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Review article

Engineering customized nanovaccines for enhanced cancer immunotherapy

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ABSTRACT

Nanovaccines have gathered significant attention for their potential to elicit tumor-specific immunological responses. Despite notable progress in tumor immunotherapy, nanovaccines still encounter considerable challenges such as low delivery efficiency, limited targeting ability, and suboptimal efficacy. With an aim of addressing these issues, engineering customized nanovaccines through modification or functionalization has emerged as a promising approach. These tailored nanovaccines not only enhance antigen presentation, but also effectively modulate immunosuppression within the tumor microenvironment. Specifically, they are distinguished by their diverse sizes, shapes, charges, structures, and unique physicochemical properties, along with targeting ligands. These features of nanovaccines facilitate lymph node accumulation and activation/regulation of immune cells. This overview of bespoke nanovaccines underscores their potential in both prophylactic and therapeutic applications, offering insights into their future development and role in cancer immunotherapy.

1. Introduction

Since bacterial toxins were first proposed as an immunotherapy strategy to treat soft-tissue and bone sarcomas in 1891, cancer immunotherapy has become a burgeoning field revolutionizing oncology [1,2]. Differing from conventional tumor treatments, cancer immunotherapy focuses on stimulating immune responses, modulating tumor microenvironment (TME), and providing unique therapeutic effects by integrating tumor-specific antibodies with cellular immune effectors [3]. Primary cancer immunotherapy strategies include vaccines-based (active), antigens-based (passive), adaptive cells, cytokines, and immune checkpoint blockade (ICB) immunotherapy [4–6]. For vaccines-based immunotherapy, cancer vaccines are primarily composed of tumor-associated antigens (TAA), immunotherapeutic agents (*e.g.*, adjuvants), and/or nanocarriers, which are elaborately-designed to activate of immune cells and provoke effective antitumor immunity [7]. For example, Sipuleucel-T, as a well-known vaccine formulation, that has already been approved by the Food and Drug Administration (FDA) and is widely used in clinical settings, which owned an ability of initiating immune responses from prostatic acid phosphatase and then eliciting the patient's own immune system to proficiently identify and engage in combatting cancer [8]. Nonetheless, a growing body of evidence underscores that efficacy of the cancer vaccines is compromised by intrinsic tumor cell resistance, potential off-target risks, and induction of local or systemic immunosuppressive mechanisms [9]. These impediments present significant challenges in both advancement and broader clinical adoption of tumor-associated vaccines [10].

Nanovaccine is a subset of cancer vaccines with unique structures and physicochemical properties, which is accumulated in lymph nodes (LN) and taken up by antigen presenting cells (APC) in order to trigger immune responses [11]. A prominent feature of the nanovaccines is tunable nanosizes, which determines entrance of active components into the LN and subsequent passive delivery of them in the TME [12]. In particular, nanovaccines with diameters of 10–100 nm easily access draining LN through peripheral lymphatic vessels (LV), whereas

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nanovaccines of larger sizes (>100 nm) are generally internalized by peripheral APC and migrated in LN after an accumulation at injection sites [13]. Dimensions of nanovaccines have also been shown to influence effectiveness of cross-presentation, with fine nanoparticles showing greater efficiency [14,15]. Tunable physicochemical properties (*e.g.*, balanced surface charges, suitable shape, trade-off elasticity, targeting ligands, *etc.*) of the nanovaccines also play a crucial role in enhancing cancer immunotherapy [16]. For instance, customized nanovaccines with positive charges were attracted to negatively-charged membranes *via* the electrostatic interaction, which effectively enhanced cellular internalization and antigen presentation [17–19]. Shape of engineered nanoparticles also influences antibody and cytokine secretions. A study comparing spherical, rod, and cubic gold nanovaccines in stimulating antibody production against West Nile Virus showed that the nanorods induced secretions of inflammasome-dependent cytokines (interleukin(IL)-1β, IL-18), while the sphere- and cube-vaccines induced secretions of pro-inflammatory cytokines (tumor necrosis factor (TNF)-α, IL-6, IL-12, *etc.*) [20]. Furthermore, nanovaccines with high permeability, biocompatibility, and stability also affect pharmacological properties of immune reagents and protect biological drugs from premature release or degradation [21].

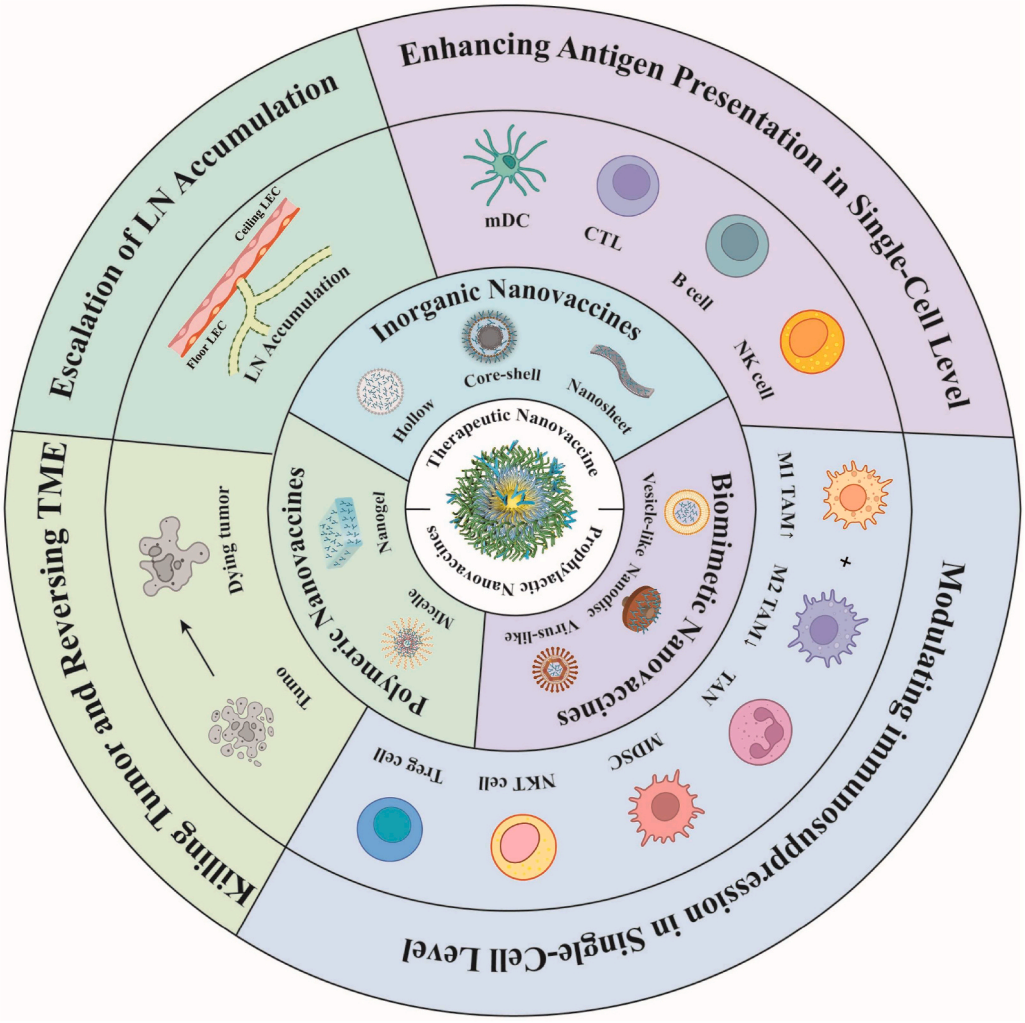
Inorganic (hollow, core-shell, and nanosheet), polymeric (micelle and nanogel), and biomimetic (vesicle-like, nanodisc, and virus-like) nanovaccines with diverse morphologies have been systematically-explored, where proficiencies and efficiencies of these nanovaccines in delivering active components to tumor sites have been summarized [22]. For example, polymer-based nanovaccines are identified with properties of exceptional stability, biocompatibility, adjuvanticity, and abilities of high endocytosis and trafficking within TME [23]. Inorganic carriers like manganese ion-based nanovaccines enhance antigen presentation and amplify synergistic effects towards photothermal and photodynamic therapies [24]. Moreover, inorganic carriers such as ferric ions mitigate risks associated with off-targeting effects, instability, and rapid clearance *in vivo* also facilitate timely unloading of active components after being quickly arrived at LN [25]. Notably, incorporation of the targeting ligands involving artificial APC (aAPC), chemokines, agonists, inhibitors, cytokines, adjuvants, receptors, or tumor-specific peptides endows nanovaccines with the high specificity to combat tumors [26]. This specificity allows for precise migration to LN and activation/regulation of immune cells [27]. For instance, Wang et al. reported that α-peptides-based nanovaccines M2-like tumor--associated macrophages (TAM) dual-targeting nanoparticle (M2NP) specifically depleted M2-like TAM and blocked M2-like TAM signaling pathways by loading anti-colony stimulating RNA [28]. Hence, customized nanovaccines elaborately-designed from nanocarriers and active components on the basis of a specific clinical scenario, will effectively accumulate TME to induce activity of body's own immunological effectors, suppress intrinsic resistance of tumor cells, and reduce immunosuppressive effects [29].

After delivery of major active vaccine components towards the TME, personalized nanovaccines unearth capacities to amplify LN accumulation, bolster antigen presentation, and finely regulate immunosuppressive mechanisms at the single-cell level [30]. Process of enhanced antigen presentation primarily involves inducing dendritic cell (DC) maturation, activating cytotoxic T lymphocytes (CTL), and targeting both B cells and natural killer (NK) cells [31]. As principal APC, employing appropriate active or passive targeting strategies for DC (*e.g.*, modifications involving mannose, C-type Lectin, *etc.*) can promote effective nanovaccine phagocytosis [32]. Moreover, stimulating activation and proliferation of CTL is of paramount importance for achieving efficacious immunotherapy [6]. Concurrently, leveraging both B and NK cells as effective anchors can enhance nanovaccine accumulation and retention within tumors [33]. Furthermore, meticulous modulation of the immunosuppressive microenvironment at the single-cell level primarily entails a targeted approach involving immune cells, including TAM, tumor-associated neutrophils (TAN), myeloid-derived suppressor cells (MDSC), natural killer T (NKT) cells, and regulatory T (Treg) Cells. Customized nanovaccines, furnished with functional ligands such as M2 macrophage-targeting peptides (M2pep), folate (FA), and stimulatory cytokines, have been employed with success in directing regulation of TAM [34]. In a parallel manner, nanovaccines with a plethora of functional ligands, such as α-galactosylceramide (GalCer), have feasibility in modulating NKT cell functions. Additionally, TAN regulation has been achieved by administration of the captopril-based vaccines, while MDSC can be anchored *via* tadalafil (TAD)-based vaccines.

This review presents a comprehensive overview of the most recent progress in design and applicability of nanovaccines, especially for the bespoke nanovaccines with tweaked antigens and/or adjuvants. These nanovaccines exhibit versatilities by effectively targeting LN, activating and/or regulating diverse immune cells, as depicted in Scheme 1. Firstly, it is imperative to categorize diverse nanovaccines in a comprehensive manner, delineating their characteristics based on distinct typologies, including inorganic (hollow, core-shell, and nanosheet), polymeric (micelle and nanogel), and biomimetic (vesicle-like, nanodisc, and virus-like) vaccines. Secondly, it is worth noting that tailored nanovaccines function versatility at level of immune cells, which can be stratified into distinct stages. These functions encompass following as: 1) escalation of LN accumulation, 2) enhancement of antigen presentation at the single-cell level, and 3) modulation of immunosuppression at the single-cell level. Ultimate goal of such painstakingly-customized nanovaccines is a convergence of tumor eradication, tumor recurrence inhibition, and TME modulation. Finally, objective evaluations of advantages, disadvantages, and challenges of these customized nanovaccines applied in clinical trials are also presented. This review provides an exhaustive and in-depth exposition of the meticulously-tailored nanovaccines and their pivotal role in advancing cancer immunotherapy.

2. Engineering customized nanovaccines

Valid cancer vaccines including customized nanovaccines should meet a requirement of effectively *co*-delivering anti-tumor antigens as well as immunologic adjuvants to lymphoid tissues and APC (*e.g.*, macrophages and DC) for successful activation of immune system [35]. Considering principal mechanism of the nanovaccines, various types of antigens and adjuvants have been developed and applied in nanoscale vaccines. The antigens, as crucial components, which constitute a pivotal component in cancer vaccines, often classified into pre-defined and unidentified antigens [36]. Predefined antigens predominantly encompass TAA or tumor-specific antigens (TSA), such as neoantigens arising from aberrant gene expression or stochastic somatic mutations within cancer cells. Besides, biomimetic carriers, derived from biological entities like cell membranes (CM) or liposomes, skillfully integrate a diverse range of antigens. This integration yields personalized nanovaccines by embraced multi-targeting and multi-epitope capabilities. Up to now, nanovaccines harboring blends of unidentified antigens such as whole cancer cells or cellular lysates, have emerged as a promising avenue in cancer immunotherapy. As another essential component, the universal adjuvant mainly includes stimulator of interferon genes (STING) agonists (*e.g. 2′,3′*-cGAMP, *3′,3′*-cGAMP, *c-di*-GMP, *etc.*) [37,38], cytokines [39], *co*stimulatory ligands (*e.g.*, *4*-1 BBL (CD137L)) [40], toll-like receptor (TLR) agonists (*e.g.*, poly(I:C) [41], cytosine-phosphate-guanosine oligodeoxynucleotide (CpG-ODN) 1826 [42], R837 [43], resiquimod (R848) [44], *etc.*) and monophosphoryl lipid A (MPLA) [45]. Specific inorganic ions, like manganese ions, and polymers, such as polyethylene glycol (PEG), are notable for their dual functionality in nanovaccine development, simultaneously acting as carriers and exhibiting adjuvant or adjuvant-like properties. This multifaceted role of nanoparticles enhances design flexibility of bespoke nanovaccines and amplifies benefits of their inherent characteristics



Scheme 1. Customized nanovaccines for enhanced cancer immunotherapy.

(shape, size, charge, *etc.*). These dual capabilities are also instrumental in fine-tuning the balance between adjuvants and antigens, optimizing these nanovaccines for specific therapeutic targets. Their distinct structural composition serves dual purposes: functioning as efficient vehicles and promoting antigen presentation, thereby activating immune responses and eliminating cancers.

Challenges faced by engineering nanoscale vaccines are how to effectively immobilize and precisely deliver various immune reagents (antigens and adjuvants) to ensure prompt and efficient immune responses [46]. After bearing substantial active components, nanomaterials, functioning as vehicles and/or adjuvants, are precisely delivered to TME *via* various routes such as tissues (skin or mucosa), blood vessels, and nasal passages. Meanwhile, these components are released with or without endogenous or exogenous responses, activating specific immune responses against cancer through immune signal pathways [47]. In this chapter, custom designs of nanovaccines comprising inorganic- (hollow structure, core-shell structure, and nanosheet), polymeric- (micelle and nanogel), and biomimetic-nanovaccines (vesicle-like, nanodisc, and virus-like) are elucidated, along with their intrinsic mechanisms and behavior profiles in cancer immunotherapy. Such precise engineering profoundly influences active components' loading, delivery, internalization, and release dynamics within TME [48]. Compared with conventional vaccines, unique physical properties and physiological/biological advantages of customized nanovaccines boost immune responses, and detailed information about meticulous engineering of the nanovaccine is outlined in Table 1 [49].

2.1. Inorganic nanovaccines

Inorganic nanomaterials possess significant value-addition potential for their numerous advantages essential to nanovaccine design, such as unique size-dependency, extremely high surface area-to-volume ratio, and strong affinity for antigen binding [81]. For instance, these materials resist chemical degradation, directly influencing their lifespan *in vivo*. Gaussian size distribution of synthesized or extracted inorganic materials, with their variable number of surface atoms, facilitates formation of multilayer structures, like peripheral biocompatible polymer coatings. Additionally, tunable net charges of functional groups on inorganic materials determine endocytic efficiency of custom-designed nanovaccines. These features collectively play a strategic role formulation of bespoke nanovaccines, enhancing both cellular absorption and interactions with other biomolecules, thereby optimizing their efficacy and bioactivity.

2.1.1. Hollow structures

A vast hollow cavity is beneficial for encapsulation of components, where sufficient amounts of antigens are utilized to activate immune responses at tumor sites [82]. These sizable cavities facilitate efficient component loading and reduce risks of clearance during transportations of adjuvants and/or antigens. Functional genes-covered biodegradable H–MnO_2 as an example, offers a sizable hole to be filled and/or

Table 1
Engineering customized nanovaccines.

Customized morphologies	Antigens	Adjuvants	Nano-carriers	Nanovaccine types	Refs
Hollow structure-based	miR-145	Amino-modified oligonucleotide CpG	Manganese dioxide (H–MnO_2)	Therapeutic vaccine	[50]
	Tumor fragment (TF)	Hollow silica with spike-like aluminum hydroxide nanoparticle (SiAl NP)	SiAl NP	Therapeutic vaccine	[51]
	OVA	Ammonium bicarbonate (ABC)	Mesoporous silica nanoparticle (MSN)	Prophylactic and therapeutic vaccines	[52]
	OVA	Metal-phenolic network (MPN)	Polyethylenimine (PEI)-based MSN	Prophylactic and therapeutic vaccines	[27]
	Ovalbumin (OVA)	CpG	Europium-doped $GdPO_4$ hollow sphere	Prophylactic and therapeutic vaccines	[53]
Core-shell structure-based	OVA	PEI/$CaCO_3$ and CpG	PEI/$CaCO_3$	Prophylactic and therapeutic vaccines	[54]
	OVA	CaO_2	CaO_2	Therapeutic vaccine	[55]
	OVA	R848	MSN	Therapeutic vaccine	[56]
	Tumor cell lysate	CpG-ODN	Aluminum hydroxyphosphate (Alum) nanoparticle (NP)	Prophylactic and therapeutic vaccines	[25]
Nanosheets	Endogenous TAA	γ-MnO_2 nanodot	$Ti_3C_2T_x$	Therapeutic vaccine	[57]
	Tumor autoantigen (TA)	R848	Boron bulk	Prophylactic and therapeutic vaccines	[58]
	OVA	CpG	Layered double hydroxide (LDH)	Therapeutic vaccine	[59]
	Phenylalanine-lysine-phenylalanine tripeptide-modified antigen epitope (FKF-OVAp)	Black phosphorus (BP) nanosheet	BP nanosheet	Prophylactic vaccine	[60]
Micelles	OVA	CL264	Carboxylated-NP	Therapeutic vaccine	[61]
	Palmitoylated polypeptide	MPLA	PEG-phosphatidylethanolamine (PE)	Therapeutic vaccine	[62]
	OVA	PEG-*b*-poly(*l*-lysine)-*b*-poly(*l*-leucine) (PEG-PLL-PLLeu)	PEG-PLL-PLLeu	Therapeutic vaccine	[63]
	Endogenous TAA	R848	PEG-*ss*-polycaprolactone (PCL) (PsP)	Therapeutic vaccine	[64]
Nanogels	Tumor-associated antigen	R848	Hyaluronan (HA) dynamic hydrogel messenger RNA/R848/lipid nanoparticle (HA-mRLNP)	Therapeutic vaccine	[65]
	OVA encoding mRNA	R848	Graphene oxide-low molecular weight PEI hydrogel	Therapeutic vaccine	[66]
	OVA	Bioreducible alginate-PEI nanogel	Bioreducible alginate-poly(ethylenimine) nanogel (AP-SS)	Prophylactic and therapeutic vaccines	[67]
	OVA	Imidazo-quinolinetype TLR7/8 agonist	pH-responsive nanogel	Therapeutic vaccine	[68]
Vesicle-like	OVA	HA-decorated cationic lipid-poly (lactide-*co*-glycolide) acid (PLGA) hybrid NP (HA-DOTAP-PLGA NP)	HA-DOTAP-PLGA NP	Prophylactic and therapeutic vaccines	[69]
	Protein antigen	CpG	PH9-Aln-8020	Therapeutic vaccine	[70]
	Melanoma antigen peptide TRP2	MPLA	Liposomes-coated gold nanocage	Therapeutic vaccine	[71]
	Whole CM antigen	CpG and TLR9	Manganese porphyrin-based metal-organic framework (Mn-MOF)	Therapeutic vaccine	[72]
	Antigen from tumor cell death	MnO_2 NP	Hollow biomimetic nanoplatform (CMM-DiR)	Prophylactic and therapeutic vaccines	[73]
	Antigenic motif from tumor cell membrane (TM)	Bacterial cytoplasmic membrane adjuvant	Hybrid membrane (HM) vesicle	Therapeutic vaccine	[74]
Nanodisc	Antigen from tumor cell death	CpG and docetaxel (DTX)	Synthetic high-density lipoprotein mimicking nanodisc (sHDL)	Prophylactic and therapeutic vaccines	[75]
	Antigen peptide	Cholesterol-modified CpG	sHDL	Therapeutic vaccine	[76]
	Aldehyde dehydrogenase (ALDH) antigen peptide	CpG	ALDH/CpG-based nanodisc	Therapeutic vaccine	[77]
Virus-like	E75369-377 peptide	Bacteriophage λF7	Bacterio-phage λF7	Therapeutic vaccine	[78]
	Insulin-like growth factor-1 receptor	Human parvovirus B19	Human parvovirus B19	Prophylactic vaccine	[79]
	M and M2 proteins	P22 virus-like particle (VLP)	P22 VLP	Prophylactic vaccine	[80]

conjugated with a significant quantity of immunological reagents (Fig. 1A−D) [50]. Ce6 and DOX are encapsulated internally in this system, whereas amino-modified oligonucleotide CpG, S6-aptamers, and miR-145 are conjugated through amide reactions (Fig. 1E). Hollow MnO_2 reacts with hydrogen peroxide in a slightly acidic environment and decomposes to produce manganese ion (Mn^{2+}) and oxygen, which releases loaded drugs and alleviates tumor's hypoxic environment. A hollow SiAl NP, featuring aluminum hydroxide spikes on its surface, exhibits high loading efficiencies, as demonstrated by its capacity to accommodate DOX (17%), TF (37.0%), and OVA (29.7%)

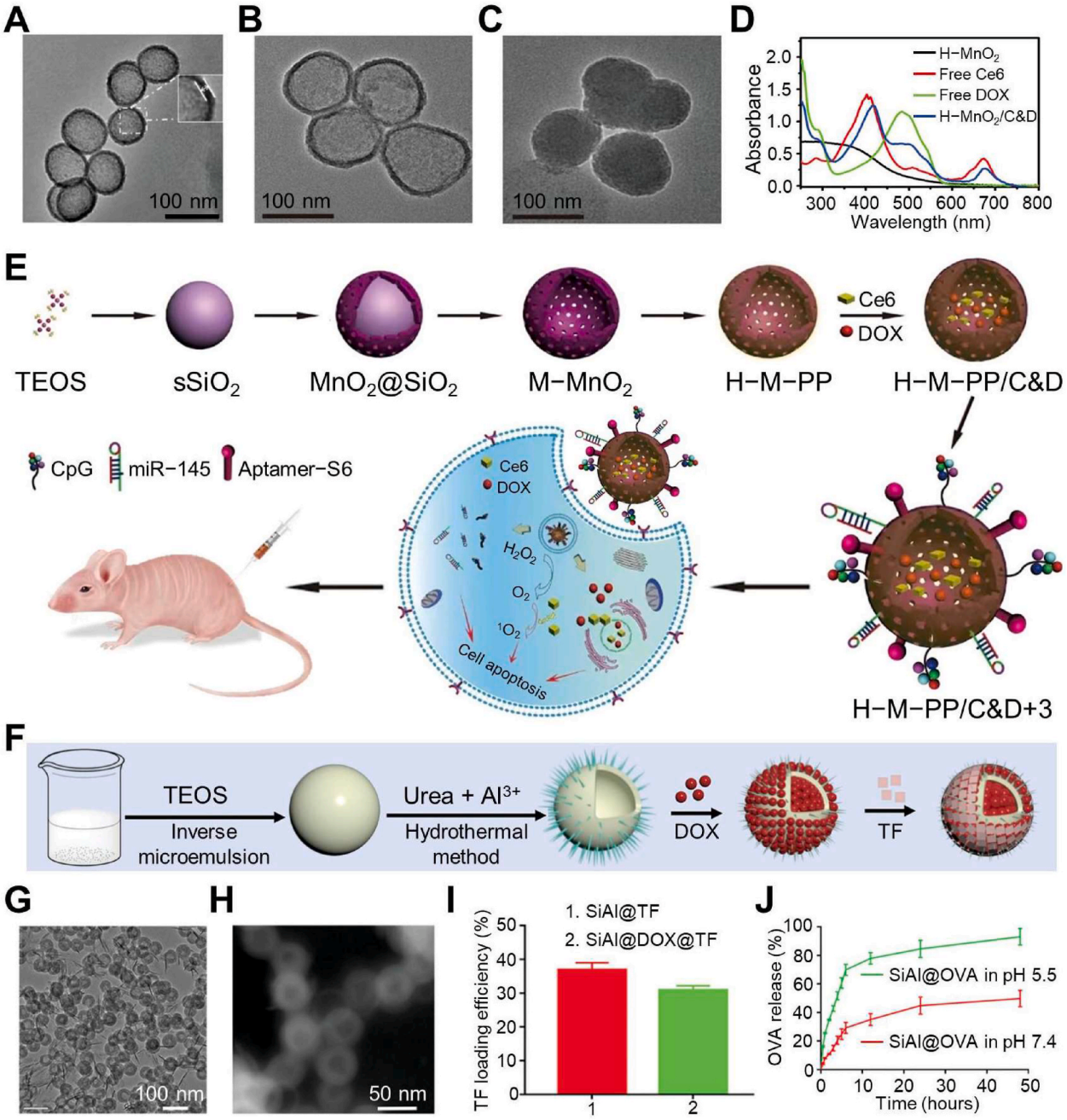


Fig. 1. Fabrication processes of hollow structure-based nanovaccines for cancer immunotherapy. Transmission electron microscopy (TEM) images depicting (A) initial H–MnO_2, (B) modification of H–MnO_2 with an external coating of acrylic acid and the polyelectrolyte poly(allylamine hydrochloride), accompanied by internal loading of doxorubicin (DOX) and Chlorin e6 (Ce6) (H-M-pp/C&D), and (C) subsequent conjugation of modified structure with amino-modified oligonucleotides including CpG, S6-aptamers, and miR-145 (H-M-pp/C&D + 3). (D) Ultraviolet–visible (UV–*vis*)−near-infrared (NIR) spectra of free Ce6, DOX, H–MnO_2, and H-M-pp/C&D. (E) Schematic of synthesis process and various functions of finally prepared nanovaccine. Reproduced with permission [50]. Copyright 2022, American Chemical Society. (F) Synthesis of SiAl NP by successive reverse microemulsion and hydrothermal processes. (G) TEM image and (H) Scanning TEM image of SiAl NP. (I) TF loading efficiencies in SiAl and its alongside incorporation of DOX. (J) OVA release profiles of SiAl@OVA in phosphate-buffered saline solution (PBS) with different pH values. Reproduced with permission [51]. Copyright 2022, Wiley.

(Fig. 1F−H) [51]. This structural design significantly enhances potential for diverse payload integration, facilitating efficient drug and antigen delivery (Fig. 1I, J). Hollow porous structures like MSN also serve as a versatile framework adaptable for designs of personalized nanovaccines based on variations in their loaded active components. A MSNs-ABC@polydopamine-OVA (MSNs-ABC@PDA-OVA) nanovaccine as an example, employed polydopamine (PDA)-modified MSNs as a porous backbone, encapsulating ABC and conjugating thiolate ovalbumin *via* Michael addition reaction [52]. Similarly, a pH-sensitive MSN-based nanovaccine is constructed by electrostatically adsorbing OVA and encapsulating MPN with numerous reducible disulfide bonds [27]. The PMSN@OVA-MPN nanovaccine embraces a high loading efficiency for OVA, and the PEI shell with “proton sponge effect” promotes antigen lysosome escape. Meanwhile, disulfide bonds in external MPN induce OVA release in presence of the reduced glutathione. Furthermore, reports on large cavity structures include lanthanide-doped $GdPO_4$ hollow spheres ($GdPO_4$:Eu), which efficiently *co*-deliver protein antigens like OVA and CpG-ODN to TME. These hollow

sphere-based vaccines also serve as dual-modal imaging agents for tracking immune processes within the TME [53].

2.1.2. Core-shell structures

Oxide-based nanocarriers with adjuvants property have been employed for developing nanovaccines. Active components are strategically modified on exterior of core-shell structure of nanocarriers to make nanovaccines with cancer immunotherapy abilities [83]. The core-shell nanovaccines are created by utilizing PEI-coated calcium carbonate ($CaCO_3$) nanocarriers (PEI/$CaCO_3$), which efficiently absorb both OVA and CpG [54]. Additionally, PEI/$CaCO_3$ works as an underlying adjuvant to activate bone marrow-derived dendritic cell (BMDC) dose-dependently, leading to an increase in CD86 expression. Together with the assistant nanoparticles PEG/PEI/pSpam1 (pSpam1@NPs), the nanovaccines activate T cells and gene-mediated extracellular matrix scavengers for tumor elimination. Another biomineralized nanovaccine is also developed by assembling OVA onto an *in-situ* growth of calcium peroxide [55]. The nanovaccine has a superhigh density of OVA antigen

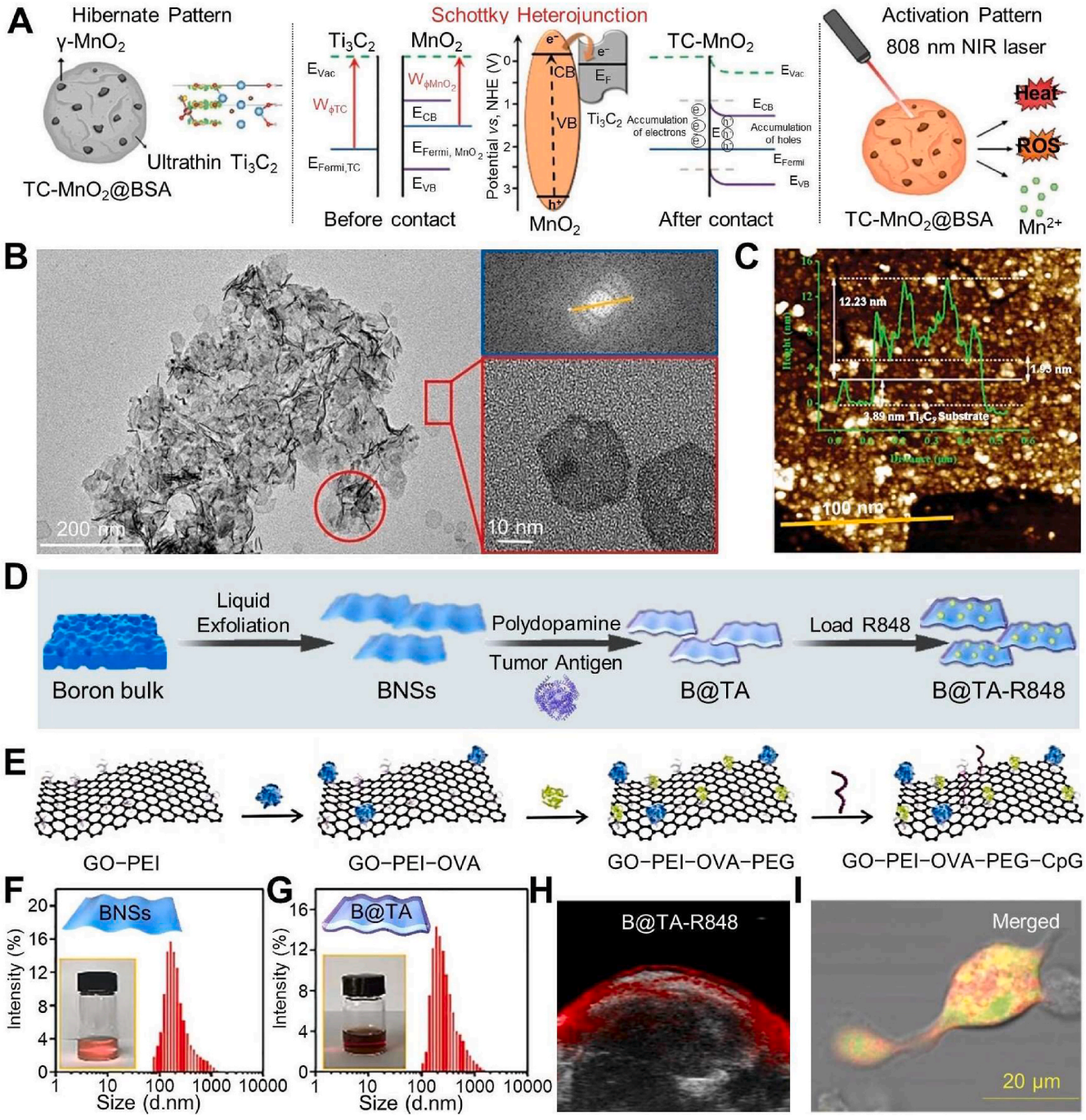


Fig. 2. Fabrication processes of layered structure-based nanovaccines for cancer immunotherapy. (A) Schematic diagram of NIR activated Schottky nanovaccine TC-MnO_2@BSA and its mechanisms towards immune effects. (B) TEM images and (C) AFM image and height of TC-MnO_2@BSA. Reproduced with permission [57]. Copyright 2023, Wiley. (D) Preparations of personalized nanovaccine of B@TA-R848. Size, dispersity, and photo images of (F) boron nanosheet and (G) its loading TA. (H) Photoacoustic images of tumor site in B@TA-R848 groups at 12 h post injection. Reproduced with permission [58]. Copyright 2021, Walter de Gruyter. (E) Formation illustration of GO/polymer-famulated nanovaccine. (I) Confocal microscope image of BMDCs incubated with GO/polymer-famulated nanovaccine and fluorescein isothiocyanate (FITC). Reproduced with permission [87]. Copyright 2022, Elsevier.

with a necessary calcium peroxide adjuvant (8.9%). Concerning acidic TME, the nanovaccine achieves lysosome escape and antigen cross-presentation within the cytoplasm. Furthermore, in the formulation of nanovaccines, a biopolymer-coated copper oxide core functioned as an adjuvant, eliciting an immunoglobulin (Ig) G response [84]. This adjuvant effectively inhibits proliferation of breast cancer (MCF-7) and cervical cancer (HeLa) cells, following activations of type 1 helper T (Th1) cells and type 2 helper T (Th2) cells.

Core-shell structure of nanoparticles excels in delivering and strategically releasing active components at multiple levels. This is demonstrated through two concise examples. The first involves synthesis of the core-shell mesoporous silica nanovaccines (MSN-R848-OVAp) utilizing a *co*-condensation method that incorporates cetyltrimethylammonium chloride and tetraethyl orthosilicate [56]. These nanoparticles feature phenyl-functionalized cores to accommodate hydrophobic R848, coupling with a pH-responsive acetal linker and a biotin-avidin complex/OVA on the surface. This configuration facilitates antigen delivery and induces T cell responses. The second is the Alum-CpG@Fe-Shikonin nanovaccine, which is composed of an Alum NP core infused with CpG-ODN and enveloped in Fe-Shikonin networks [25]. Upon disassembly, they release iron ion (II) and Shikonin, triggering immunogenic cell death (ICD) in tumor cells *via* ferroptosis and necroptosis. Subsequently, these components are absorbed by Alum NP and *co*-delivered with CpG-ODN to antigen-presenting cells, initiating a targeted, multistep antitumor immune response. Collectively, these examples underscore core-shell structure's adaptability and efficiency in targeted delivery and release of complex therapeutic agents within cancer immunotherapy.

2.1.3. Nanosheets

Active components are also immobilized onto two-dimensional nanomaterials, capitalizing on their distinctive attributes, including exceptional electrochemical and mechanical properties. These advantages confer upon two-dimensional nanomaterials elevated thermal conductivity and outstanding photothermal conversion efficiency. Notably, intrinsic metallic-based nanosheets ($Ti_3C_2T_x$, graphene oxide (GO), and two-dimensional $MoSe_2$ nanosheets) have become predictable reactive oxygen species (ROS) manufacturers, triggering ICD to release TAA and damage-associated molecular patterns [85–87]. In this context, a Schottky heterojunction is engineered in the TC-MnO_2@BSA nanovaccine by immobilizing ultrasmall γ-MnO_2 nanodots onto intrinsic metallic $Ti_3C_2T_x$ nanoflakes, followed by bull serum albumin (BSA) decoration (Fig. 2A) [57]. This Schottky heterojunction endows the nanovaccine with exceptional photoelectric performance and capabilities towards ROS generation and photothermal conversion. TEM and atomic force microscopy (AFM) images reveal a tightly integrated heterojunction, with Ti_3C_2 maintaining its monolayer morphology and exhibiting distinctive wrinkles (Fig. 2B, C). Experimental findings also indicate that the nanovaccines induce ROS production after 24 h. Simultaneously, they also lead to expression of CD44 on $CD8^+$ T cells and a reduced proportion of Treg cells within TME. In addition, ultrathin thickness and high surface area-to-mass ratio of two-dimensional nanomaterials enhance drug release profiles alongside optimization of delivery and efficacy of therapeutics. As an illustration, boron nanosheet-based nanovaccine (B@TA-R848) is constructed with nanosheet from exfoliated boron bulk, coated PDA, and then modified with TA from triple-negative breast cancer (TNBC) as well as adjuvant of R848 (Fig. 2D, F, **2**G) [58]. Such B@TA-R848 increases DC internalization by intracellular endocytosis, thus promoting antigen release and presentation based on an ultrathin of *β*-rhombohedral hexahedral boron structure. As expected, the B@TA-R848 also bespeaks high enrichment at tumor sites and desired photoacoustic imaging and synergetic photothermal therapy (PTT) in TNBC model (Fig. 2H). Similarly, a GO/polymer-famulated nanovaccine enhances antigen cross-presentation ability and amplifies cytokine productions of immune cells (Fig. 2E, I) [87].

Moreover, well-defined layered structures of these nanovaccines augment blood flow, concurrently modifying interstitial pressure and increasing accumulation in tumor sites [88]. For instance, LDH is utilized as nanoadjuvants with an average size from 77 to 285 nm, and prompts accumulation in spleen as the most prominent secondary lymphoid organ owns highest density of APC and B/T cells. The LDH-based CO-LDH nanovaccine is also built with LDH, CpG, and OVA [59]. Customized LDH structure endows this nanovaccine with a high spleen enrichment at 24 h post *i.v.* injection. Taking *in situ* nanovaccine (LDHs-cGAMP) formed by LDH carrying cGAMP and adsorbed TAAs as another paradigm, it is demonstrated that this vaccine effectively accumulates in TME, inducing a robust response of type I interferon (IFN–I) [89]. Furthermore, BP-based nanovaccine possesses biocompatibility, biodegradability, and multiple immunostimulatory properties. For instance, phenylalanine-lysine-phenylalanine (FKF) tripeptide-modified antigen was coated onto BP to generate a minimalized nanovaccine of FKF-OVAp@BP [60]. The FKF-OVAp@BP nanovaccine harnessed immunomodulatory properties of BP and displayed significant compatibility with ICB, resulting in robust therapeutic efficacy in a melanoma mouse model. Besides, adjuvant effect mediated by BP is evidenced by efficient delivery of the mRNA nanovaccines. Yang et al. introduced the mRNA nanovaccines highlighting BP-mediated adjuvant effect being contributed efficient protein expression and enhanced immune activation [90]. Compared to nanoerythrosomes (NER) without BP, the BP-NER combination efficiently delivered mRNA for coronavirus receptor-binding domain, significantly increasing antibody titers and pseudovirus neutralization effect.

In short, inorganic materials, characterized by innate attributes such as photophysical properties, hold promise for developing customized nanovaccines. However, these "hard NP materials" (referred to as inorganic materials) often emanate limited inherent solubility, necessitating surface modifications to hasten their dissolution or maintain stability in aqueous environments [81]. Such modifications in tandem with intrinsic characteristics of inorganic materials significantly determine versatility of inorganic-based vaccines, thereby influencing chemical properties recognized by biological organisms and dictating nature of their interactions with immune cells. Consequently, when employing these materials as carriers or adjuvants, there is a critical need to strike an optimal balance between surface functionalization with soluble polymers and efficient loading of antigens.

2.2. Polymeric nanovaccines

Polymers are particularly-important in the personalized design of nanovaccines due to their high biocompatibility, adjustable side chain length, stimuli-responsive surface as a point of anchored chain, and structural flexibility, enabling their practical use as carriers and/or adjuvants. In this field, polymer modifications are indispensable in nanovaccines based on inorganic or biomimetic materials. They enhance solubility of inorganic nanovaccines and facilitate *co*-delivery of antigens and adjuvants in biomimetic formulations. As a pivotal component of nanovaccines, their discussion primarily focuses on nanomicelles with a two-dimensional arrangement and nanogels forming three-dimensional polymeric networks. A detailed examination of the polymer structures reveals their distinct properties and functions, providing critical insights into their mechanisms and instrumental role in advancement of nanovaccine technologies. As for other secondary or bridging components, they are succinctly described in other sections dedicated to inorganic and biomimetic-based nanovaccines.

2.2.1. Micelles

Amphiphilic block copolymers typically engage in self-assembly to form micelles, and these micelle-centered nanovaccines possess several advantageous characteristics including targeting capabilities, enhanced cellular uptake, and specific stimulus responsiveness [91,92]. Owing to their functional embedded designs, micelles inherit endocytic receptor

targeting properties, presenting an alternative avenue for enhancing vaccine internalization, as exemplified by Pluronics [93–95]. Amphiphilic diblock copolymer of poly(*2*-ethyl-*2*-oxazoline)-poly(*d*, L-lactide) (PEOz-PLA) and carboxylterminated-pluronic F127 are utilized to yield micelles (denoted as carboxylated-NPs) as an example [61]. These micelles demonstrate aptitudes to infiltrate LV and precisely reach LN due to strategic incorporation of carboxylic groups. This design confers targeting capability to the micelles, allowing them to utilize a scavenger receptor-mediated endocytosis pathway for precise delivery.

Polymeric micelles, including polypeptides, exhibit efficient cytosolic delivery and enhanced adjuvanticity [96,97]. As depicted, the self-assembled micelles are consisted of PEG-PE, palmitoylated polypeptide, and MPLA, where palmitoylated polypeptide and MPLA are inserted into hydrophobic core of micelles (Fig. 3A) [62]. Designed PEG-PE micelles not only serve as chaperons for TLR signaling and perform adjuvant effects towards DC, but also transform soluble peptides into α-helix and enhance cytosolic delivery efficiency (Fig. 3C). These self-assembled cationic micelles, derived from PEG-PLL-PLLeu, exhibited particle stability during OVA transportation [63]. *In vivo* results showed that PEG-PLL-PLLeu-based nanovaccine significantly enhanced adjuvanticity, vaccine-induced germinal center formation, and antibody production. Efficient delivery of contents is also evidenced by mannose-modified stearic acid-grafted chitosan (M–CS–SA) micelles; upon being taken up by DC *via* mannose receptors, these micelles escape lysosomes and disperse in the cytoplasm [98]. The dispersed micelles trigger mitochondrial ROS generation, activating cytosolic DNA/cyclic GMP-AMP synthase (cGAS)-STING signaling pathway and stimulating IFN-I secretion. Moreover, Hubbell et al. reported two different PEG-conjugated-poly(propylene sulfide) (PEG-PPS)-based micelles [99,100]. These micelles were capable of conjugating antigens and adjuvants comprising CpG [99] or MPLA [100], thereby enhancing antigen presentations. Also, such micellar vaccine formulation markedly enhanced cellular and humoral responses while eliminating the need for dual adjuvants, simplifying platform preparation, and reducing costs.

The personalized micelles are meticulously engineered to incorporate sensitivity groups, such as pH-responsive functionalization and disulfide bonds, enabling them to effectively deliver and release their contents upon deconstruction. pH-sensitive micelles have been formulated when peptide antigens are conjugated to pH-sensitive hydrophobic blocks [101–103]. A notable example is a mannosylated Virus-Inspired Polymers for Endosomal Release (Man-VIPER) nanosystem comprising formulations with disulfide-conjugated OVA antigens. These formulations include either releasable disulfide-conjugated membranolytic melittin (Man-VIPER-R) or non-releasable pentafluorobenzyl-conjugated melittin (Man-VIPER-NR) (Fig. 3B) [102]. These formulations undergo self-assembly to form well-defined micelles, characterized by their preferential endocytosis mediated by mannosylated hydrophilic segments. The micelles disintegrate upon endosomal maturation, leading to either endosomal disruption and cross-presentation of major histocompatibility complex (MHC) I epitopes or lysosomal maturation and presentation of MHC II epitopes, targeting specific T cell subsets (Fig. 3D, E). In a similar vein, amphiphilic diblock of PCL-based arginine-glycine-aspartic acid (RGD)-PEG-*ss*-PCL (RPsP) is introduced where PCL is grafted with PEI *via* disulfide bonds and modifies with RGD [64]. These nano-sized micelles are disintegrated by a high concentration of glutathione in tumor cells, leading to on-demand release of DOX and R848 and inducing activation of DC.

2.2.2. Nanogels

Nanogels constitute nanoscale three-dimensional polymeric networks with the inherent capacity to encapsulate a diverse arrange of immune reagents. This encapsulation process is accomplished through widespread utilization of cross-linking agents, harnessing electrostatic interactions and oxidative self-polymerization mechanisms, culminating in sustained immune potency [104,105]. In cancer vaccine delivery, nanogels have demonstrated their overwhelming utility in facilitating controlled and prolonged release of encapsulated therapeutic agents [34,106]. For instance, HA-mRLNPs were developed to *co*-load mRNA-based lipid nanoparticles (LNP) and R838 into a hyaluronic acid (HA) dynamic hydrogel with a high molecular weight, resulting in long-lasting cancer immunotherapy [65]. HA-based hydrogels controlled release of the mRLNPs after undergoing state transitions in a physiological environment. Further, the nanovaccines in the LNPs-hydrogel system retained their functions after 14 days of storage at room temperature. Similarly, an injectable hydrogel based on graphene oxide and low molecular weight PEI is electrostatically combined and employed to encapsulate mRNA (OVA and antigen) and adjuvants (R848) [66]. After an injection into subcutaneous layers, these transformable nanogels release mRNA for at least thirty days.

Apart from their outstanding biocompatibility, abundant raw material resources, and substantial antigen-loading capacities, nanogels also possess abilities to facilitate controlled release and degradation of antigens [107]. Based on these, AP-SS nanogel is fabricated by disulfide cross-linking before electrostatic interaction of negatively-charged alginate sodium with branched PEI_{2k} [67]. These nanogels exhibit minimal cytotoxicity, great antigen-loading capacity, and enhanced vaccine-elicited humoral and cellular immune responses. In addition to promoting antigen uptake by BMDC, reducible AP-SS nanogels also promote antigen release and cytosolic degradation. Except for this, a pH-degradable nanogel containing block copolymer micelles covalently functionalized with TLR7/8 agonist *1*-(*4*-(aminomethyl)benzyl)-*2*-butyl-1*H*-imidazo[*4*,*5*-*c*]quinolin-*4*-amine (IMDQ) and Texas Red cadaverine is proposed [68]. Precise calculation of hydrodynamic radii deduced from resultant autocorrelation functions, substantiates not only conjugation of dibenzyl cyclooctyne-modified OVA but also degradation of IMDQ-loaded nanogels upon acidification. Such a nanogel carrier system is pre-defined in morphology, and guarantees control over *co*-delivery of each vaccine component. This nanogel emphasizes importance of incorporations of immune adjuvant and antigen into the same carrier system. Also, the self-adjuvant nanovaccine that is assembled by amphiphilic pH-sensitive galactosyl dextran-retinal and OVA, facilitates cytosolic antigen release and improves cancer vaccine efficacy after triggering a lysosomal rupture [108].

In brief, utilizing polymeric micelles and nanogels provides outstanding functionality and adaptability in engineering bespoke nanovaccine. Micelles, synthesized from amphiphilic block copolymers, exhibit their distinctive structural and compositional attributes, which is crucial for significant cellular uptake and specific stimulus responsiveness. These engineered micelles enable structure transformation, precise targeting and potentiate effective immune activation. Meanwhile, meticulously-engineered polymeric network structures within the nanogels ensure stable encapsulation and prolonged release of the vaccine constituents. Such a configuration of nanogels is pivotal in preserving biocompatibility while facilitating effective encapsulation and incremental release of diverse immunogenic elements. This strategic approach significantly augments therapeutic efficacy and longevity of the personalized nanovaccines. However, the development of polymeric nanovaccines underscores the crucial balance between innovation and practicality. While the structural design of micelles and nanogels provides promising pathways for targeted delivery and sustained release, the associated complexities in clinical translation highlight the need for continued research to optimize their therapeutic efficacy and safety in varied treatment contexts. Challenges such as potential toxicity from degradation products, non-specific immune reactions including allergic responses, and barriers to stable antigen release are notable considerations.

2.3. Biomimetic nanovaccines

Biomimetic syntheses entail synthesis and presentation of protein cargos on cell surfaces, offering a promising approach for efficient

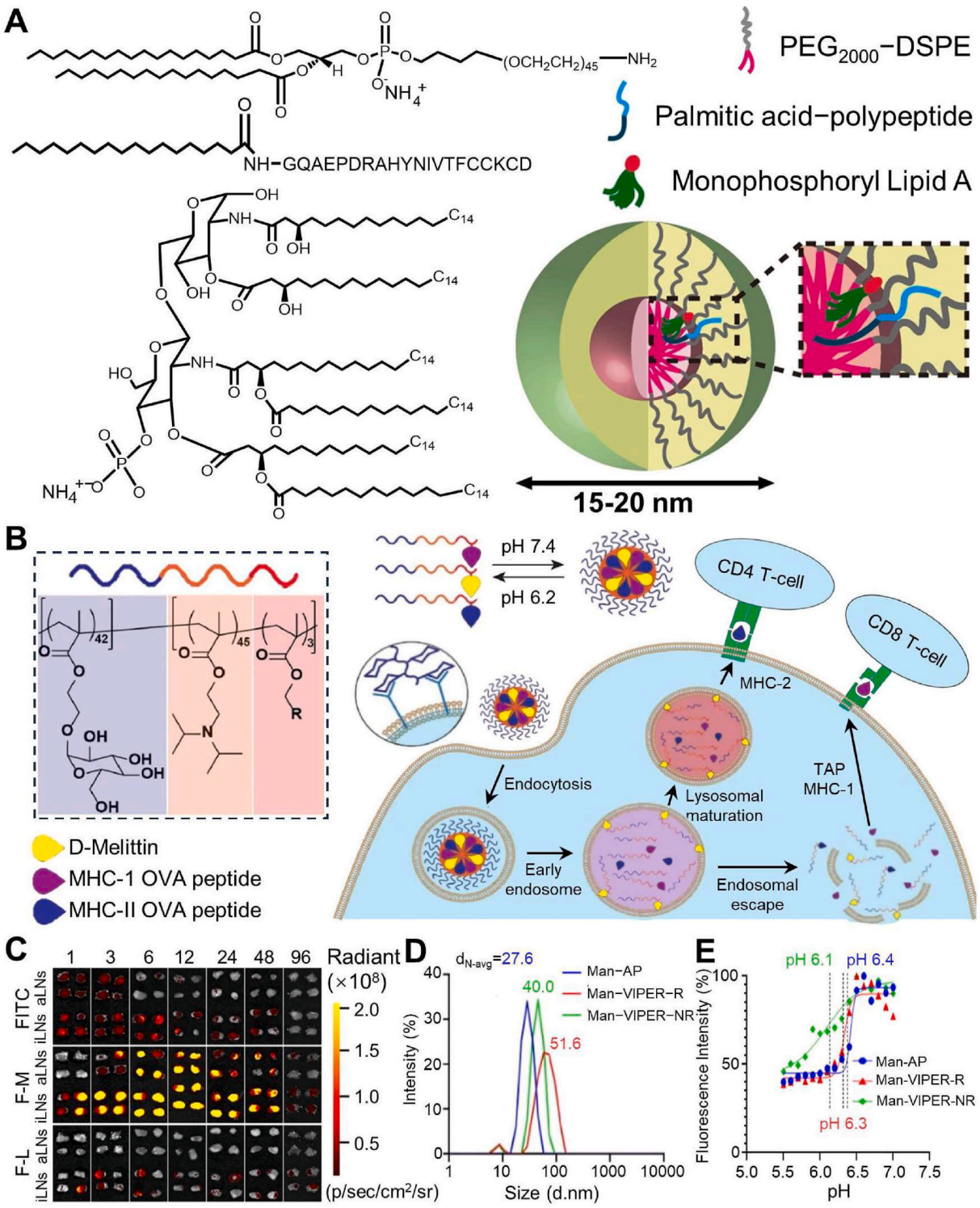


Fig. 3. Fabrications and applications of micelles in cancer immunotherapy. (A) Schematic diagram of self-assembly micelle, comprising PEG-PE, palmitoylated polypeptide, and MPLA, where hydrophobic components, palmitic acid, and MPLA are integrated into micelle's hydrophobic core. (C) Accumulation of different FITC formulations (FITC; FITC-labeled micelle, F-M; FITC-labeled liposome, F-L) in draining LN (DLN) at indicated time points (axillary LNs are referred as "aLNs" and inguinal LNs are referred as "iLNs"). Reproduced with permission [62]. Copyright 2017, Springer. (B) Schematic illustration of Man-VIPER delivery systems, consisting of disulfide-conjugated OVA antigens and membranolytic melittin (either releasable Man-VIPER-R or non-releasable Man-VIPER-NR). System self-assembles into micelles is endocytosed *via* mannosylated segments, leading to disassembly in endosomes and subsequent MHC I or MHC II epitope presentation to respective T-cell subsets. (D) Size distributions of non-membranolytic D-melittin-free analogues (Man-AP), Man-VIPER-R and Man-VIPER-NR characterized by dynamic light scattering (DLS; d_{mean} = 27.6 nm, 51.6 nm, 40 nm, respectively). (E) pH-dependent micellization of Man-AP, Man-VIPER-R and Man-VIPER-NR. Reproduced with permission [102]. Copyright 2023, Elsevier.

development of the ligand-targeted nanovaccines. Such biosynthesis process has been upheld native conformations, structures, and activities of functional proteins/lipids of interest. Depending on different preparation sources or approaches, biomimetic nanovaccines can be broadly categorized into vesicle-like, nanodisc, virus-like-oriented nanovaccines.

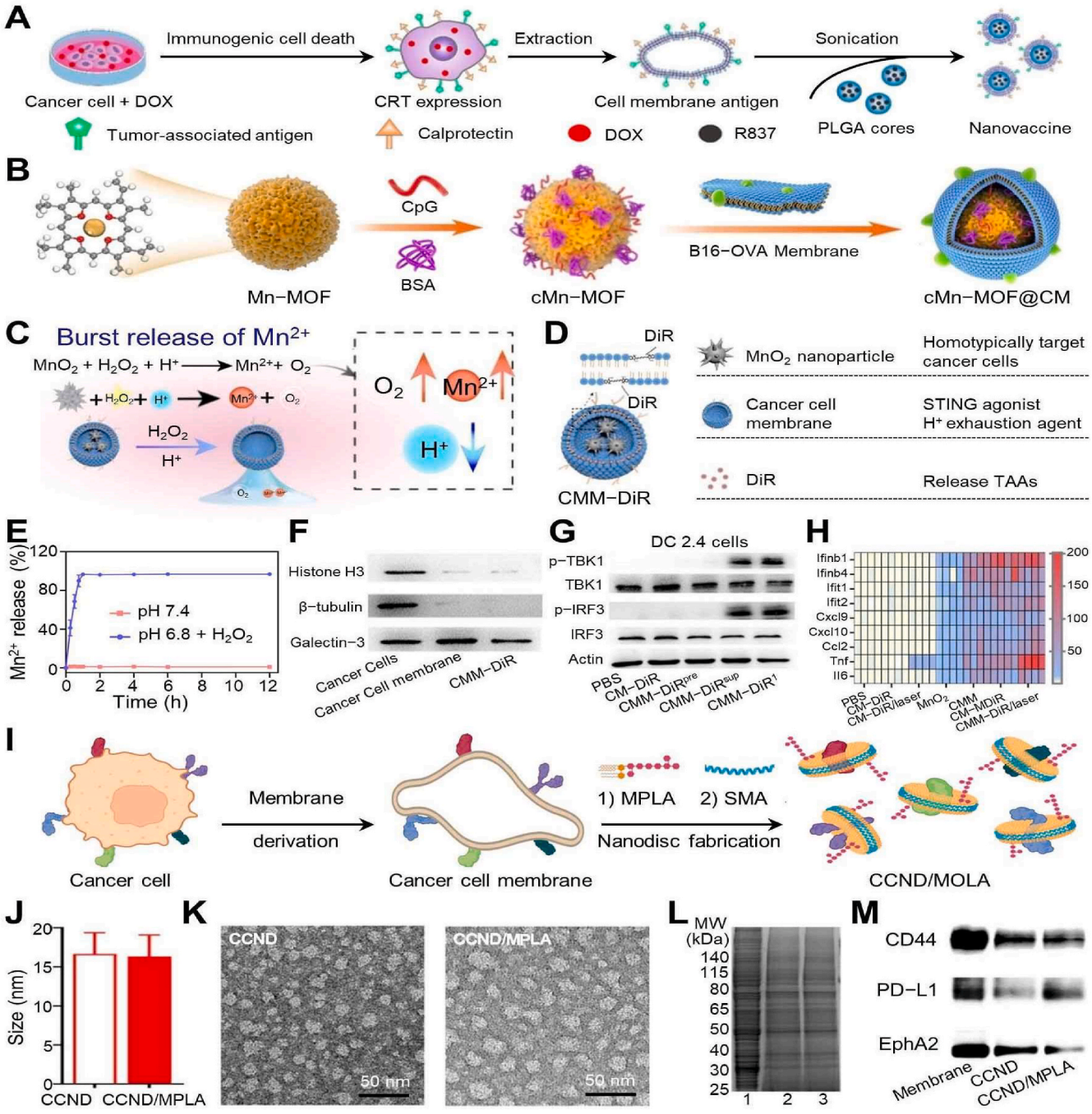


Fig. 4. Fabrications and applications of vesicles or nanodisc in cancer immunotherapy. (A) Schematic illustration of personalized nanovaccine by coating adjuvant R837-loaded PLGA NP with calcinetin-expressed Luc-4T1 cell membrane antigens. Reproduced with permission [130]. Copyright 2021, American Chemical Society. (B) Diagram of cMn-MOF@CM nanovaccine. Reproduced with permission [72]. Copyright 2021, Elsevier. (C) Detail mechanism of *in situ* STING-activating vaccination strategy. (D) Composition of CMM-DiR and functions of each component. (E) Mn^{2+} release profiles in pH 7.4 and pH 6.8 solutions (H_2O_2). (F) Expression of proteins on different groups. (G) Western blot for activation of cGAS-STING pathway in DC 2.4 cells with different treatments: Complete reaction liquid (CMM-DiR^{1}), supernatant (CMM-DiR^{sup}), and precipitation (CMM-DiR^{pre}) from *co*-incubated CMM-DiR and H_2O_2 solution (pH 6.8). (H) Real-time quantitative polymerase chain reaction analysis for relative expression of cGAS-STING axis in tumor sites of mice with different treatment ($n = 5$). Reproduced with permission [73]. Copyright 2021, Elsevier. (I) Whole cancer cell derived of TM, followed by incubation with MPLA and styrene-maleic acid to form MPLA-loaded cancer cell membrane nanodisc (CCND/MPLA). (J) Size of cancer cell membrane-based nanodisc (CCND) and CCND/MPLA ($n = 3$). (K) TEM images of CCND (left) and CCND/MPLA (right) negatively stained with uranyl acetate. (L) Protein profiles of MC38 cell membrane (1), CCND (2), and CCND/MPLA (3) after gel electrophoresis. (M) Western blot probing for tumor antigens in MC38 cell membrane, CCND, and CCND/MPLA. Reproduced with permission [135]. Copyright 2023, American Chemical Society.

2.3.1. Vesicle-like

Large amphiphilic molecules form vesicles as nanoscale containers extending liposome skeletons. Their self-assembly into vesicles protects biomolecules, facilitating endocytosis and subsequent release in early endosomes before lysosomal fusion. This design is leveraged in lipid-based antigen delivery systems, inducing membrane fusion or endosomal destabilization for effective cytoplasmic antigen delivery. Nanocarriers with natural lipid-embedded vesicular structures are amenable to functionalization to form personalization nanovaccines, which achieve antigen-specific immune responses *via* multiple signaling pathways [109]. An example of HA-DOTAP-PLGA NPs has been investigated as vaccine delivery vehicles, exhibiting enhanced antigen presentation *via* both MHC I/II pathways after HA-CD44 receptor-mediated endocytosis [69]. Self-assembled liposomes-based nanovaccines, that were composed of monophosphatidyl (A) and CpG-ODN, had desirable antitumor immunities, especially Th1 cell response through activations of nuclear factor-κB (NF-κB) and protein kinase (MAPK) signaling pathways [110]. Liposomal vesicles based on pH-responsive systems represent one of the most common design strategies towards nanovaccines [111]. Yuba and colleagues have documented a series of highly pH-sensitive liposomes that have been shown promise in augmenting cancer immunotherapy [112–115]. By incorporating pH-sensitive *3*-methylglutarylated residues (MGlu-Dex) as the antigen delivery system, the mGlu-Dex-modified liposome is internalized by DCs through endocytosis and subsequently entrapped within endosomal compartments [112]. A mildly acidic microenvironment destabilizes liposomes, thereby prompting release of antigenic molecules confined within the endosome. Besides solid lipids [116], phospholipids [117], lipids [118], and cationic/helper polymers [70] -centered nanovesicles have also been explored for personalized treatment of cancer.

Exosomes represent a category of diminutive extracellular vesicles, characterized by approximate diameters spanning from 30 to 100 nm [119]. They encompass considerable therapeutic potential by virtue of their multifaceted cargo, containing proteins, lipids, nucleic acids, microRNAs, and long non-coding RNAs [120]. From diverse cellular sources, the exosome-based vaccines manifest a broad spectrum of immunomodulatory activities, endowing them with remarkable versatility as antigen-delivery vehicles [121]. For instance, exosomes derived from DCs possess capacity to activate $CD4^+$ and $CD8^+$ T cells *via* antigenic complexes adorning their surface [122]. Similarly, exosomes derived from B cell lymphoma cells can induce both clonal expansion of T cells and secretion of cytokines including IL-6 and TNF-α [123]. Given their interactions with immune cells and ability to instigate downstream signaling cascades, these exosome-based vaccines function as indispensable antigen carriers and immunomodulatory adjuvants within cancer immunotherapy [124]. Furthermore, exosomes have been identified as effective biomarkers for gauging adaptive immune activation, playing a crucial role in the diagnosis and treatment of cancers [121].

Besides, artificial cytomembranes-based nanovesicles are also derived from various sources, including DC [125], cancer cells [126], bacteria [127], red CM [128], TM [85], *etc*. The cytomembrane-base vesicle widened nanovaccine applications for multiple tumor types [71]. For instance, a personalized cancer vaccine based on recombinant adenovirus-infected DC membranes was genetically engineered, inheriting complete surface functional proteins of mature DC and enabling direct antigen presentation to naive T cells [125]. Immune reagents coated on CM [129], such as TMs, allow acquisitions of a comprehensive array of CM protein antigens, thereby eliciting a specific immune response against corresponding tumors (Fig. 4A) [130]. For instance, the cMnMOF@CM nanovaccine is established from TM derived from OVA-overexpressing melanoma B16 cells after encapsulations of CpG and TLR9 within Mn-MOF (Fig. 4B) [72]. cMn-MOF@CM nanovaccines obtain a comprehensive CM antigen array exposed to calreticulin and enhance DC endocytosis. Similarly, an advanced biomimetic nanovaccine, CMM-DiR, encapsulates STING agonists (MnO_2 nanoparticles) and photothermal agent DiR within TM (Fig. 4D) [73]. This formulation promotes a rapid, explosive release of Mn^{2+} and enhances tumor cell uptake *via* homotypic adhesion properties (Fig. 4C, E). Notably, Mn^{2+} activates intracellular STING pathway and is a robust activator of cGAS within innate immune system's response against malignancies [131, 132]. Mechanistically, Mn^{2+} enhances binding affinity between cGAMP and STING while simultaneously increasing sensitivity of cGAS to double-stranded DNA, amplifying STING signaling and eliciting downstream immunostimulatory responses (Fig. 4F−H). Moreover, membrane fusion technology facilitates formations of HM vesicles, combining Escherichia coli cytoplasmic membrane with TM derived from resected autologous tumor tissue [74]. These autologous HM vesicles extend antigen-specific tolerance, while pathogen-associated molecular patterns (PAMP) in bacterial membranes trigger innate immune responses by engaging pattern recognition receptors on epithelial and immune cells. Fusion of tumor neoantigens and bacterial PAMP is also an effective cancer vaccine strategy, potentially eliciting robust antitumor immunity.

2.3.2. Nanodiscs

Among the systems above, high-density lipoprotein (HDL) represents a naturally occurring nanodisc characterized by its prolonged circulation in plasma (with a half-life of approximately 3∼4 days), distinguishing it from many synthetically engineered nanovesicles [75]. Integration of small molecule drugs into HDLs has been shown to augment therapeutic efficacy, principally by enhancing the small molecules' solubility, circulation half-life, and distribution profile. Pre-formed sHDL nanodiscs offer a streamlined approach, wherein they can be readily combined with cholesteryl-CpG and tumor antigen peptides, including neoantigens identified through tumor DNA sequencing [76]. This process yields homogeneous, stable, and ultra-small nanodiscs at ambient temperature in less than 2 h. Employing sHDL as a matrix for encapsulating various bioactive compounds has proven effective in promoting immunotherapeutic interventions targeting MC38 tumors, glioblastoma multiforme, and cancer immunotherapy directed against cancer stem cells [77,133]. Furthermore, alternative formulations, such as CM fortified with styrene-maleic acid as a scaffold, have been employed in construction of nanodiscs, in which designs function as potent modalities for anti-tumor vaccination strategies (Fig. 4I) [134,135]. Following characterization, the CCND/MPLA nanodiscs, measuring 16 nm in diameter and displaying circular morphology, exhibit protein profiles akin to the MC38 plasma membrane (Fig. 4J−L). Notably, these nanodiscs have been confirmed to contain tumor-promoting markers such as CD44, programmed death ligand 1 (PD-L1), and the tumor-associated antigen EphA247 (Fig. 4M). This nanodisc-based formulation thus holds potential for applicability across a broad spectrum of cancer types.

2.3.3. Virus-like

Biomimetic nanovaccines, originating from viral sources, employ self-assembled viral capsid proteins devoid of genetic material and have found widespread applications in vaccine design, especially in the context of cancer vaccines [78,79,136]. These VLPs, functioning as biomaterial scaffolds characterized by pathogen-like polyvalent structures and versatile chimeric multiepitope, hold the potential to serve as nanocarriers for antigen delivery and the induction of immune responses [137]. Cervarix, the FDA-approved human papillomavirus (HPV) vaccine, consisting of HPV16 and HPV18 L1-protein-based VLP has been produced using the virus-like nanoformulation. Another instance involved engineered *Salmonella typhimurium* bacteriophage P22-based VLP, which were *co*-encapsulated with two proteins of respiratory syncytial virus (M and M2) [80]. *In vivo* results showed that the P22-M/M2-treated mice exhibited significantly decreased lung viral titers, indicating potential of the VLP-based strategies in designing nanovaccines generating immune responses towards multiple subunit antigens. Except for that, those of prokaryotic or eukaryotic origin, which are called protein cages and vaults, are generally for immune

molecular transportation and induce robust immune responses. Cages like the 13 nm cage of human heavy chain ferritin (an iron storage protein) [138], 25 nm E2 cage derived from the pyruvate dehydrogenase complex of *Bacillus stearothermophilus* [139], and 24 nm encapsulins of bacteria and archaea, have all been employed as nanocarriers for delivering antigens and eliciting immune responses post-immunization [140]. In addition, eukaryotic ribonucleoproteins assembly of a cage-like barrel-shaped structure is also provided to design protein-based nanovaccines, increasing antigen-specific $CD4^+$ T cell responses with multiple cytokine secretion patterns [140,141].

Table 2
Customized nanovaccines targeting LN and immune cells.

Targeting sites	Nanovaccine names	Essential components	Features	Tumor types	Refs
LN	AlO(OH)-polymer NP	OVA and CpG	Nanosized vaccine (90 nm) for LN	B16-OVA and B16–F10 melanomas	[142]
	Melittin-lipid based nanovaccine	Whole-cell tumor antigen	Nanosized vaccine (10−20 nm) for LN	B16–F10 melanoma	[143]
	Amphiphiles-based molecular vaccine	Peptide antigen	"Albumin hitchhiking" strategy	TC-1 tumor and B16–F10 melanoma	[144]
	Tu-NP_{FN}(+)/Ln-NP_{R848}	Ferrimagnetic nanocube (FN) and R848	Nanosized vaccine (~100 nm) for LN	CT26 colon tumor	[145]
	OVA/CpG	OVA and CpG	Small size, narrow distribution, negative charge, and good stability for LN targeting	E.G7-OVA tumor	[146]
	Gold nanoparticle (GNP)	OVA	Nanosized vaccine (10−20 nm) for LN	E.G7-OVA tumor	[147]
	Pluronic-stabilized poly (propylene) sulfide NP	CpG and paclitaxel	Nanosized vaccine (30 nm) for LN	B16–F10 melanoma	[148]
	OVA@CpG (mNV)	OVA and CpG-SH	Extended "antigen depot" effect	B16-OVA melanoma	[149]
T Cell	Poly-lactide-*co*-glycolide (PLG) scaffold	Granulocyte-macrophage colony-stimulating factor (GM-CSF) and CpG-ODN	Release cytokine to recruit and house host DC	B16–F10 melanoma	[150]
	Multifunctional bacterial membrane-coated nanoparticle (BNP)	PC7A/CpG and Neoantigen	Capturing cancer neoantigens resulting in enhancement of DC uptake and cross presentation	B78 melanoma and NXS2 neuroblastoma	[151]
	MSN-TY	Screened peptide (TY), OVA, and CpG	DC targeting peptide	B16-OVA melanoma	[152]
	NP-supported cytomembranes (NP@FM)	Whole tumor antigen complexes and immunological *co*-stimulatory molecules	Mimicking both APC and cancer cells	4T1 breast cancer	[153]
	PLA-PEI NP	TLR9, CpG, and protein antigen	Antigen cross-presentation through "proton sponge effect"	B16-OVA, MC38, and E0771 tumors	[154]
	iDR-NCs/neoantigen complex	CpG, *Stat3* shRNA, and PPT-*g*-PEG	Neoantigen-specific T cell response	MC38 tumor	[155]
	DNA nanodevice-based vaccine	Tumor antigen peptide, dsRNA, CpG loop, locking strands	Amenable size and pH-responsive manner in respond to acidic endosomal environment	B16-OVA melanoma	[156]
	mRNA/LNP	LNP, mRNA encoding CMV glycoproteins gB, and pentameric complex	Higher affinity between antigen and T cell	–	[157]
B Cell	^{D}CDX modified liposome (^{D}CDX-sLip)	Brain-targeted *D*-peptide ligand (^{D}CDX) and OVA	IgM-Fc receptor (FcμR) pathway to targeting B cell	–	[158]
NK Cell	Cyclic diguanylate monophosphate (cdGMP)/MPLA-encapsulated immuno-NP	cdGMP and MPLA	Cytokine gradient drive of NK cell upregulation	TNBC	[159]
	Fe_3O_4/SiO_2 core/shell NP	Cyanine5.5 (Cy5.5) and NK-92MI cell	Modulation NK cell	Human B cell lymphoma	[160]
	Fe_3O_4@PDA NP	Labeled NK cell	NK cell recruitment and its infiltration into tumor site	A549 cancer	[161]
TAM	Hybrid PEG micelle	BLZ-945, OVA, and NLG919	BLZ-945 and NLG919 caused effective M2-like TAM depletion	E.G7-OVA tumor	[162]
	PEG-FA-based liposome (PEG-FA-Lip)	CpG, FA, and DOX	FA-receptor mediate endocytosis	4T1 breast cancer	[163]
	Dual-inhibitor loaded supramolecular NP	MCSF 1 receptor (CSF1R) and MAPK inhibitor	Inhibitions of CSF1R and MAPK signaling pathway to enhance repolarization of M2-TAM	4T1 breast cancer	[164]
	M2NP	α-peptide	M2-TAM binding peptide	B16 melanoma	[165]
	Peptide hydrogel	TLR7/8a	TLR7/8 for driving polarization of macrophage towards M1-TAM	4T1 and B16 tumors	[166]
	Fe-MOF	Diclofenac and peptide	Decrease efflux by hepcidin/ferroportin signaling pathway	H22 tumor	[167]
TAN	Mesoporous silica	Fe(III)-captopril	Repolarized N2 phenotype	H22 tumor	[168]
MDSC	TAD-based (FIT) NP	TAD and indocyanine green	Inhibit MDSC function by TAD	Colon tumor	[169]
	Lipid nanocapsule	Gemcitabine-C12	Gemcitabine-C12 targeting monocytic MDSC subset	Lymphoma and melanoma tumors	[170]
	Glyceryl-monooleate-based liquid-crystal core NP	CCL2, OVA, and RNAi sequence	Chemokine targeting MDSC	MCA-203 fibrosarcoma	[171]
NKT Cell	PEGylated lipid-PLGA NP	CpG-ODN and MPLA	Presentation of GalCer *via* MHC I-like molecule (CD1) to NKT cell	B16–F10 melanoma	[172]
Treg Cell	Layer-by-layer hybrid NP	IR 780, Imatinib, and glucocorticoid-induced TNF receptor	Reductions of transcription factors of STAT3 and STAT5 in Treg cell	B16 and BL6 tumors	[173]
	CpG/cGAMP-hybrid liposome-Man (C/G-HL-Man)	Fenofibrate, cGAMP, CpG, and TM	Fenofibrate, activated peroxisome proliferator-activated receptor (PPAR)-α pathway, and downstream genes related to FA metabolism	B16–F10 melanoma	[174]

Biomimetic nanovaccines, comprising vesicles, nanodiscs, and VLP, advance cancer immunotherapy by optimizing antigen delivery and immune response specificity. These nanoscale entities emulate biological processes for targeted antigen presentation and activation of immune cells. However, their fabrication, being more complex than nanovaccines derived from inorganic materials and polymers, poses significant challenges in selecting and processing diverse nanomaterials for development of tailored vaccines, necessitating a sophisticated approach to their production methodology.

3. Nanovaccines-based strategies for enhanced cancer immunotherapy

Based on the above description, engineering, and characterization of nanocarriers from a diverse array of sources, including inorganic, polymeric, and biomimetic materials, alongside their adjuvant attributes, are of paramount importance. Efficacy of these nanovaccines in the context of enhanced cancer immunotherapy depends on various factors: vaccination methodologies, antigen specificity, active constituents anchored to different immune cells, and dynamic profiles of TME specific to diseases.

In strategies aimed at augmenting cancer immunotherapy, nanovaccines necessitate a focused approach on LN targeting for antigen delivery, efficacious antigen presentation, initiation of immune response signaling pathways, and synchronized modulation of TME under distinct disease profiles. Integration of different active components, encompassing adjuvants, receptors, agonists, cytokines, and chemokines, into formation of custom nanovaccines is advantageous for targeting immune cells and mitigating immunosuppressive milieu (Table 2). Specifically, efficacy of LN targeting and subsequent accumulation is intricately-linked to the vaccination strategy employed, including *in situ* and tumor-specific modalities. For activation of the immune system, stimulation and proliferation of T and B cells are fundamental. Addressing immunosuppressive TME, which encompasses TAM, and MDSC, among others, necessitates a strategic focus on personalized targeting ligands or antigens and modulation of associated signaling pathways. Subsequent sections will extensively examine these critical aspects in context of enhancing therapeutic potential of custom nanovaccines towards enhanced cancer immunotherapy.

3.1. Escalation of lymph node accumulation

In addition to their conventional surgical removal, increasing attention has been paid to modulation of the LN as a cancer treatment [175]. LN are secondary-lymphoid tissues regarded as crucial hubs linking immune cells and regulating adaptive immune responses [176]. They are distributed throughout the body and recruited leukocytes from the circulation screen antigen-laden lymph draining to different tissues [177]. Efficient delivery of vaccines to LN is crucial in achieving cancer immunotherapy, with administration modes significantly influencing antigen accumulation and enrichment within LN. Nanovaccine delivery to LN commonly employs intratumoral and interstitial methods, resulting in a "depot effect" that prolongs antigen exposure within TME, thus inducing a potent immune response.

Intratumoral injection is the direct and effective way for delivering *in situ* vaccines directly towards LN. This process involves engineered delivery of exogenous antigens directly into LN within tumors, eliciting immune responses [142]. For instance, a high-density lipoprotein-mimicking peptide-phospholipid scaffold (termed α-peptide-NP) was developed after lading melittin, forming an ultra-small (10−20 nm) melittin-lipid nanoparticle (named α-melittin-NP) [143]. Compared with melittin, which had a molecular weight of 2840 Da, as-fabricated α-melittin-NP, within an ultra-small size range of 10–20 nm, was favorable for LN uptake, and induced release of whole tumor antigen, retaining multiple immunogenic epitopes to trigger a robust immune response. Exogenous antigens are structurally encoded for LN delivery [178]. Another innovative approach is the "albumin hitchhiking" strategy, designed for specific LN targeting by molecular vaccines [144]. This strategy exploits albumin's role as a fatty acid transporter, whereby antigens or adjuvants, modified with a lipophilic albumin-binding domain, accumulate in lymphoid organs post-injection through *in situ* complexation and transportation with endogenous albumin. *In situ* vaccine programming within tumor sites provides another targeting-LN delivery method. For example, intratumoral injection of a composite containing adjuvant-loaded Ln-NP and antigen-inducing Tu-NP yields nanovaccines approximately 100 nm in size with neutral/negative charge (Fig. 5A) [145]. Under an alternating magnetic field, Tu-NP_{FN} (100 nm) generates prolifically antigens, while Ln-NP_{R848} (35 nm) captures a portion of the produced antigens, inducing *in situ* nanovaccines targeting LN after traversing interstitial space and LV (Fig. 5B, C). After intratumoral injection, the *in situ* programming nanovaccines convert primary tumors into whole-cell antigens for targeted LN delivery. Leveraging a hydrogel-based system, these *in situ* nanovaccines enable ROS-responsive DOX and nanoadjuvant (CpG-P-*ss*-M) releases, accumulating abundant tumor antigens within tumors [15]. The CpG-P-*ss*-M's charge reversal facilitates adsorption and conversion into small, negatively charged tumor vaccines, optimizing LN priming.

Intratumoral injection, while direct and efficient, often requires surgical, ultrasonic, or tracer dye guidance, adding complexity to the vaccination process [179]. An alternative approach is to utilize interstitial administration methods such as subcutaneous, intramuscular, and intradermal injections to enable nanovaccines to enter capillary LV and reach LN. Efficiency of this transfer depends on the nanovaccines' characteristics like size, charge, and hydrophilic modifications, *etc.* These characteristics influence their movement through lymphatic pathways, interstitial structures (compositions of tangled collagen fibers and negatively charged HA), and blood flow rates [146]. Size of antigen-bearing carriers reconciles diameter of LN vascular channels, approximately 100 nm; larger nanoparticles fail to reach capillary LVs and are intercepted by tissue-resident DC, while particles smaller than 10 nm are typically cleared through blood capillaries from intestine due to blood capillary flow rates being 100–500 times faster than LV [180]. GNP-based nanovaccines of various sizes have been synthesized to evaluate their capacity for delivering payloads to the LN [147]. Specifically, GNPs with 7, 14, and 28 nm diameters are functionalized with OVA, resulting in corresponding hydrodynamic diameters of 10, 22, and 33 nm, respectively. Significantly, OVA-GNPs with dimensions of 22 and 33 nm exhibit superior delivery efficiency in targeting the draining LN compared to those with a diameter of 10 nm. An adjuvant-targeted strategy also achieves passive accumulation within tumor-draining lymph nodes (TDLN), modulating effector responses and counteracting tumor-induced immunosuppression [181]. Polymeric nanoparticles with a size of 30 nm are prone to TDLN, mainly when administered in limbs on the same side as the tumor [148].

The "minimalist" nanovaccine design, which effectively captures nearly all cancer-related antigens [149], exemplifies how extended antigen "depot" enhances LN-targeting potential of the nanovaccines. The nanovaccine (mNV), with a diameter of 50 nm, is formulated using OVA and thiol-modified CpG (CpG-SH), resulting in a composition of 500 antigen molecules *per* nanoparticle [149]. This substantial antigen-loading capacity of the nanovaccine facilitates efficient drainage into the LV and subsequent high retention in the LN, thereby initiating immune responses (Fig. 5D, G). Furthermore, an efficient accumulation of cargo within LN is achieved through application of the external forces, such as magnetic guiding mechanisms [182]. Notably, functionalization of magnetic responsive components such as superparamagnetic oxides are harnessed as frameworks or scaffolds to guide homing of LN, with classical examples including ferric oxide as a magnetic nanocarrier. These intricately-crafted nanovaccines showcase a remarkable propensity for accumulation within profound regions of LN. Another example of superparamagnetic iron oxide coated with zinc

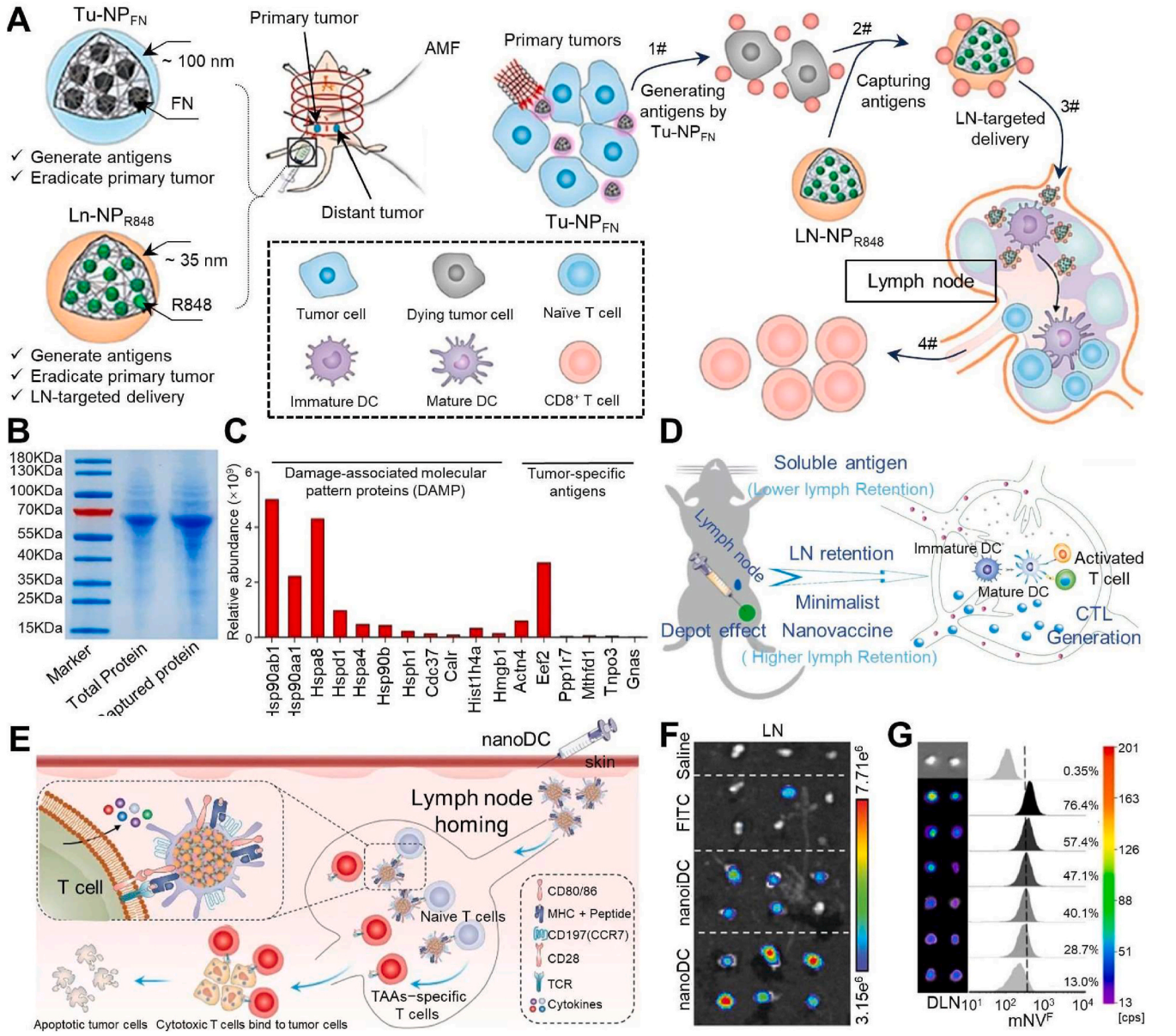


Fig. 5. Nanovaccines for LN-targeted delivery and their enhanced cancer immunotherapy. (A) *In situ* programming of vaccines *via* two synergetic nanomedicines, Tu-NP_{FN} and Ln-NP_{R848}. (B) Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of total proteins generated by Tu-NP_{FN} under an alternating magnetic field and proteins captured by Ln-NP_{R848}. Proteins were stained with Coomassie Brilliant Blue. (C) Relative abundances of tumor antigens captured by Ln-NP_{R848} as determined by liquid chromatography/tandem mass spectrometry. Reproduced with permission [145]. Copyright 2022, American Chemical Society. (D) Schematic illustration of mNV-triggered antitumor immune responses. (G) Representative fluorescence images of DLN for groups of mNV that FAM-labeled CpG (mNV^F) at the indicated time points. Reproduced with permission [149]. Copyright 2018, American Chemical Society. (E) Personalized nanoDC that efficiently accumulates in LN after subcutaneous injection, directly stimulating TAA-specific T cells to kill tumor cells. (F) *Ex vivo* fluorescence image of FITC, FITC-labeled immature DCs membrane-based vaccines (nanoiDCs) or nanoDCs treated LN. Reproduced with permission [185]. Copyright 2022, Wiley.

oxide efficiently expedited LN homing through synergistic interactions between external forces and LN-homing leukocytes [183]. Reports also indicate that DC-based vaccines exhibit enhanced LN targeting efficiency by incorporating key protein CC-chemokine receptor 7 from DC membrane vesicles, facilitating lymphatic homing [184]. By maintaining *co*-stimulatory markers, MHC I antigen complexes, and lymphocyte homing receptors, a personalized DC-mimicking nanovaccine (nanoDC) also efficiently migrates to LN and elicits potent antigen-specific T-cell responses (Fig. 5E, F) [185].

In short, administration of the vaccination generally employs intratumoral and interstitial methods, efficiently facilitating antigen accumulation within LN and consequently triggering robust immune responses. Nanovaccine delivery strategies, encompassing intratumoral and interstitial routes, are meticulously designed to align with specific characteristics and structural complexities of LN. These passive targeting approaches, whether implemented *via* subcutaneous, intramuscular, or direct introduction into LV, are adept at ensuring targeted antigen accumulation within LNs in various tumor models. Furthermore, incorporation of active targeting mechanisms, driven by external forces, enhances precision of nanovaccine localization in LN. This holistic and versatile vaccine delivery approach significantly advances customized nanovaccines development in cancer immunotherapy. While these strategies hold promise, they also present challenges such as potential systemic toxicity, the necessity for precise targeting, and the complex interplay within TME that may impede effective vaccine delivery and action. The "albumin hitchhiking" strategy and *in situ* vaccine

programming within tumor sites further illustrate the innovative approaches being explored to improve cancer immunotherapy. Addressing these challenges requires a nuanced understanding of the TME and a development of sophisticated nanovaccine systems capable of precise navigation and targeted delivery. As such, future research should not only aim to optimize these delivery methods but also to explore new targeting ligands and nanocarrier designs to enhance specificity, efficacy, and safety of the custom nanovaccines in cancer treatment.

3.2. Enhancing antigen presentation in single-cell level

3.2.1. Enhancement of antigen presentation

DC plays a central role in antigen presentation within context of cancer immunotherapy, which initiates and sustains effective immune responses through their efficient antigen presentation mechanisms [186]. To ensure executing sufficient immune responses, customized nanovaccines are initially engulfed by DC. These tailored nanovaccines are internalized *via* receptor-mediated pathways in DCs, guaranteeing an effective immune response [187,188]. Specifically, the antigen presentation mediated by receptors from the C-type lectin family, such as DC-SIGN receptor, is one strategy for targeting DCs with custom nanovaccines [189]. Additionally, nanovaccines engineered with mannose fragments, targeting overexpressed mannose receptors on APC surfaces, enhance cross-presentation of antigens [190]. Moreover, appropriate delivery of regulatory cytokines, such as GM-CSF, creates a simulated infection microenvironment, enabling precise DC recruitments and proliferations [150,191,192]. Omar et al. have underscored a critical role of GM-CSF released from PLG scaffolds in enhancing DC recruitment and proliferation in a dose-dependent manner [150]. Experimental results demonstrated that implanting GM–CSF–based PLG matrices into mice significantly increased proportion of DC and regulated their maturation and dispersion. Furthermore, BNPs, abundant in PAMP such as TLR agonists, are recognized for their capacity to stimulate innate immunity and activate DC [151]. Peptides are specifically binding to BMDCs and splenic DCs, identified through phage display technology, have also been incorporated into nanovaccine to targeting DCs effectively [152,193]. In brief, engineering inherent or specifically designed targets is a key strategy for activating and recruiting DCs with nanovaccines [32].

T cells, being integral to cell-mediated immunity and expressed by T-cell receptor (TCR), are pivotal in advanced cancer immunotherapy strategies [194]. Central to these strategies is activation and proliferation of cytotoxic T-cells, notably $CD8^+$ T cells. Low immunogenicity and stability of antigens necessitate efficient antigen-specific delivery systems, with an emphasis on nanovaccines that stimulate $CD8^+$ T cell-mediated immunity [195]. An ideal process should proficiently transport antigens to the cytoplasm of APC for MHC I-antigen complex formation through cross-presentation, thereby activating T cells for immune defense and pathogen clearance [196]. Customized nano-based vaccination strategies, aimed at enhanced cross-presentation and T-cell responses can be categorized into several methods: aAPC based on membrane fusion, endosomal escape (*e.g.*, endosomal swelling rupture), photochemical internalization, and nucleic acid vaccines capable of sustained expression in APC [197]. For example, a cytomembrane nanovaccine, engineered to mimic tumor cells and function as an APC, has demonstrated significant therapeutic effects (Fig. 6A) [153]. Fusions of two types of cells result in high expressions of immunological *co*-stimulatory molecules and whole tumor antigen complexes on FM, allowing nanoparticle-supported FM (NP@FM) to behave as APC for T cell activation. Lipid bilayer, emulating natural APC membrane system, incites expansion of antigen-specific cytotoxic T-cell subpopulations *via* T-cell receptor stimulation [198]. Similarly, nanosized artificial APC (naAPC)-based formulation induces antigen cross-presentation to T cells *via* size-transformation and peptide-MHC (pMHC) I complex/TCR signaling (Fig. 6C–G) [199].

Polymers like PEI or PEG are increasingly used in nanovaccine development to enhance antigen cross-presentation through the "proton sponge effect''. This effect involves rupturing endosomal membranes and releasing antigens into cytosol, thereby facilitating increased antigen cross-presentation and T-cell priming (Fig. 6B) [154]. Nanovaccines, such as those with PEG-grafted polypeptide (PPT-*g*-PEG) copolymers, leverage acid-labile nature of the PEG for optimal solubility and to amplify the "proton sponge effect" [155]. This effect enhances intracellular delivery following PEG detachment in an acidic endolysosomal environment, along with exposure to cationic polypeptide for improved cellular uptake and antigen presentation. PEG-based nanovaccines with pyridyl disulfide groups facilitate antigen conjugation through thiol-disulfide exchange, destabilizing acidic endosomes and releasing vaccine contents into cytosol for MHC I presentation and differentiation-associated protein 5 signaling pathway activation [200]. Moreover, a streamlined and scalable platform, incorporating beta-cyclodextrin and PEI, provides a distinctive cavity structure, high charge density, and reactive disulfide bonds, facilitating endosomal escape of the neoantigens without inducing damage (Fig. 6H) [201]. This unique composition not only enhances cross-presentation significantly but also mediates activation and expansion of naïve T lymphocytes, thus effectively strengthening antitumor immunity.

Nucleic acid-based vaccines like DNA and mRNA are emerging as effective alternatives to traditional protein or peptide-based subunit vaccines, capable of inducing robust T-cell responses through host cellular mechanisms [202]. Specifically, DNA illustrates this by transferring gene sequences to APC, which releases payloads in acidic endosomal environments, thereby eliciting strong antigen-specific T-cell responses [203]. This mechanism is further exemplified by DNA nanodevices that also release payloads in response to acidic endosomal environments [156]. These nanovaccines are particularly adept at stimulating $CD8^+$ T cell-mediated cellular immunity owing to their mode of intracellular expression [204]. In comparison, mRNA vaccines present lower genetic risks and operate without need for nuclear entry, degrading after activation. This characteristic renders them promising for clinical applications, particularly in LNP-based systems [205,206]. These LNPs, including liposome-entrapped mRNA vaccines, have been successful in stimulating virus-specific CTLs [207]. Furthermore, a versatile platform of the mRNA/LNP nanovaccine is demonstrated in its application for heterologous prime/boost T-cell responses [157]. The recent remarkable success and demonstrated safety of mRNA lipid nanoparticle technology have been pivotal in production of the vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [208].

Photochemical internalization offers a powerful approach for endosomal escape *via* light-induced rupture [209]. This technique involves integrating photosensitizers into nanovaccines which triggers ROS generation and endosome rupture upon exposure to specific light. This strategy enhances antigen internalization and cross-presentation, effectively stimulating antigen-specific $CD8^+$ T cell activation [210]. The HA-OVA-AuNPs nanovaccine, based on gold NP adorned with HA and OVA, demonstrates this by generating a prompt antigen-specific $CD8^+$ T cell response when exposed to NIR irradiation [211]. This response is attributed to increased proteasome activity and MHC I antigen presentation, driven by heat-mediated disruption of endo/lysosomes. Besides, a protein-based nanovaccine has also shown potential in photochemical internalization, causing $CD8^+$ T cell infiltration and caspase-3-dependent death, both of which inhibit tumor progression [212].

Simply put, activation and expansion of the cytotoxic T cells, facilitated by advanced nanovaccine strategies, represent a cornerstone in evolution of the cancer immunotherapy. The utilization of aAPC based on membrane fusion, endosomal escape mechanisms, photochemical internalization, and nucleic acid vaccines delineate a multifaceted approach towards optimizing antigen presentation and T-cell activation. These strategies, while promising, underscore the complexities of immune modulation at the cellular level, highlighting the delicate balance

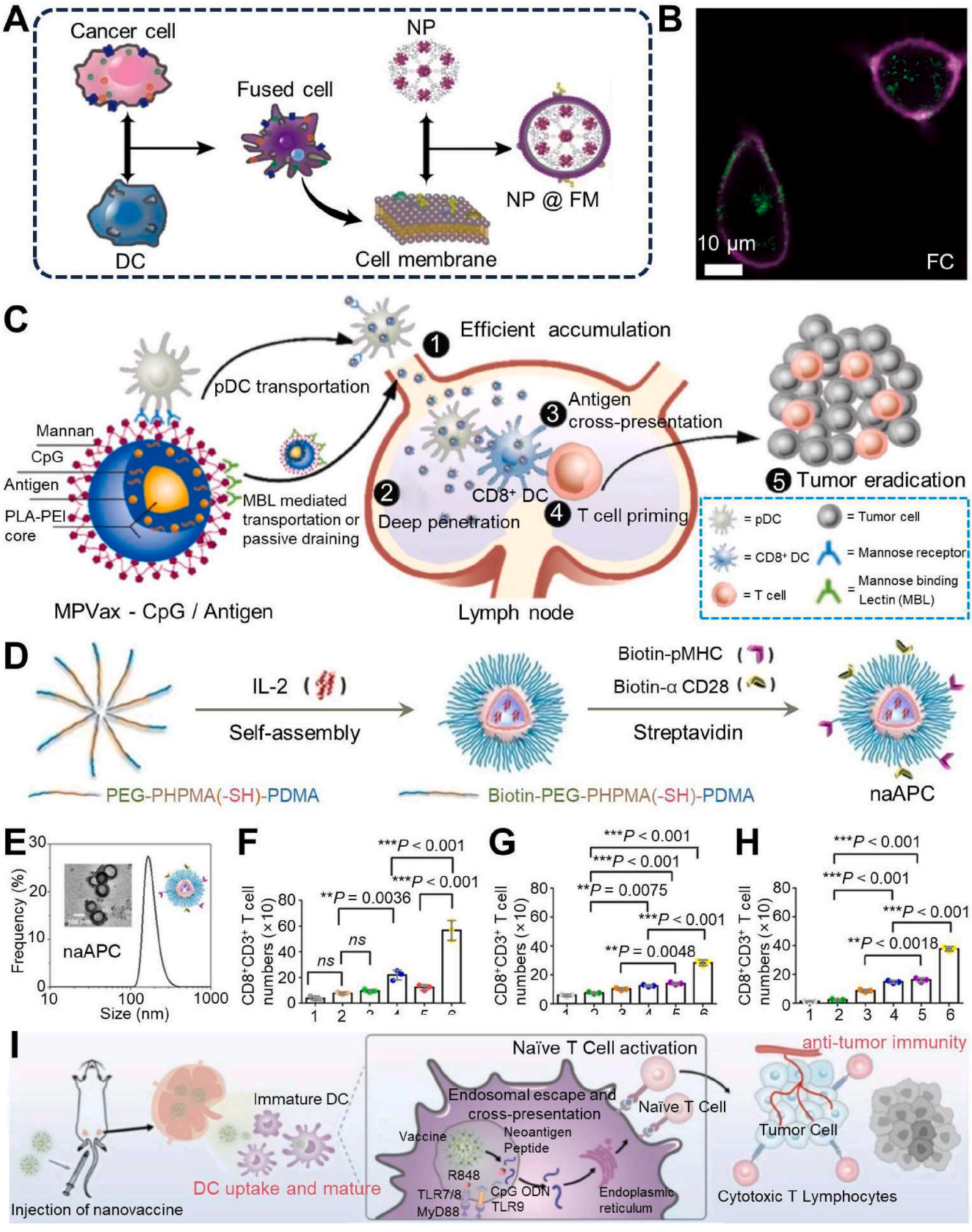


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Fig. 6. Enhancement of antigen presentation with customized nanovaccines in cancer immunotherapy. (A) Preparation of MOF@cytomembrane. (B) Confocal laser scanning microscopy observation of fusion of DC (green fluorescence from anti-MHC II-FITC antibody) and 4T1 cell (red fluorescence from anti-CD44-APC antibody). Reproduced with permission [153]. Copyright 2019, Springer. (C) Schematic illustration of mannan-decorated pathogen-like polymeric nanoparticle system (MPVax) and mechanism in eliciting antitumor immune responses. MPVax-CpG/Antigen is constructed with PLA-PEI core, loaded with CpG and antigens and shielded with oxidized mannan. MPVax-CpG/Antigen efficiently accumulates in LN by passive drainage or pDC and mannose-binding lectin mediated active transportation. After arriving at $CD8^+$ DC, antigens are presented to $CD8^+$ T cells and results in antigen-specific tumor eradication. Reproduced with permission [154]. Copyright 2022, Elsevier. (D) Formation of size-transformable naAPC. Achieved through self-assembly of copolymer biotin-PEG-*b*-poly(*N*-*2*-hydroxypropyl methacrylamide-*g*-thiol)-*b*-poly[*2*-(dimethylamino) ethyl methacrylate], naAPC encapsulates IL-2 within their aqueous core and features a surface adorned with pMHC monomer and αCD28. (E) Size and structure characterization of naAPC tested by DLS and TEM, respectively. *In vitro* $CD3^+CD8^+$ T cell proliferation by (F) *co*-incubation of naïve T cells with mature DC 2.4 cells, and *co*-incubation of mature DC 2.4 cells and dying EG7-OVA cells with (G) T cells; and (H) preactivated T cells by photodynamic therapy (PDT) after treatment with different groups including (1) PBS, (2) naAPC, (3) OVA, (4) NP-OVA, (5) OVA-naAPC, and (6) NP-OVA/naAPC. Mixed cells had PBS or naAPC alone serve as control. ($n = 3$; $^{**}P < 0.01$, $^{***}P < 0.001$; *ns*, not significant; one-way ANOVA with multiple comparisons). Reproduced with permission [199]. Copyright 2020, American Association for the Advancement of Science. (I) Schematic illustrations of responsive release and process for triggering anti-tumor immune response of cyclodextrin/PEI-based nanovaccine. Reproduced with permission [201]. Copyright 2023, Wiley.

required to elicit a potent controlled immune response. The challenge lies not only in achieving efficient antigen delivery to APCs but also in navigating the myriad of immune regulatory mechanisms to ensure a sustained and targeted antitumor response. Furthermore, the integration of nucleic acid-based vaccines introduces a novel dimension to traditional immunotherapy paradigms, offering a dynamic and adaptable platform for inducing robust T-cell responses. However, success of these innovative approaches necessitates a comprehensive understanding of underlying biological interactions and development of sophisticated delivery systems capable of precise targeting and controlled release. As such, future research should endeavor to refine these strategies, exploring the potential of novel nanocarrier designs and targeting ligands to enhance specificity and efficacy of the bespoke nanovaccines in mediating cancer immunotherapy.

3.2.2. Activating B cells

B cells play a pivotal role in orchestrating adaptive immune responses through communication mediated by B-cell receptor (BCR) [213–215]. Signaling pathway of BCR entails participation of a membrane-anchored surface Ig, the distal portion of which is characterized by variable regions with antigen-binding sites [216–218]. IgM is recombined Ig variable region genes and expressed on immature or mature B cells [219]. Based on this finding, IgM-based nanovaccines (^{D}CDX-sLip/OVA) are formulated using ^{D}CDX-modified liposomes, OVA, and IgM *via* electrostatic interactions, demonstrating a significantly-targeting ability to splenic B cells [158]. IgM, alongside decorations of FcμR and CD21/35, plays a crucial role in enhancing antigen presentation and uptake by B cells residing in the splenic marginal zone. This phenomenon is evidenced by a robust biosafety profile observed in response to ^{D}CDX-sLip/OVA, characterized by sustained higher antibody titers (IgG1), which is facilitated through both IgM-complement and IgM-FcμR pathways. Complement-mediated B-cell targeting approach is also demonstrated by lectin-coated surfaces of dextran coated ferrous-based nanovaccines where surface-deposited active complement factor 3 (C3) results in predominant targeting to CR1/2-expressing B cells [220]. BCR signaling is additionally believed to contribute to how malignant B cells proliferate and survive in individuals with lymphomas or leukemias [219]. Development of the therapeutic medications that emphasize BCR signaling is gaining momentum. Examples of these medications are bruton tyrosine kinase inhibitors [221] and phosphoinositide 3-kinase isoform-specific inhibitors [222], which sparks further enthusiasm for development of the customized nanovaccines targeting B cells-related therapeutic pathways.

3.2.3. Activating natural killer cells

Given their capacity for cytokine production and participation in immunosurveillance, NK cells have emerged as compelling targets for cancer immunotherapeutic approaches [223]. An effective approach to enhance infiltration of NK cells into tumors involves inductions of stimulatory cytokines associated with NK cell activation [224]. Utilizing functionalized ligands as an active targeting strategy, precisely-tailored nanovaccines can be designed to stimulate cytokine production and facilitate the trafficking of NK cells to tumor sites. Immune-NPs, which are engineered by cdGMP (a STING agonist), MPLA, and a TLR4 agonist, have shown promise in catalyzing production of type I IFN-β and increasing accumulation of NK cells in TME [159]. These nanovaccines are demonstrated to have significant therapeutic effects in a murine model of metastatic TNBC. In addition, the passive strategy to mediate NK cell activation is to sense chemokine attraction by an external stimulator. Magnetic-mediation nanovaccines enhance infiltration of NK cells. For example, Fe_3O_4/SiO_2 core/shell NPs conjugated with Cy5.5 exhibited a satisfactory cancer immunotherapy effect and significantly-increased infiltration of NK-92MI cells (17-fold greater than that detected without NP treatment) under an external magnetic field [160]. Magnetic nanoparticles alongside PDA layer are also confirmed to improve accumulation and retention of NK in TME [161]. By focusing on the intricacies of cytokine modulation, it underscores potential of customized nanovaccines to activate NK cells, enhancing efficacy of cancer immunotherapies.

3.3. Modulating immunosuppression in single-cell level

3.3.1. Modulating tumor-associated macrophage strategies

Macrophages are integral components of the mononuclear phagocytic system and play pivotal roles in tumor progression [225]. These versatile cells exhibit two distinct phenotypes: M1 macrophages with pro-inflammatory and anti-tumorigenic properties, and M2 macrophages with anti-inflammatory and pro-tumorigenic properties [226]. Their inherent plasticity allows macrophages to adapt their functions and phenotypes based on the specific tissue microenvironment, making them amenable to reprogramming for targeted immunotherapies [227]. TAM is the predominant cell type in TME, and clinical research has revealed a strong correlation between increased TAM infiltration in tumors, poor prognosis, and heightened metastasis risk. Therefore, targeting TAM involves activating M1 phenotype while inhibiting M2 phenotype [228]. In this context, strategies for nanovaccines targeting TAM emphasize two aspects: inhibiting recruitment and viability of M2-type TAM and reprogramming TAM phenotypes [227].

Nanovaccines incorporated functionalized ligands, including small molecule CSF1R kinase inhibitors (pexidartinib, PLX7486, RG7155, and BLZ-945) and FA receptor-targeting agents, effectively redound conversion of M2-type to M1-type TAM [162,163,229]. For example, a newly-developed bioactive nanovaccine generated a “depot effect” for NLG-919 and BLZ-945 into tumors, inducing M1-like TAM and depleting M2-like TAM. This approach also led to inhibition of indoleamine *2*, *3*-dioxygenase activity and effective depletion of M2-like TAM [28,230]. In addition, targeting overexpressed FA receptors in various solid malignancies, FA-mediated endocytosis-driven strategies have been applied. The matrix metalloprotease 2 responsive liposome (PEG-FA--Lip), focuses on M2-TAM and tumor cells, inhibiting Treg cell activation, reversing M2-TAM-mediated immunosuppression, and suppressing

tumor growth and metastasis [231]. Additionally, supramolecular nanoparticles loaded with CSF1R and MAPK inhibitors advance macrophage-targeting immunotherapy by blocking relevant signaling pathways [164].

Engineered nanovaccines are also effectively reprogramming TAM by incorporating anchored ligands like M2pep and TLR agonists [232,233]. These nanovaccines, such as M2NPs, integrate α-peptides with targeting abilities to specifically deplete M2-like TAM and block their signaling pathways [165]. Moreover, TLR agonist-based nanovaccines are repolarized M2-type macrophages towards an anti-tumor M1 phenotype, as demonstrated by a TLR7/8a conjugated hydrogel that aids in reprogramming TAM and enhances efficacy of PD1-blockade (Fig. 7A−C) [166]. The DNA-polymer hybrid nanocomplex containing *co*-assembly of TLR9 agonist (CpG) and TLR7 agonist (loxoribine) also converts of suppressive M2 macrophage to active M1 macrophage (Fig. 7D−F) [234]. Furthermore, iron ions are being explored for their role in repolarizing M2-like TAM, with innovations like an iron-based nanovaccine (Dic@M2pep-Fe-MOF) amplifying this repolarization and bolstering efficacy of cancer immunotherapy. These advancements underscore potential of customized nanovaccines in modulating immunosuppressive TME and improving efficacy of cancer immunotherapy [167].

Furthermore, surface markers on macrophages, particularly on TAM, are being targeted for phenotype reprogramming in cancer immunotherapy. For instance, overexpression of placental growth factor (PIGF) and vascular endothelial growth factor (VEGF) on M2-TAM and breast cancer cells led to their synergistic down-regulation, repolarization of M2-TAM as well as inhibiting breast cancer cell proliferation [235,236]. Similarly, a specialized nanoplatform referred to as PEG = MT/PC NPs (PEI, and mannose doubly modified trimethyl chitosan (PEG = MT) along with citraconic anhydride grafted poly (allylamine hydrochloride) (PC)) is engineered to facilitate deliveries of VEGF siRNA (siVEGF) and PIGF siRNA (siPIGF) to M2-TAM, thereby reprogramming of TAM [237]. Vaccination with miR155-loaded of detachable PEG-PLL/galactose-PLL-poly(L-cysteine) (sPEG/GLC/155) nanovaccines, as an example, not only enhanced expression of miR155 and M1-TAM markers like IL-2 and MHC II but also suppressed expressions of M2-TAM markers such as arginase 1 and macrophage scavenger receptor 2 [238]. Furthermore, an innovative "two-in-one" nanovaccine formulation, incorporating a legumain-derived antigenic sequence (a TAM biomarker) and trichosanthin, effectively stimulates cytokine secretion and initiates antitumor immunity by specifically targeting TAM and orchestrating a transformation in TME [239,240].

Essentially, the focused modulation of TAM within TME is crucial for enhancing efficacy of the nanovaccine-based cancer immunotherapies. This section has highlighted the significance of selectively inhibiting M2 type TAMs while promoting activation of M1 type TAMs, a strategy that directly addresses immunosuppressive nature of TME. The successful application of this approach relies on the precise engineering of nanovaccines to target specific TAM receptors and signaling pathways, thereby reprogramming TAM phenotypes to support anti-tumor immunity. However, challenges remain in achieving selective targeting without affecting systemic immune response and in understanding dynamic interactions within TME. Future research must focus on overcoming these hurdles to fully realize the potential of TAM-modulating nanovaccines in cancer immunotherapy.

3.3.2. Modulating tumor-associated neutrophil strategies

Neutrophils, the most abundant circulating leukocytes in humans, are a type of myeloid cells derived from the bone marrow, characterized by their short half-life and multilobed nuclear morphology [241–243]. They are crucial players in tumor progression, especially within TME, and like TAM, TAN shows significant plasticity [244,245]. This variability is influenced by tissue types and specific molecular cues of their environment [246,247]. In the context of cancer immunotherapy, manipulating TAN polarization, which means transitioning the pro-tumor N2 phenotype to the anti-tumor N1 phenotype, is a key therapeutic target [248]. Custom-designed nanovaccines have been developed to induce this polarization [249]. For instance, Fe (III)-captopril-based nanovaccines had successfully repolarized TAN in a hepatocellular carcinoma model [168]. Experimental results revealed that captopril was activated within the acidic TME, facilitating conversion of protumoral TAN into an antitumor phenotype. This transformation led to significant immune effects, resulting in complete tumor regression (83%) in H22 tumor-bearing mice. Additionally, Bacillus Calmette-Guérin has also shown potential benefits in modulating TAN function [250]. Although TAN are promising targets in cancer immunotherapy, further research is needed to understand molecular mechanisms for effectively targeting TAN with the customized nanovaccines.

3.3.3. Modulating myeloid-derived suppressor cell strategies

MDSC constitute another pivotal class of immunosuppressive immune cells. Numerous high-quality studies, encompassing both preclinical and clinical research, have elucidated the strong correlation between abundant infiltration of MDSC within TME and unfavorable patient prognosis [181]. Recent years have witnessed significant advancements in development of the inhibitory agent-based nanovaccine targeting MDSC at tumor sites. These advancements are grounded in various mechanisms, such as deactivation or depletion of MDSC, inhibition of MDSC development, and induction of MDSC differentiation into mature cells, among others [251]. Notably, FDA's recent approval of the phosphodiesterase 5 inhibitor TAD has shown promise in enhancing antitumor immunity by inhibiting MDSC function and revitalizing T-cell responses [252]. In this context, a supramolecular TAD nanovaccine has been developed to mitigate MDSC-induced suppression and enhance immunogenicity (Fig. 8) [169]. These TAD-based vaccines are formulated by assembling indocyanine green and TAD in presence of Fe^{3+} to form FIT NPs (Fig. 8A). The FIT NPs trigger ICD and relieve immunosuppressive activity of MDSC by releasing TAD at tumor sites, a process validated by observed apoptosis of MDSC (Fig. 8B−D). Besides, other strategies like manipulating chemokine like CCL2 *via* CCAAT/enhancer-binding protein beta pathways or employing low-dose gemcitabine-loaded lipid nanocapsules, have been effective in targeting MDSC, thus enhancing cancer immunotherapy by modulating TME [170,171]. Despite these advancements, further exploration in MDSC-targeting vaccines is needed to develop more effective nanovaccines to reshape TME and enhance antitumor efficacy [181].

3.3.4. Modulating invariant natural killer T cell strategies

NKT cells divide into different types (I and II) as follows: Type II includes variant NKT cells identified by sulfatide/CD1d-tetramers [253–255], whereas type I includes as invariant NKT cells that communicate with a semi-invariant TCR (Vα14Jα18 gene segment paired with Vβ2, Vβ7, and Vβ8.2 in mice and Vα24Jα18 paired with Vβ11 in humans) [256,257]. These NKT cells function as a bridge between adaptive and innate immune responses, influencing DC maturation, and activating downstream immune effectors such as B cells, NK cells, $CD4^+$ T cells, and $CD8^+$ T cells [258]. Since they are recognized as both self and foreign by DC *via* the MHC I-like molecule CD1 (CD1-9 TCR ligand), type I NKT cells have attracted significant attention, and are activated by glycosphingolipid such as GalCer [172,258,259]. GalCer-based nanovaccines modified with melanoma peptides and TLR ligands suppress melanoma [172]. These nanovaccines enhance infiltrations of NKT and NK cells, and promote high-level secretions of INF-γ and IL-4. It is anticipated that development of more tailored nanovaccines targeting NK cells will be a focus of future research endeavors in this field.

3.3.5. Depletion of regulatory T cells

Treg cells, known for their immunosuppressive role, are prevalent in TME, where they impede antitumor immunity, contributing to tumor progression [260]. These cells are chemotactically attracted to the TME

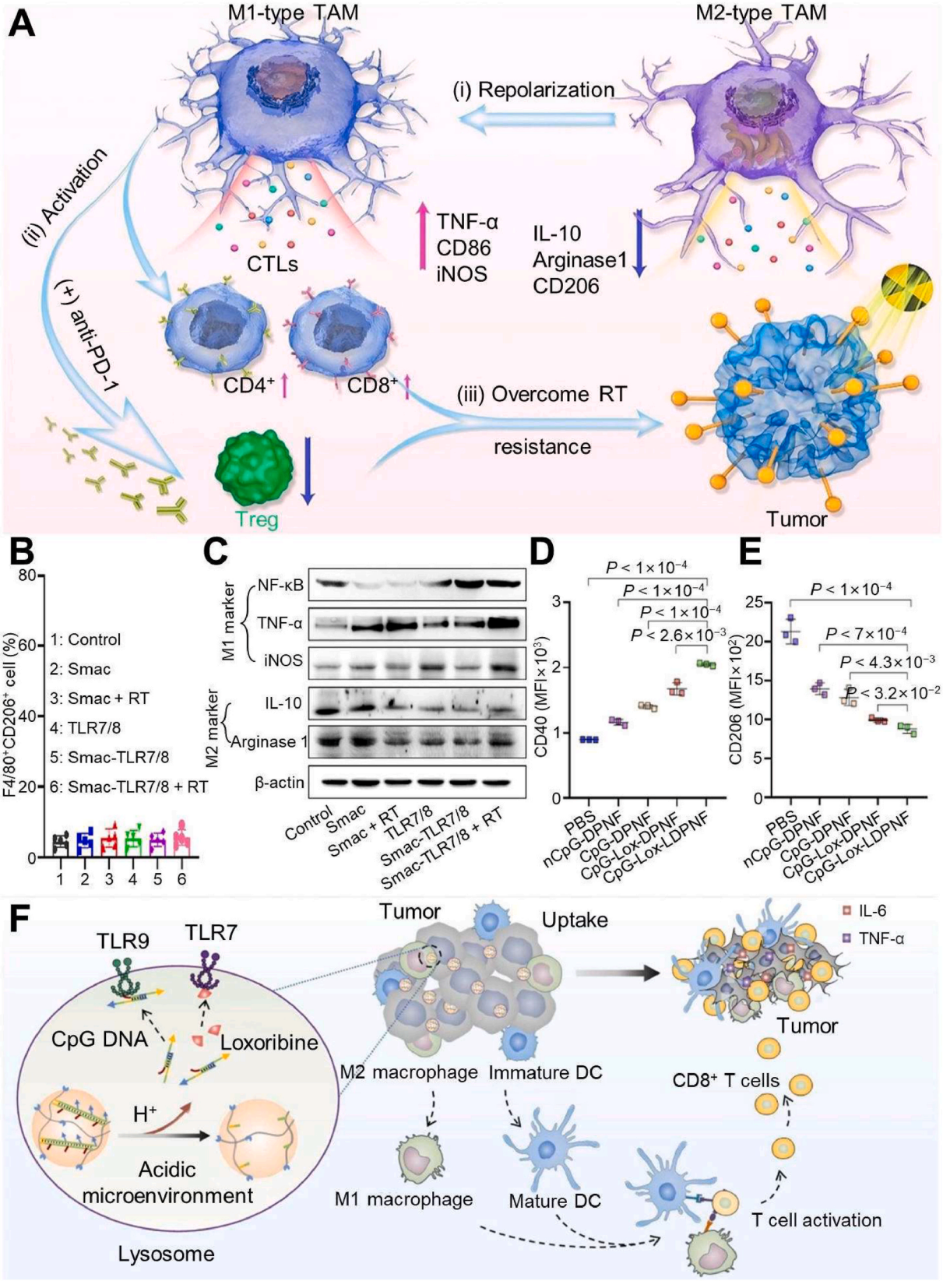

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Fig. 7. Designs of targeting TAM-specific nanovaccines in cancer immunotherapy. (A) Schematic illustration of macrophage repolarization regulated by peptide hydrogel (Smac-TLR7/8 hydrogel) for overcoming radioresistance. Smac-TLR7/8 peptide self-assembles into nanofibrous hydrogel. Then, (i) after peritumoral injection, Smac-TLR7/8 hydrogel effectively reprograms TAM from M2 type toward M1 type, secreting inflammatory factors and activating anti-tumor functions. (ii) Immunosuppressive TME is rebuilt through tumor infiltrating lymphocytes recruitment, and downregulating Treg cells. (iii) Radioresistance is overcame which further improves anti-tumor efficacy combined with immunotherapy. (B) Percentage of M2-related ($F4/80^{+}CD206^{+}$) macrophages ($n = 5$). (C) Protein expression level of NF-κB, TNF-α, inducible isoform of nitric oxide synthase (iNOS), IL-10, arginase 1 in macrophages determined by western blotting. RT: Radiotherapy. Reproduced with permission [166]. Copyright 2022, KeAi Communications Co. Expression level of CD40 (D) and CD206 (E) on bone-marrow-derived macrophage cells that treated with different groups. All the data represented as mean ± SD, $n = 3$. (F) Application of CpG-Lox-DPNFs vaccines composed of CpG, loxoribine, and *co*-loaded DNA-polymer hybrid nanocomplex in synergistic reprogramming tumor immune microenvironment for efficient cancer immunotherapy. Reproduced with permission [234]. Copyright 2024, Elsevier.

via specific chemokine gradients like CCR4-CCL17/22 and CCR8-CCL1, among others [261]. Their high infiltration correlates with poor prognosis in various cancers. Treg cells suppress immune responses through mechanisms such as inhibition of *co*-stimulatory signals, interleukin-2 consumption, and metabolic modulation [262]. Consequently, cancer immunotherapy focuses on depleting Treg cells or modulating their functions to enhance antitumor responses. Targeted therapies include antibodies or small molecules against Treg-specific markers like immune checkpoint molecules, chemokine receptors, metabolites, *etc.*, with aim of strengthening antitumor effects while avoiding systemic autoimmunity. Combinational cancer immunotherapy involving imatinib (IMT)-loaded glucocorticoid-induced TNF receptor family-related protein/PLGA (GITR-PLGA) with IR780 dye has shown promise [173]. IMT triggers signal transducer and activator of transcription- (STAT)3 and STAT5 activation, thereby inhibiting Foxp3 expression and rendering Treg dysfunctionality. Additionally, genetically modified megakaryocytes stably expressing murine PD-1 have been developed to produce PD-1-presenting platelets, capable of carrying cyclophosphamide [263]. This approach not only targets PD-L1 but also depletes Tregs in TME, enhancing antitumor effects of $CD8^{+}$ T lymphocytes. Furthermore, a combination of PPAR-α agonist fenofibrate, PD-1 antibody, and custom nanovaccines has shown potential in modulating T-cell metabolism and enhancing CTL activity through PD-1 blockade [174]. However, studies indicate that PD-1-blocked Treg cells exhibit reduced immunosuppressive activity, necessitating further research to fully understand the role of PD-1 in effector T cells and Treg cells in cancer contexts [264].

4. Nanovaccines applied in cancer immunotherapies

As discussed previously, nanovaccines have demonstrated capabilities to elicit a robust immune response and activate immunogenicity, owing to their adaptable nano-size ranges and customizable structures [265]. These inherent advantages equip nanovaccines with diverse functionalities, allowing them to effectively-target immune cells and find applications in immunotherapies. These vaccines under consideration can be categorized as prophylactic, intended to avert future infections, or therapeutic, to treat existing diseases, including cancer and/or bacterial diseases. Prophylactic nanovaccines are designed to bolster immunogenic memory and trigger both antibody-mediated and cell-mediated immune responses. For instance, nanovaccines had been demonstrated a significant potential for preventing infectious diseases like acquired immunodeficiency syndrome, malaria, tuberculosis, influenza, and cancer [202]. On the therapeutic front, custom-designed nanovaccines induce accumulation and expression of exogenous or neoantigens at tumor sites, curtailing tumor growth. Studies suggest that nanovaccines adeptly modulate the immune system, offering targeted preventive or therapeutic interventions for various pathological conditions. While prophylactic nanovaccines primarily focus on infection prevention, therapeutic nanovaccines are increasingly utilized in cancer immunotherapy.

4.1. Prophylactic functionalities

Despite progress in vaccine development, creation of effective vaccines for viruses like HIV and influenza is still a work in progress [266]. Coronavirus disease 2019 (COVID-19) pandemic has accelerated development of viral vaccines, although there's a risk of these vaccines reverting to a pathogenic form [267]. Prophylactic vaccines are given prior to onset of a disease to establish long-lasting immunogenic memory against infections [126]. In response to these challenges, bespoke nanovaccines, have shown promise, enhancing both antibody-mediated and cell-mediated immune responses. There's growing recognition of efficacy of $CD8^{+}$ T cell-mediated cellular immunity in combating viruses and providing extended protection beyond traditional focused on neutralizing antibodies [268]. This form of immunity targets eradicating viral infections within the body, while humoral immunity works by neutralizing the viruses in bodily fluids by producing soluble antibodies.

The COVID-19 pandemic, caused by SARS-CoV-2, has rapidly spread globally, leading to significant mortality [269]. Vaccination remains the most effective defense against COVID-19, with multiple innovative approaches being developed. One example was the SARS-CoV-2 DLNP vaccine, which was shown robust immunities in various animal models and offered single-shot protection against lethal challenges [270]. Another prophylactic nanovaccines involved formulations of the virus's S1 subunit and dual adjuvants, successfully eliciting robust humoral immune responses and potent IgA antibodies in mice [271]. Dual-adjuvant systems have been shown to enhance systemic and lung immunities by combining MnO_x and CpG with a dimeric antigen version of the virus's receptor-binding domain [272]. Additionally, several nanoadjuvants like selenium [273], manganese [274], and antigen-caged-adjuvants [275], have also been employed in developing subunit vaccines for SARS-CoV-2. Innovative inhalable nanovaccines, such as biomimetic coronavirus structure-based [276] and chitosan-based, have also been reported [277]. Interestingly, the Bacillus Calmette-Guerin (BCG) vaccine has shown effectiveness against COVID-19, being attributed to its nonspecific protective effects against respiratory infections [278]. Research indicated that BCG induced a robust biphasic innate immune response and antigen-specific Th1 cell response in lungs [279]. In mouse models, BCG also protected against weight loss following infection with SARS-CoV-2 BA.5, SARS-CoV, and SHC014 coronaviruses. Overall, nanovaccines demonstrate significant potential in eliciting durable immune responses against pathogen infections or re-infections, with biosafety being a crucial consideration, especially for clinical preventive applications.

4.2. Therapeutic functionalities

Therapeutic nanovaccines have shown promising potential in cancer treatment, particularly in development of highly potent foreign non-self-antigens (TSA), which are overexpressed at specific tumor sites but minimally presented in normal tissues [265]. For instance, an intertwining DNA-RNA nanocapsule (referred to as iDR-NCs) has been demonstrated favorable prospects in cancer immunotherapy [155]. The iDR-NCs nanovaccines efficiently delivered APC in draining LN, inducing durable neoantigen-specific T cell responses and significantly inhibiting progression of neoantigens-specific colorectal tumors. These neoantigen-based nanovaccines exhibited robust cancer immunotherapy, as evidenced by the syngeneic C57BL/6 mice bearing MC38 syngeneic colon adenocarcinoma tumor models. Similarly, a dual adjuvant-based nanoformulation (R848 and CpG) for colorectal cancer,

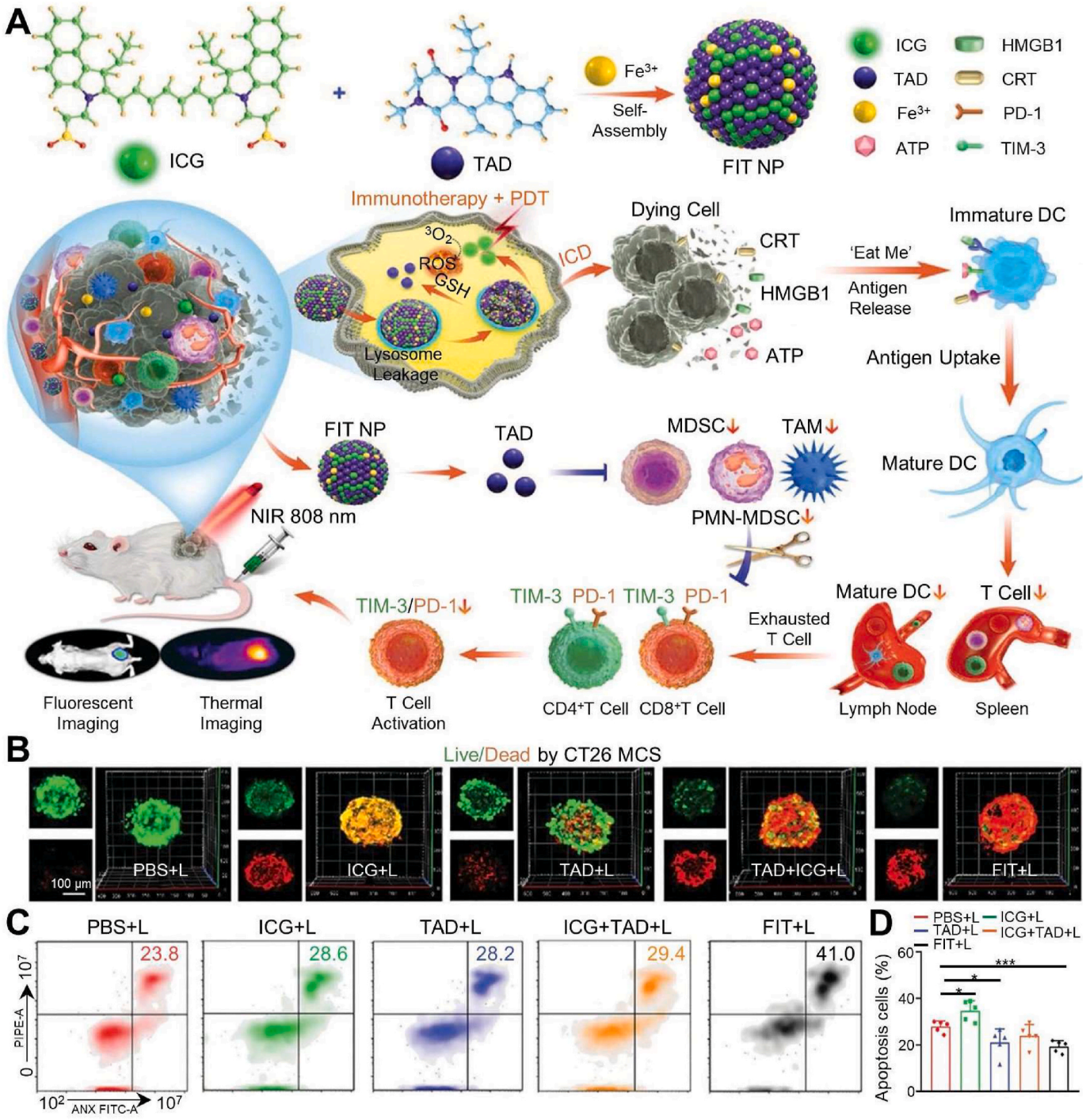

Fig. 8. Deductive procedure of FIT nanovaccine for cancer immunotherapy. (A) Preparation process of FIT nanoparticle, mechanism of MDSC regulation, ICD induction process, and dual-imaging medicated enhanced cancer immunotherapy. *In vitro* cellular experiment with FIT NP, (B) confocal laser scanning microscopy images of CT26 multicellular spheroids treated with different samples for 6 h and stained with FDA (green) and propidium iodide (red). (C) Flow cytometry and (D) qualitative analysis of MDSC in tumors ($n = 3$; $^{*}P < 0.05$, $^{**}P < 0.01$). Reproduced with permission [169]. Copyright 2021, Wiley.

combining neoantigens and adjuvants, has enhanced immunogenicity of neoantigens and reduced acute systemic toxicity [280]. Personalized neoantigens nanovaccines have also shown promise in treatment of advanced pancreatic cancer [281].

Although cancer therapy faces numerous limitations, therapeutic nanovaccines offer effective alternatives or complements to conventional treatments, especially in combination with other modalities such as ICB therapy, PTT, PDT, chemotherapy, *etc.* [282–286] PD-1 checkpoint blockade immunotherapy is the primary method and synergistic with nanovaccines for cancer immunotherapy [287]. Su et al. reported on nanovaccines engineered to enhance efficacies of ICB, aiming to broaden repertoire of antitumor cells and increasing immune checkpoint expression levels to sensitize ICB [35]. These vaccines, by *co*-delivering *bi*-adjuvants (R848 and CpG) along with TSA to LN, successfully induced enduring antigen-specific T cell responses and immune memory. When combined with ICB, these nanovaccines demonstrate significant therapeutic effects in different mouse tumor models [288,289]. Besides, tandem nanovaccines with PD-1 checkpoint blockade immunotherapy

have also shown remarkable therapeutic effects in diverse cancer models, particularly when integrations of RT [89], chemo-immunotherapy [290], ultrasound [291], PTT [292], and PDT [293]. Although therapeutic nanovaccines have demonstrated immense potential through formulation of effective antigens and their synergistic interactions with existing therapies, therapeutic efficacies of nanovaccines across various models and practical considerations of treatment strategies in clinical applications necessitate further assessment.

5. Conclusions and perspectives

The last decade has witnessed a shift from a focus on cytotoxic anticancer therapies towards approaches that increase anti-tumor immunity, as emerging immunotherapy shows promise in extending survival of patients [294]. As a subtype of cancer immunotherapy, nano-based cancer vaccines have gained significant momentum owing to their advantage of size and proximity to pathogens as well as their controllable physicochemical and biophysical properties. A remarkable characteristic of nanovaccines lies in their exceptional diversity and tunability, which is engineered with various morphologies such as hollow, core-shell, nanosheet, micelle, nanogel, vesicle-like, nanodisc, and virus-like [295]. These inherent characteristics bestow nanovaccines with notable targeting capabilities, prolonged bio-persistence, highly efficient transport capabilities, safeguarding of antigens against degradation, and potential for long-term therapeutic efficacy. Individualized nanovaccines, when laden with antigens and/or adjuvants, tend to accumulate within LN *via* LV. This distinctive accumulation pattern serves as a mitigation strategy against risks linked to leaky tumor vasculature, impaired lymphatic drainage, and potential off-target effects [296]. Furthermore, tailored targeting nanovaccines are encapsulated or conjugated with antigens and/or adjuvants that exhibit targeting recognition capabilities for immune cells. As a result, a diverse range of nanovaccines has been meticulously-designed and deployed to passively or actively target different immune cell populations [297]. This strategic targeting aims to enhance antigen presentation and modulate immunosuppression upon accumulation within LN. Consequently, these nanovaccines contribute to eradication of tumor cells, augmentation of the immune response, mitigation of TME resistance development, and inhibition of cancer recurrence [298]. Considering complexity of the TME during tumor development, prophylactic and/or therapeutic nanovaccines are always combined with radiotherapy, ICB, PDT, PTT, and other therapeutic modalities to further magnify immune responses and generate sufficient long-lasting immune memory [266,292,299,300]. Overall, nanovaccines with design flexibility have numerous inherent advantages as they are tailored to target various immune cells. These attributes not only position nanovaccines as a viable substitute for conventional cancer treatments but also establish them as valuable clinical tools for screening vaccines tailored to different types of cancer.

While nanovaccines represent a promising frontier in the field of personalized vaccines, there remain several formidable challenges that need to be addressed before their successful translation into clinical practice [288]. In nanovaccine formulation, it requires a precise architecture for effective immune cell engagement and stability, ensuring antigen to release and targeting circulating immune cells [16]. An integrated nanovaccine system, incorporating all vital components, is key to achieving varied therapeutic and diagnostic objectives in cancer treatment. In terms of nanovaccine fabrication, meticulous consideration and assessment of streamlined synthesis processes for purification of nanovaccines, coupled with minimizing use of organic solvents, are imperative. Synergy effects between immunotherapeutic agents and targeting carriers, in aspects of dosage and classification, are critical in securing efficacious therapeutic results. Second, toxicity assessment of the nanovaccines is currently in an incipient stage, and the long-term safety profile of these engineered nanovaccines demands further evaluation. Special attention should be directed towards potential emergence of the autoimmune responses. It is imperative to recognize that physicochemical properties of the nanoparticles may undergo alterations as they interact with various biological entities within human bodies; hence, an exhaustive examination of the final metabolites is warranted. Furthermore, there is a major hurdle to immunogenicity of the nanomaterial-based vaccines [301]. Nanovaccines exhibit antigenic characteristics but often face swift clearance prior to manifestation of their anti-tumor therapeutic efficacy. Not only that, a vigorous immune response may inadvertently precipitate severe complications, such as hemolysis and thrombogenesis [302]. Finally, limited knowledge of immune networks during tumorigenesis hinders widespread applications of the nanovaccines in cancer immunotherapy. Innate and adaptive immune systems are complex networks, and the influence of depletion or inhibition of one component on the entire network remains controversial [303].

Taken together, research progress in customized targeting nanovaccines lays a theoretical foundation for further development of novel cancer therapy options, and many excellent studies are exploring their potential in targeting and regulating/training immune cells. In the future, refinement of the nanovaccine design is likely to necessitate a closer alignment with clinical translation and the establishment of collaborative immune responses. This endeavor aims to enhance patient compliance by integrating diverse components (such as biepitope antigens) within the same nanosystem [304]. This multifaceted approach seeks to achieve precise targeting of distinct elements, controlled release mechanisms, and tailored treatments at various stages of the disease. Nanovaccine development is also set to be shaped by key advancements in precise immunomodulation, focusing on targeted interventions within TME to mitigate systemic toxicity. Exploration of the therapeutic synergies, combining nanovaccines with existing treatments like radiation therapy and checkpoint inhibitors, promises to amplify immune responses and enhance efficacy. Technological innovations, such as mRNA-based and STING-activating nanovaccines, are pivotal for improving vaccine performance and patient compliance. Critical to this progress is the clinical translation of nanovaccines, necessitating rigorous safety evaluations and the development of scalable, stable formulations. Moreover, addressing economic and accessibility barriers will broaden patient access to these advanced therapies. Collectively, vaccine nanotechnology has been demonstrated with significant promise in experimental investigations. Synergistic integration of expertise from nanomaterial science, immunology, virology, oncology, and pharmaceutical sector is pivotal for advancing clinical translation and implementation of nanovaccines. This collaborative approach is essential for effectively addressing and managing a spectrum of formidable infectious diseases and malignancies.

Ethical statement

Hereby, I Prof. Jin Zhang, consciously assure that for the manuscript entitled "**Engineering customized nanovaccines for enhanced cancer immunotherapy**" the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of coauthors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.

7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

CRediT authorship contribution statement

Jinyu Guo: Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Conceptualization. **Changhua Liu:** Writing – review & editing, Methodology. **Zhaoyang Qi:** Validation. **Ting Qiu:** Supervision. **Jin Zhang:** Supervision, Funding acquisition, Conceptualization. **Huanghao Yang:** Supervision.

Declaration of competing interest

The authors declare no conflict of interest.

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