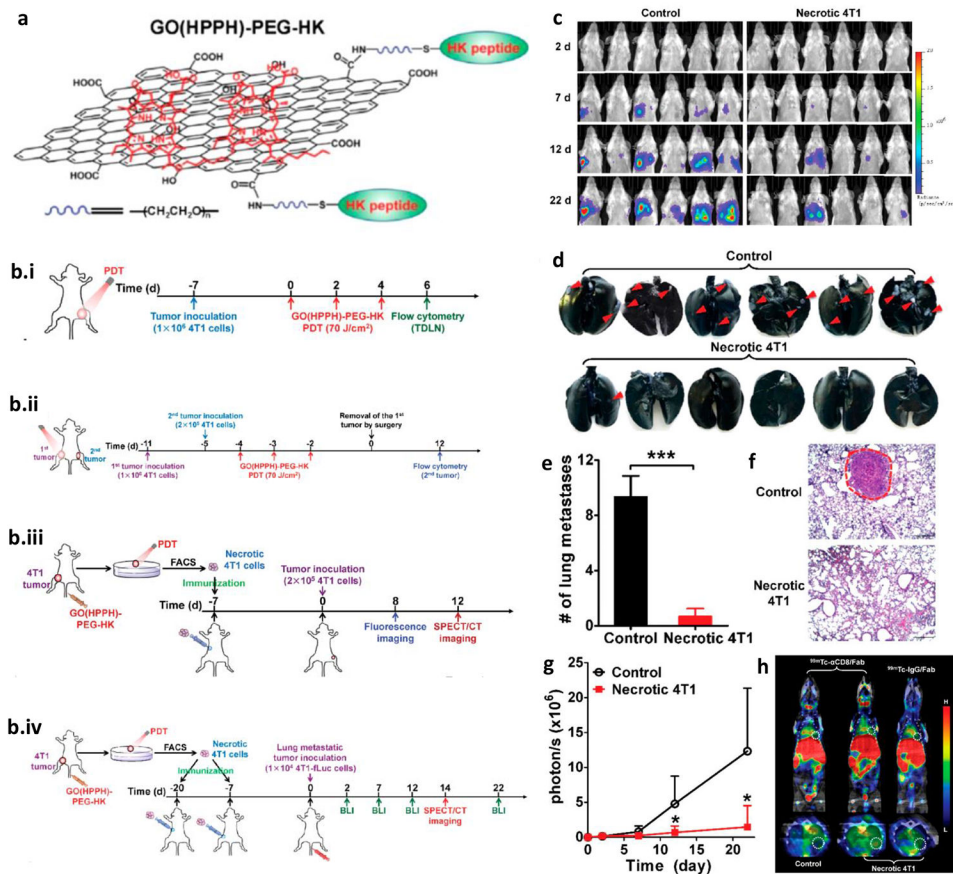
Fig. 9.
a) Schematic showing the fabrication of GO(HPPH)-PEG-HK. **b.i, ii, iii, iv)** Different regimens of GO(HPPH)-PEG-HK driven PDT in the subcutaneous 4T1 tumor model (i), GO(HPPH)-PEG-HK driven PDT at one tumor model to stimulate immunity at the second tumor (ii), GO(HPPH)-PEG-HK driven PDT to induce the necrotic 4T1 cells to use them for tumor vaccination (iii, iv). **c,g)** Representative bioluminescence images (c), and quantitative analysis (g). **d)** Representative images of the lung filled with Indian ink. **e, f)** Quantitative analysis (e) and H&E staining (f) of metastatic lesions in lungs. **h)** Representative SPECT/CT images of mice after the 99mTc-αCD8/Fab and 99mTc-IgG/Fab administration and vaccination using PBS and necrotic 4T1 cells, respectively. Adopted with permission from reference [196].
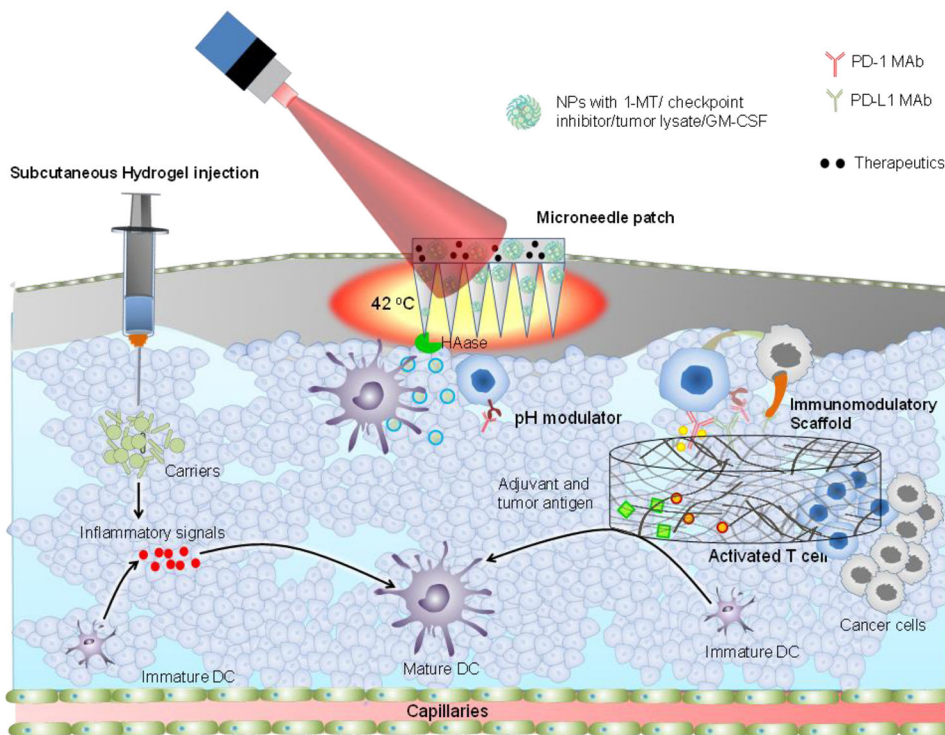
Fig. 10. Approaches for the localized modulation of the tumor microenvironment.
The current approaches mainly include the scaffold, microneedle patches, and injectable hydrogels. The scaffold helps in the activation of T cells, immune checkpoint blockade, as well as the maturation of dendritic cells. The microneedle patches and injectable hydrogel are less invasive and used for the triggered and controlled release of different immune modulators.
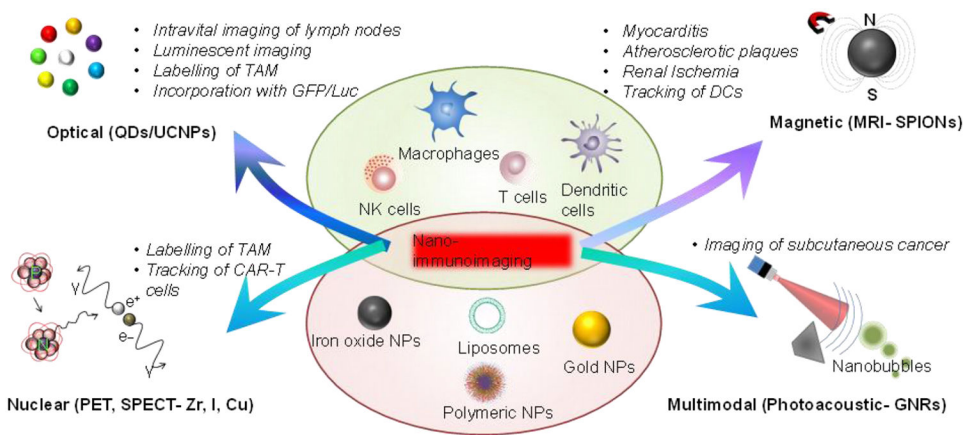
Fig. 11. Application of nanomaterials in immunoimaging.
The nano-immunoimaging involves the integration of diagnostic nanomaterials for the imaging of immune cells like dendritic cells, macrophages, T cells, and NK cells.
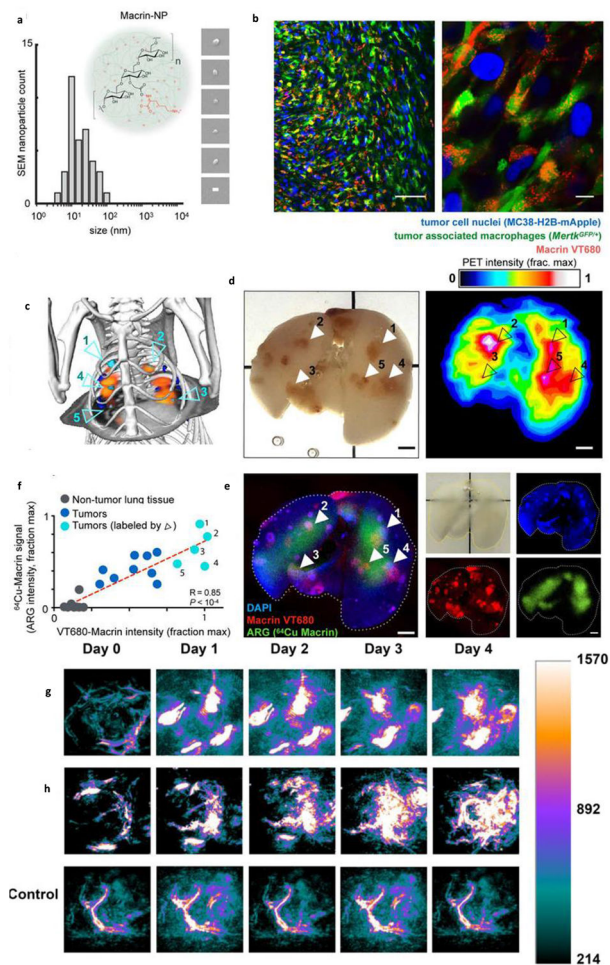
Fig. 12.
a) Size distribution of polygluocse nanoparticles (macrin) along with representative images of SEM, scale bar is 20 nm; inset: L-lysine (red) functionalized macrin (black) to attach the chelators for ^{64}Cu and other labels. **b)** Confocal images of MC38 tumor at low and high magnification in MertkGFP/+ mice. **c)** Reconstructed PET/CT image showing the tumors in lungs (cyan and blue) and accumulation of macrin (orange). **d-e)** Ex vivo PET image corresponding to *in vivo* highlighted tumors(d), confocal images of optically cleared lung tissue(e). **f)** The relation of optical (VT680) and nuclear (^{64}Cu) imaging. **g, h)** Phototoacoustic imaging with Au NR@SiO2 nanoparticles (g), NP-CIK cells (h) containing 6.7 µg of gold after peritumor injection. Part (a-f) adapted from reference [284], part (g-h) adapted from ref. adapted from reference [288].

Table 1.

List of approved and under clinical trial cancer immunotherapies.

Type	Name (trade name)	Manufacturer/ CTid	Target/ Platform	Indication (Phase)
Cytokines	IFN-α2b (Intron A)	Merck & Co., Inc		Kaposi Sarcoma (II), leukemia (IV), lymphoma (IV), melanoma (III)
	IFN-α2a (Roferon-A)	Genentech, Inc.		Kaposi Sarcoma (II), leukemia (IV)
	Recombinant IL-2 (Aldesleukin)	Novartis		RCC (III), melanoma (III)
	1-isobutyl-1H-imidazo (Imiquimod)	Perrigo		Superficial basal cell carcinoma (III)
	IFN-α2b	NCT02634294		Hematological malignancies (II/III)
	IFN-α2a	NCT03253250		Hepatocellular carcinoma (IV)
		NCT02829775		Advanced tumors (II/III)
	GM-CSF	NCT03363373		Neuroblastoma (II)
Checkpoint inhibitors	Ipilimumab (Yervoy)	Bristol-Myers Squibb	CTLA-4	Melanoma (IV)
	Pembrolizumab (Keytmda)	Merck & Co	PD-1	HL (III), lung cancer (IV), melanoma (IV), head and neck cancer (IV), stomach cancer (III)
	Nivolumab (Opdivo)	Bristol-Myers Squibb	PD-1	Melanoma (IV), RCC (IV), HL (III), liver cancer (IV), bladder cancer (III), NSCLC (IV)
	Atezolizumab (Tecentriq)	Roche, Genentech	PD-1	Lung (IV), breast (III), bladder (III), urinary tract cancer (III)
	Avelumab (Bavencio)	Merck KGaA and Pfizer	PD-L1	Merkel cell carcinoma (III)
	Durvalumab (Imfinzi)	Medimmune/AstraZe neca	PD-L1	Bladder (III), urinary tract cancer (III), NSCLC (IV)
	Cemiplimab	Sanofi	PD-L1	Squamous cell carcinoma (III)
	IMP321	NCT00365937, NCT01308294, NCT02614833, NCT03625323	LAG-3	Advanced melanoma (I/II), Metastatic breast cancer (II), Advanced NSCLC and HNSCC (II),
	Relatlimab	NCT01968109, NCT02488759, NCT02061761, NCT03459222, NCT03623854, NCT03743766, NCT03642067, NCT03607890, NCT02996110, NCT02935634, NCT02750514, NCT02060188, NCT02519322	LAG-3	Virus associated cancer (I/II), hematologic malignancies (I/II), Advanced solid tumors (II), chordoma (II), melanoma (II), RCC (II), GC (II), NSCLC (II), CRC (II),
	LAG525	NCT02460224, NCT03365791, NCT03499899, NCT03484923	LAG-3	Advanced Solid tumor (I/II), hematological malignancies (II), TNBC (II), melanoma (II)
	MK-4280	NCT03598608, NCT03516981	LAG-3	Advanced NSCLC (II), hematological malignancies (I/II),
	BI754111	NCT03697304	LAG-3	Advanced solid tumor (II)
	TSR-022	NCT03680508	TIM-3	Liver Cancer (II)
	MBG453	NCT02608268	TIM-3	Advanced malignancies (I/II)
	BMS-986258	NCT03446040	TIM-3	Advanced solid tumor (I/II)

Type	Name (trade name)	Manufacturer/ CTid	Target/ Platform	Indication (Phase)
	Tiragolumab	NCT03563716	TIGIT	Advanced NSCLC (II)
	BMS-986207	NCT02913313	TIGIT	Advanced solid tumor (I/II)
	Enoblituzumab	NCT02923180	B7-H3	Prostate cancer (II)
	131I-8H9/omburtamab	NCT03275402	B7-H3	Neuroblastoma/leptomeningeal metastases (II/III)
CAR-T cells	Tisagenlecleucel (Kymriah)	Novartis Pharma	CD19	Leukemia (III), lymphoma (III)
	Axicabtagene ciloleucel (Yescarta)	Kite Pharma	CD19	NHL (II)
		NCT03631576, NCT02937103, NCT03398967	CD123	AML (II/III), myeloid malignancies (I/II)
		NCT03398967	CD19 and CD20 or CD22	B cell leukemia and lymphoma (I/II)
		NCT02958397	CD33	myeloid malignancies (I/II)
		NCT03754764	CD38	B-ALL (I/II)
		NCT03196414	CART-138	MM (I/II)
		NCT03778346	CD38/CD138	MM (I)
		NCT03767751	Dual CD38/ BCMA	MM (I/II)
		NCT03222674	Muc1/CLL1/ CD33/CD38/ CD56/CD123	AML (I/II)
Vaccine	Spiuleucel-T (Provenge)	Dendreon Pharmaceuticals	Autologous immuno therapy	Hormone-refractory prostate cancer (III)
	BCG	Merck & Co., Dianon Systems, Evans Vaccines, Statens Serum Institut, Japan BCG Laboratory NCT03300843	Attenuated Mycobac terium bovis DC	Bladder cancer (IV) solid cancers (II)
		NCT03480152	RNA	solid cancers (I/II)
		NCT03598816	DNA	RCC (II)
		NCT03633110	Synthetic peptide	Solid cancers (I/II)
		NCT03639714	RNA	Solid cancer (I/II)

Abbreviation: Bacillus Calmette Guerin (BCG), acute myeloid leukemia (AML), multiple myeloma (MM), renal cell carcinoma (RCC), B-cell acute lymphoblastic leukemia (B-ALL), triple-negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), gastric cancer (GC), colorectal cancer (CRC), head and neck squamous cell cancer (HNSCC), Hodgkin lymphoma (HL), non - Hodgkin lymphoma (NHL)

Table 2:

Progress of nano-and micro-formulation in the improvement of immunotherapy.

Micro and Nanoformulation	Type	Surface functionalization	Adjuvant	Average Size	Publications, Patents, and Clinical trials
Polymeric NPs and MPs	PLGA, PLA, PGA, PCL, Chitosan, Polyester, Dextran, PLHMGA, polystyrene	PEG, polyhydroxy, PEI, Carboxyl, cancer cell membrane, sulfate, LHRH peptide, Cy5.5	CpG, OVA, anisamide, listeriolysin, α-GalCer, HSPs, montanide	20 mn-5μm	82, 2, 0
Lipid NPs (Liposomes, solid lipid NPs)	Phospholipid, cationic lipid, DOTAP, DSPE-PEG, phosphatidylcholine, DOPE, NBD-DOPE	Maleimide, PEG, protamine, hyaluronic acid, LHRH peptide, Cy5.5	OVA, CpG, pIC, zymosan, R848, LPS, L-PAM, Pam3CSK4, MPLA, DiC14-amidine, BCG-CWS, HSP	150 nm-1.5 μm	500, 19, 23
Inorganic NPs	Gold, iron oxide, zinc oxide, calcium phosphate, QDs, copper sulfide, CNT, Ce6, MOF, UCNPs, aluminum oxide, silica	Amino, mannose, dextran, avidin, polydopamine	CEA, CpG, GMCSF, 1MT, imiquimod, IDO inhibitors, HSPs, alum	2-50 mn	298, 4, 0
Nanogels	Gelatin, chitosan	Quaternary amino	IL-2, IL-15SA	130-250 mn	15, 0, 0
Dendrimers	Succinamic acid dendrimers G4), polyamidoamine dendrimers (G5)	DGBA, LHRH peptide, Cy5.5	CpG, PADRE,	58-68 nm	28, 0, 0 21, 0, 0
Cyclodextrins	α-CD, β-CD, γ-CD, Succinyl-β, Methacrylate β, HP-β-CD, M-β-CD, SBE-β-CD	PEG, Porphyrin,			
Micelles	PPS, MPEG- OH, PLL-g-PEG, PEI, PCL, PLH–PEG, dextran-grafted-poly (histidine), PGA, LMWH-d- (TOS), PEG-CDM-PEI	Cancer cell hybrid membrane, CaCO3-crosslinked, heparin	CpG, Poly I:C, M-CSF, IMQ	23 mn	78, 0, 0
Microneedles, Scaffold, Hydrogel, rods	Hyaluronic acid, Alginate, PLGA, Chitosan, PVA, silica, gelatin, aluminum hydroxide	Melanin, PEI	GMCSF, CpG, IL-2, IL-15SA, FLT3L, CCL20		258, 7, 1

Abbreviation: polystyrene nanoparticles (PSNPs), l-dioleoyl phosphatidylethanolamine (DOPE), N-(7-nitro-2,1,3-benzoxadiazol-4-yl) labeled dioleoyl phosphatidyl ethanolamine (NBD-DOPE), phenylalanine Mustard (L-PAM), monophosphoryl lipid A(MPLA), Bacille Calmette–Guerin cell wall skeleton (BCG-CWS), Carcinoenbryonic antigen (CEA), Poly(amidoamine)(PAMAM), Guanidinobenzoic acid (DGBA), Galactosylceramide (α-GalCer), Guanidinobenzoic acid (DGBA), cytosine-guanine dinucleotides (CpG), PAn DR epitope (PADRE),2-Hydroxypropyl-β-cyclodextrin (HP-β-CD), Methyl-β-cyclodextrin (MβCD), sulfobutylether-β-cyclodextrin (SBE-β-CD), Methoxy poly (ethylene glycol) (MPEG- OH), poly(l-histidine)–poly(ethylene glycol) (PLH–PEG), Poly (glutamic acid) (PGA20k), low molecular weight heparin (LMWH)-d-α-tocopheryl succinate (TOS), macrophage colony-stimulating factor (M-CSF), macrophage colony-stimulating factor (M-CSF), polypropylene sulfide (PPS), polycaprolactone (PCL), luteinizing hormone releasing hormone (LHRH), 1,2-dioleoyl-3-(trimethylammonium)propane (DOTAP), 1, 2-Distearoyl-sn-glycero-3-phosphoethanolamine-Poly (ethylene glycol)(DSPE-PEG), TLR2 ligand Pam 3 CysSerLys 4 (Pam 3 CSK 4), Nt-butyl-N′-tetradecyl-3-tetradecylaminopropionamidine (diC 14-amidine), chlorine e6 (Ce6), Metal–organic frameworks (MOFs), Poly(L-lysine)-graft-poly(ethylene glycol) (PLL-g-PEG), 2-propionic-3-methylmaleic anhydride (CDM),

Table 3.

List of nano and macro-materials used for the cancer immunotherapy.

Nanomaterial	Functionalization	Delivering agent	Target/Action
Vaccine development			
Iron and Zinc NS		Gene of interest	DC
Polymeric NPs	UPNP coated	OVA	DC
DepoVax		TACE, topoisomerase II α, EDDR1, B cell receptor specific protein 31 (CDM), γ catenin	DC
PLGA NPs	PEG and mAbs	OVA and TLR ligand	DC
Liposomal complex		mRNA of neoantigen	DC
WDVAX		Tumor lysate with GM-CSF and CpG	DC
Immune cells manipulation			
Poly (beta-amino ester) NPs	Anti-CD3e f(ab')2 fragment-modified poly(glutamic) acid + peptides containing the microtubule-associated sequence + NLS	194-1BBz CAR	T cells
Polymeric NPs		CAR transgene and plasmids encoding iPB7 transpose	T cells
Liposomes	Maleimide, F(ab')2 fragment	IL-15SA and IL-21	T cells
Reduction sensitive nanogel	Anti-CD45 antibody and PEG-b-pol(l-lysine)	IL-15SA	T cells
PLGA NPs	Anti-CD3e f(ab')2 fragment, Anti-PD-1	SD208	T cells
PLGA NPs	Anti-PD-1	R848	T cells
Iron oxide NPs (ferumoxytol)			TAM
L-lysine NPs	Crosslinking with Succinyl-β-CD	R848 inhibitor	TAM
Liposomes	Protamine and hyaluronic acid	siRNA against CD47	CD47 immunoglobulin
IR700	Anti-CD25 F(ab')$_2$ fragments		T_{regs}
Methacrylated β-cyclodextrin + PEG-polylactide diacrylate NPs		SB505 + IL-2	T cells, NK cells, T_{regs}
Liposome-protaminehyaluronic acid NPs		siRNA against TGF-β + CpG	T cells, NK Cells, T_{regs}
PEG-PLGA NPs.		Methyl-2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oate	Myeloid-suppressor Cells, T_{regs}
PLHMGA microparticles		Anti-CD40 and anti-CTLA-4 antibodies	DC, T cells

Abbreviation: TNF-α converting enzyme (TACE), epithelial discoidin domain receptor I (EDDR1), nuclear localization signals (NLS), polyethylene glycol (PEG), poly lactic-co-glycolic acid (PLGA), toll-like receptor (TLR), poly (D, L-lactic-co-hydroxymethyl glycolic acid) (PLHMGA), FMSrelated tyrosine kinase 3 ligand (FLT3L), CC-chemokine ligand 20 (CCL20), 1-methyl-DL-tryptophan (1-MT), polyethyleneimine (PEI),

Table 4.

List of nanomaterials driven combinatorial immunotherapies for the treatment of cancer.

Combinatorial agent / Carrier	Immunotherapy agent	Cancer Model
Chemo-immunotherapy		
DOX / Thermoresponsive NPs, Lipoprotein nanodisc, Poly(amidoamine) dendrimer, Mesoporous silica NPs, Poly(lactic-co-glycolic) acid NPs	IFNγ, anti-PD-1Ab, CpG, ATRA, IL-2 CpG, anti-CLA4 Ab, anti-OX40 Ab	B16F10, CT26, 22RV1, B16 melanoma, EL4, A20 lymphomas
PTX / poly(glycolic acid) NPs, Poly(lactic-co-glycolic) acid NPs; IL-10 siRNA / Poly(lactic-co-glycolic) acid NPs, RBC coated chitosan nanogel	Imiquimod, LPS, CpG, IL-2	B16F10
Cisplatin / Liposomes	CpG	B16F10
Photothermal-Immunotherapy		
Copper sulfide, gold NPs, CNT, ICG, IR7, melanin	CpG, GC, GM-CSF, OVA	4T1, EMT6, B16, CT26, EG-7OVA
Polydopamine coated spiky gold NPs	DOX	CT26
SWCNT, ICG, Bremaclilorin, Ce6	Anti-CTLA-4 Ab, R837, SLPs, OVA, CpG	4T1, CT26, TCI RMAEG7-OVA
Gold nanostar, Pyrolipid, IR700, TBP	Anti-PD-L1 Ab	MB49, MC38, CT26, 4T1
Gold nanoshell	Adoptive T cells	B16F10
Temoporfin, Ce6	Anti-GR1 Ab, Anti-CD25 Ab, LCL521	SCCVII, B16F10,
PPa	PD-L1 gene silencing	B16F10
Photodynamic-Immunotherapy		
NCP-pyrolipid	Oxaliplatin + anti-PD-L1 Ab	CT26, MC38
ZnP-pyrolipid	Anti-PD-L1 Ab	4T1 and TUBO
MOF, PpIX, H4TBC	IDO inhibitor, 1MT	CT26, MC38
UCNPs-Ce6	Imiqimod + anti-CTLA-4 Ab	CT26
Radio-immunotherapy		
Gold NPs	Anti-CD40 Ab	
Hf NPs	IDO inhibitor	
Gene-Immunotherapy		
STAT3, IDO, SOCS1 siRNA / Liposome		
SOCS1 siRNA, STAT3 siRNA, IL-10 siRNA/ PLGA NPs	imiquimod, OVA,	EG7-OVA, B cell lymphoma model
TGFβ siRNA/Liposomes	CpG, (TRP2) peptide	B16F10

Abbreviation: Doxorubicin (DOX), paclitaxel (PTX), all-trans-retinoic acid (ATRA), lipopolysaccharide (LPS), carbon nanotubes (CNT), 5,10,15,20-tetra(p-benzoato)porphyrin (TBP), Pyropheophorbide-a (PPa), 5,10,15,20-tetra(p-benzoato)chlorin (H4TBC)

Table 5.

List of biomaterials being used for the localized immunotherapy.

Biomaterials for Localized tumor modulation	Functionalization	Delivering agent	Target/Action
Hyaluronic acid-based microneedle patches	Melanin	Dextran NPs co-loaded with anti-PD-1 antibody/IDO inhibitor, glucose oxidase and catalase.	DC, T cells
		PLHMGA microparticles loaded with anti-CTLA-4 antibody	T cells
		Anti-PD-1 loaded DNA NPs	T cells
		1-MT + anti-PD-1	T cells
Porous alginate scaffold		Adoptive T cells + IL-15SA	T cells
PLGA scaffold		GM-CSF + tumor lysate	DC
		FLT3L, CCL20	DC
Chitosan Hydrogel		T cells	T cells
PVA hydrogel		Gemcitabine, anti-PD-L1 antibody	T cells
Nanolipo gels: liposomes and polymers		SB505124 inhibitor + IL-2	T cells and NK cells
Self-assembled silica rods	PEI	GM-CSF, Oligodeoxynucleotides containing CpG motifs, and antigens	T cells

Table 6.

List of nano-immunoimaging agent used for the cancer immunotherapy.

Modality	Imaging agent	Functionalization	Immune cells	Findings
MRI	SPIONs	Poly(aspartic acid)-b-poly(ecaprolactone), protamine, lipofectin, TAT peptide, dextran, HA, Annexin V, sLeX	Macrophages, DC, NK, CD8+ T cells, MSCs, exosomes	Non-invasive imaging of macrophages in inflammation, atherosclerotic plaques, allograft; Tracking and accurate delivery of DC and T cells; Early prediction of rejection of transplant, myocarditis; Tracking of exosomes; Understanding activation of T cells.
Optical Imaging	**Luminescent imaging:** Quantum dots, UCNPs; **OCT:** gold nanorods	PEI, Oligo-arginine, OVA, GFP/Luc	DC, TAM	Luminescent imaging of UCNPs to lymph node,
Nuclear Imaging	Polyglucose NPs, gold, silver, tantalum, and bismuth NPs	^{89}Zr, ^{124}I, ^{64}Cu	TAM	Quantification of TAM in the tumor; Tracking of CAR-T cells
Multimodal	**Photoacoustic:** gold nanorods; **Magnetic and Optical:** SPIONs	Silica, peptides	Cytokine-induced killer cells	Imaging of gastric cancer, endothelium

Table 7.

Advantages and disadvantages of commonly used biomaterials for cancer immunotherapy.

Biomaterials	Advantage	Disadvantage
Zinc	Easily functionalized, capability for multimodal imaging, optical and piezoelectric properties, antibacterial and antifungal nature.	Low stability, non-uniform size distribution, requirement of advanced equipment, risk of cytotoxicity and genotoxicity, skin and environment hazard
PLGA	High reproducibility and purity over natural polymer, no requirement of highly toxic solvents.	High size variability with change in concentration, low drug entrapment efficiency, high-cost, lack of surface functionalization
PLHMGA	Tailorable release rate, better compatibility with protein, not susceptible to acids during degradation	Difficult to prepare
Chitosan	High biocompatibility and biodegradability, wound healing and antimicrobial properties.	Low solubility in physiological pH, low porosity, stability & mechanical resistance.