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Bioactive Nanomaterials for Cancer Immunotherapy

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Abstract Cancer immunotherapy has revolutionized oncology by harnessing the immune system to recognize and eliminate malignant cells, yet its clinical efficacy is often limited by tumor immune evasion, low immunogenicity, and an immunosuppressive tumor microenvironment (TME). Recent advances in nanotechnology offer opportunities to overcome these barriers by precisely modulating both tumor and immune landscapes. In this review, we summarize three representative strategies developed by our group: (i) surface-adaptive nanomaterials (SANs), which respond dynamically to physiological and tumor-specific cues to enable prolonged systemic circulation, efficient barrier translocation, and controlled intratumoral activation; (ii) antigen-engineering nanoplatforms, designed to enhance tumor immunogenicity *via* delivering exogenous antigens to antigen-presenting cells (APCs), inducing tumor cells to re-express or re-generate, or anchoring immunogenic epitopes onto tumor surfaces, thereby promoting T cell activation and converting "cold" tumors into "hot" ones; and (iii) TME-modulating nanomaterials, which alleviate immune suppression *via* targeted delivery of inhibitors, neutralization or degradation of suppressive cytokines, and gene-level reprogramming of tumors to restore effector immunity. Together, these approaches provide a multifaceted framework for reinvigorating antitumor immune responses and offer mechanistic insights and design principles for the next generation of bioactive polymeric nanomaterials with potential translational application in cancer immunotherapy.

Keywords Bioactive nanomaterials; Cancer immunotherapy; Low immunogenicity; Immunosuppressive tumor microenvironment (TME); Physiological barriers

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INTRODUCTION

Cancer remains one of the most formidable challenges for global health and socioeconomic stability.[1,2] According to the Global Cancer Observatory (GLOBOCAN), approximately 20 million new cases and 9.7 million deaths are reported worldwide in 2022, and the incidence is projected to exceed 30 million annually by 2040.[3] Despite significant advances in surgery, chemotherapy, and radiotherapy, the prognosis for many advanced cancers remains poor, particularly for metastatic or recurrent disease[4] underscoring the urgent need for more effective therapeutic strategies. Over the past decade, cancer immunotherapy has fundamentally transformed oncology by harnessing the immune system to recognize and eliminate malignant cells.[5,6] Unlike cytotoxic or targeted therapies that act directly on tumors, immunotherapy restores and amplifies the intrinsic capacity of the body for tumor surveillance and eradication.[7] A pivotal breakthrough came with the discovery of immune checkpoint inhibition, for which James P. Allison and Tasuku Honjo were awarded the 2018 Nobel Prize in Physiology or Medicine.[8,9] By uncovering how tumors exploit inhibitory pathways such as cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) to evade immune attack, this discovery led to the development of checkpoint inhibitors,[10] including ipilimumab, nivolumab, pembrolizumab, and atezolizumab, which have achieved unprecedented success in melanoma, lung cancer, and renal cell carcinoma.[11,12] Beyond checkpoint blockade, other immunotherapeutic strategies, including chimeric antigen receptor T-cell (CAR-T) therapy, cancer vaccines, oncolytic viruses, and cytokine-based therapies, have produced durable remissions in various refractory malignancies.[13,14] Collectively, these breakthroughs have opened a new era in cancer treatment, offering durable, systemic, and specific antitumor effects once considered unattainable.[15,16]

Despite these achievements, the overall response rate to immunotherapy remains low.[17] Approximately 80% of patients either fail to respond or eventually develop resistance,[18] while systemic immune activation can cause immune-related adverse events (irAEs) such as colitis, dermatitis, pneumonitis, and endocrinopathies.[19] These challenges highlight the intricate interplay between tumors, therapeutic agents, and the immune system, emphasizing the need to enhance both efficacy and safety. Obstacles to effective immunotherapy are multifactorial, encompassing both biological and physicochemical barriers. Physiologically, the

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body presents multiple delivery barriers, including the vascular endothelium,[20] dense extracellular matrix,[21] elevated interstitial pressure, and protective interfaces, such as the blood-brain barrier and lymphatic stroma,[22,23] which collectively hinder the accumulation and retention of immune agents within solid tumors.[24] Tumor genetic heterogeneity and instability further compromise immune recognition by altering or masking tumor-associated antigens (TAAs), downregulating major histocompatibility complex (MHC) molecules, or deleting antigenic targets, thereby promoting immune escape and both primary and acquired resistance.[25,26] Moreover, tumors construct an immunosuppressive tumor microenvironment (TME) enriched with regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2-type tumor-associated macrophages (TAMs).[27,28] These cells secrete inhibitory cytokines (*e.g.*, interleukin-10, IL-10, transforming growth factor-β, and TGF-β) and contribute to metabolic dysregulation (*e.g.*, hypoxia, redox imbalance, pH reduction), creating a biochemical and physical fortress that restricts immune activation and cytotoxic infiltration.[29,30] Overcoming these barriers and reprogramming the immunosuppressive TME have therefore become central objectives in next-generation cancer immunotherapy.

Recent advances in nanoscience and material engineering have offered promising strategies to address these challenges.[31,32] Nanomaterials, with their tunable physicochemical properties, high loading capacity, and ability to interact with biological systems at the molecular level, provide unique opportunities to enhance the efficacy and safety of immunotherapy.[33–35] Over the past decade, our research group has been dedicated to developing bioactive nanomaterials capable of overcoming immunological and physiological barriers that limit cancer immunotherapy. In this review, we systematically summarize three representative strategies developed by our group (Fig. 1). (1) Developing surface-adaptive nanomaterials (SANs) that dynamically adjust their physicochemical properties (*e.g.*, pH, enzyme, or redox responsiveness) to traverse multiple physiological barriers, thereby enhancing tumor targeting and minimizing off-target effects; (2) Developing antigen-engineering nanoplatforms that either deliver exogenous antigens to antigen-presenting cells (APCs) or induce tumor cells to express or expose novel antigens, thereby enhancing tumor immunogenicity, promoting dendritic cell (DCs) maturation, and converting "cold" tumors

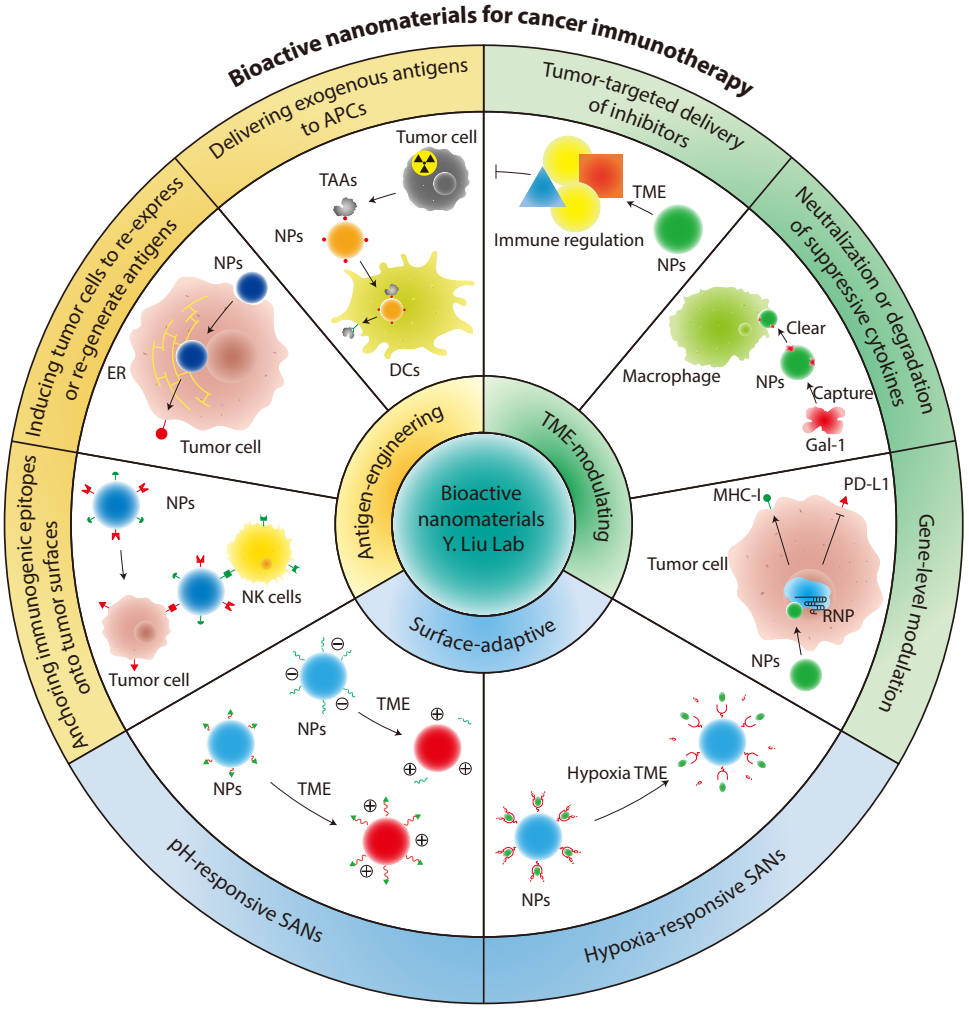

Fig. 1 Schematic illustration of bioactive nanomaterials developed by our group for enhanced cancer immunotherapy.

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into "hot" ones responsive to immunotherapy; (3) Constructing TME-modulating nanomaterials that alleviate or reverse immune tolerance within the TME by depleting immunosuppressive cell, reprogramming macrophage polarization, or neutralizing inhibitory cytokines, ultimately restoring a proinflammatory, immune-active milieu that enhances T-cell infiltration and cytotoxicity. Together, these strategies offer a multifaceted approach for reinvigorating antitumor immunity. In the following sections, we integrate mechanistic insights and representative studies from our group's work to illustrate these principles, and propose conceptual frameworks and design strategies for the next generation of bioactive polymeric nanomaterials in cancer immunotherapy, highlighting their translational potential for clinical application.

SURFACE-ADAPTIVE NANOMATERIALS (SAN) FOR EFFICIENT TRANSLOCATION ACROSS MULTIPLE PHYSIOLOGICAL BARRIERS

Systemic administration of immune agents to exert antitumor effects within tumor tissues involves a complex series of biological processes. Among them, two steps are particularly critical: (1) maintaining stable circulation in the bloodstream to prevent premature clearance and unintended immune activation[36] and (2) achieving prolonged retention and potent immune activation within the TME.[37] These contradictory requirements, being inert and stealthy in circulation but active and interactive within the tumor, pose significant challenges for the design of immune therapeutics, often resulting in suboptimal efficacy and potential systemic toxicity.[38] To address this dilemma, our group proposed the construction of SANs capable of dynamically tuning their surface properties in response to distinct physiological cues. These nanocarriers were designed as core-shell structures that encapsulate immune payloads in the inner core, whereas the outer shell is composed of stimuli-responsive polymers capable of detachment or structural transformation under specific TME conditions. In the bloodstream, the hydrophilic outer layer minimizes nonspecific interactions between plasma proteins and immune cells, thereby prolonging circulation and avoiding off-target immune activation. Upon reaching the tumor site, environmental stimuli such as acidity, redox gradients, or enzymatic activity trigger transformation or shedding of the outer layer, leading to enhanced tumor retention and efficient immune activation.

pH-Responsive SANs

Among the various TME features, tumor acidity is one of the most universal and well-characterized hallmarks. The acidic microenvironment (pH=6.5–6.8) originates from the elevated glycolytic metabolism of tumor cells, known as the Warburg effect, which produces excessive lactic acid and protons.[39,40] This unique biochemical feature provides an exploitable trigger for the design of pH-responsive, surface-adaptive nanomaterials that undergo tumor-selective activation. Among the diverse acid-labile moieties, 2,3-dimethylmaleic anhydride (DMMA)[41] has been extensively utilized because of its ability to undergo a pH-dependent ring-opening reaction with primary amines, yielding negatively charged carboxyl groups. Under physiological pH conditions, DMMA modification imparts a negative surface charge, conferring colloidal stability, and minimizing nonspecific interactions. However, in a mildly acidic TME, DMMA rapidly hydrolyzes, leading to charge reversal from negative to positive, which promotes electrostatic interactions with cellular membranes and enhances tumor-specific uptake.[42,43] Leveraging this property, we designed a multistage delivery nanoparticle (MDNP) for tumor-targeted gene delivery (Table 1).[44] In this construct, the therapeutic genes were first complexed with polyethyleneimine (PEI) to form a cationic inner core, which was then electrostatically coated with DMMA-modified poly(ethylene glycol)-*b*-polylysine to form a PEGylated core-shell architecture (Fig. 2). During systemic circulation, the PEG shell provides a hydrophilic "stealth" barrier, which prolongs blood retention and reduces immune clearance.[45] Upon encountering the acidic TME, DMMA cleavage induced charge conversion and electrostatic repulsion between the shell and core, resulting in PEG layer dissociation and exposure of the cationic inner core. This transformation facilitates strong adhesion to negatively charged tumor cell membranes, thereby enhancing cellular uptake, deep tumor penetration, and intratumoral retention. In parallel, we also employed other pH-responsive functional motifs, such as 2-propionic-3-methylmaleic anhydride (CDM)[46] and cis-aconitic anhydride (CA),[47] to construct analogous pH-sensitive SANs, which demonstrated efficient translocation across multiple physiological barriers and robust immune activation both *in vitro* and *in vivo*.

Beyond this "shell-shedding" strategy, we further developed a shell-retaining, surface-adaptive approach that allows for pH-responsiveness without disassembly. This method exploits the intrinsic physicochemical plasticity of certain polymers that are capable of reversible transitions in response to local stimuli. A representative system is based on poly(*β*-amino ester)-1-(3-aminopropyl) imidazole (PAE), a polymer that remains hydrophobic and electrically neutral at physiological pH, but becomes protonated, positively charged, and hydrophilic under mildly acidic conditions.[48] Taking advantage of this behavior, we synthesized poly(*ε*-caprolactone)-*b*-poly(*β*-amino ester) (PCL-*b*-PAE) and co-assembled it with poly(*ε*-caprolactone)-*b*-poly(ethylene glycol) (PCL-*b*-PEG) under mildly acidic conditions to form mixed-shell polymeric micelles (Fig. 3).[49,50] At physiological pH, deprotonated PAE collapses between the hydrophobic PCL core and hydrophilic PEG shell, yielding a neutral or slightly negative surface that resists protein adsorption and immune recognition. Within the acidic TME, PAE becomes protonated and hydrophilic, leading to outward extension of the PAE chains and intermixing with the PEG corona. This dynamic rearrangement reverses the surface charge from negative to positive, enabling nanocarriers to transition from a stealthy to an adhesive state that enhances tumor retention and cellular uptake *via* electrostatic interactions. Building on this concept, we further exploited the hydrophobic PCL core and interfacial domains of the mixed shell to encapsulate immune-regulatory molecules, including adjuvants, antigens, and cytokines. The resultant pH-responsive SANs exhibited excellent circulation stability and minimal systemic toxicity while achieving potent *in situ* immune activation within tumor tissues, providing an effective and safe platform for cancer immunotherapy.

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Table 1 Bioactive nanomaterials for effective cancer immunotherapy.

Nanomaterial	Strategy	Tactic	Payload	Function	Ref.
Multi-stage delivery nanoparticle (MDNP)	Overcome multiple biological barriers	pH-responsive-based surface adaptive	CRISPR/dCas9-miR-524	Upregulate miR-524 expression in tumors	[44]
Mixed-shell polymeric micelles (MSPMs)	Overcome multiple biological barriers	pH-responsive-based surface adaptive	Diverse immune-regulatory molecules	Facilitate immune activation and overcome immunosuppression	[50]
Macrocyclic host	Overcome multiple biological barriers	Hypoxia-responsive-based surface adaptive	PTX/NLG919/DOX /HCQ/MMC/CPT	Facilitate immune activation and overcome immunosuppression	[54]
NK cell-activating nano-immunomodulator (NK-IMN)	Amplifying tumor immunogenicity	Anchoring immunogenic epitopes onto tumor surfaces	Function through surface modification	Facilitate the recognition of tumor cells by NK cells	[61]
TAMs-activating nano-immunomodulator (TAM-IMN)	Amplifying tumor immunogenicity	Anchoring immunogenic epitopes onto tumor surfaces	Function through surface modification	Facilitate the recognition of tumor cells by macrophages	[64]
Nano-formulated ICD inducer (nanoICD)	Amplifying tumor immunogenicity	Re-express or re-generate immunogenic antigens	Function through surface modification	Accumulate in ER to induce ER stress and activate ICD-associated antitumor immunity	[69]
Lysosome-targeted aggregation nanoplatform (LTANP)	Amplifying tumor immunogenicity	Re-express or re-generate immunogenic antigens	Function through surface modification	Accumulate in lysosome to activate ICD-associated antitumor immunity	[71]
Heat shock protein (HSP)-inspired nanochaperone (nChap)	Amplifying tumor immunogenicity	Facilitate antigens transport into APCs	OVA/R848	Delivering OVA and facilitate APCs maturation	[73]
Antigen-capturing stapled liposome (ACSL)	Amplifying tumor immunogenicity	Facilitate antigens transport into APCs	L-arginine	Delivering antigens and facilitate antigen presentation	[75]
Multifunctional nanomodulator (MFNM)	TME-modulating	Tumor-targeted delivery of inhibitors	Anti-PD-L1 antibodies	Prevent T cell exhausting by disrupting PD-1/PD-L1 binding	[81]
Nanoscale coordination polymers (NCPs)	TME-modulating	Tumor-targeted delivery of inhibitors	4-phenylimidazole (4PI), NLG919	Inhibit IDO-1 activity and restore T-cell function	[84]
Antibody-like polymeric nanoparticle (APN)	TME-modulating	Neutralization or degradation of suppressive cytokines	Function through surface modification	Facilitate macrophage-mediated removal of Gal-1	[86]
Bifunctional lysosome-targeting chimeras (NLTCs)	TME-modulating	Neutralization or degradation of suppressive cytokines	Function through surface modification	Facilitate PD-L1 degradation	[87]
Nanocapsule (Cas9NC)	TME-modulating	Gene-level modulation	RNP	Knockdown CD47 to restore macrophage phagocytic activity	[90]
Dual-locking nanoparticle (DLNP)	TME-modulating	Gene-level modulation	CRISPR/Cas13a pDNA	Specifically killing PD-L1 high tumor cells	[91]
Dual-activatable binary CRISPR nanomedicine (DBCN)	TME-modulating	Gene-level modulation	CRISPR/dCas9 pDNA	Upregulate MHC-I expression	[93]

Hypoxia-responsive SANs

In addition to pH-responsive SANs, we developed hypoxia-responsive molecular containers for tumor-targeted delivery of immunomodulators, particularly small-molecule immune regulators. Hypoxia resulting from insufficient oxygen supply is a defining hallmark of most solid tumors. It arises when the rapid proliferation of tumor cells outpaces the development of functional vasculature, leading to an imbalance between oxygen consumption and delivery. The consequent hypoxic regions profoundly affect tumor metabolism, angiogenesis, and immune suppression.[51,52] Among the various hypoxia-sensitive moieties, azo bonds have been widely exploited because they undergo selective cleavage under reductive conditions, catalyzed by azoreductase enzymes overexpressed in hypoxic tumor tissues.[53] Leveraging this property, we incorporated azo linkages into the backbone of macrocyclic host molecules, thereby constructing a family of hypoxia-responsive molecular containers capable of precise loading and controlled release in tumor tissues. For instance, we rationally designed an amphiphilic macrocyclic host, quaternary ammonium-modified azocalix[4]arene dodecyloxy ether (QAAC4A-12C),[54] by modifying the upper rim of aminocalix[4]arene pentadodecyl ether (NH2C4A-12C) with azophenyl and quaternary ammonium groups. QAAC4A-12C possesses spacious internal cavities decorated with multivalent quaternary ammonium groups along its macrocyclic rim (Fig. 4). Through combined electrostatic attraction, hydrogen bonding, and hydrophobic interactions, QAAC4A-12C stably encapsulates diverse small-molecule drugs and immune regulators (*e.g.*, paclitaxel, PTX; NLG919), maintaining them in an inert and shielded state during systemic circulation to prevent premature activation. Upon entry into the hypoxic TME, the azo bonds undergo enzymatic cleavage, resulting in disassembly of the macrocyclic framework and loss of host-guest interactions. This structural disruption triggers spatiotemporally controlled drug release within hypoxic tumor regions, thereby achieving localized immune activation while minimizing systemic side effects. We further modified the upper rim of the aminocalix[4]arene (NH2C4A-12C) with azophenyl, carboxyl, and sulfonic acid groups, resulting in carboxylated azocalix[4]arene (CAC4A) and sulfonate azocalix[4]arenes (SAC4A). These molecular containers maintained excellent stability in the bloodstream and enabled the hypoxia-triggered precise release of doxorubicin (DOX), hydroxychloroquine (HCQ), mitomycin C (MMC), and camptothecin

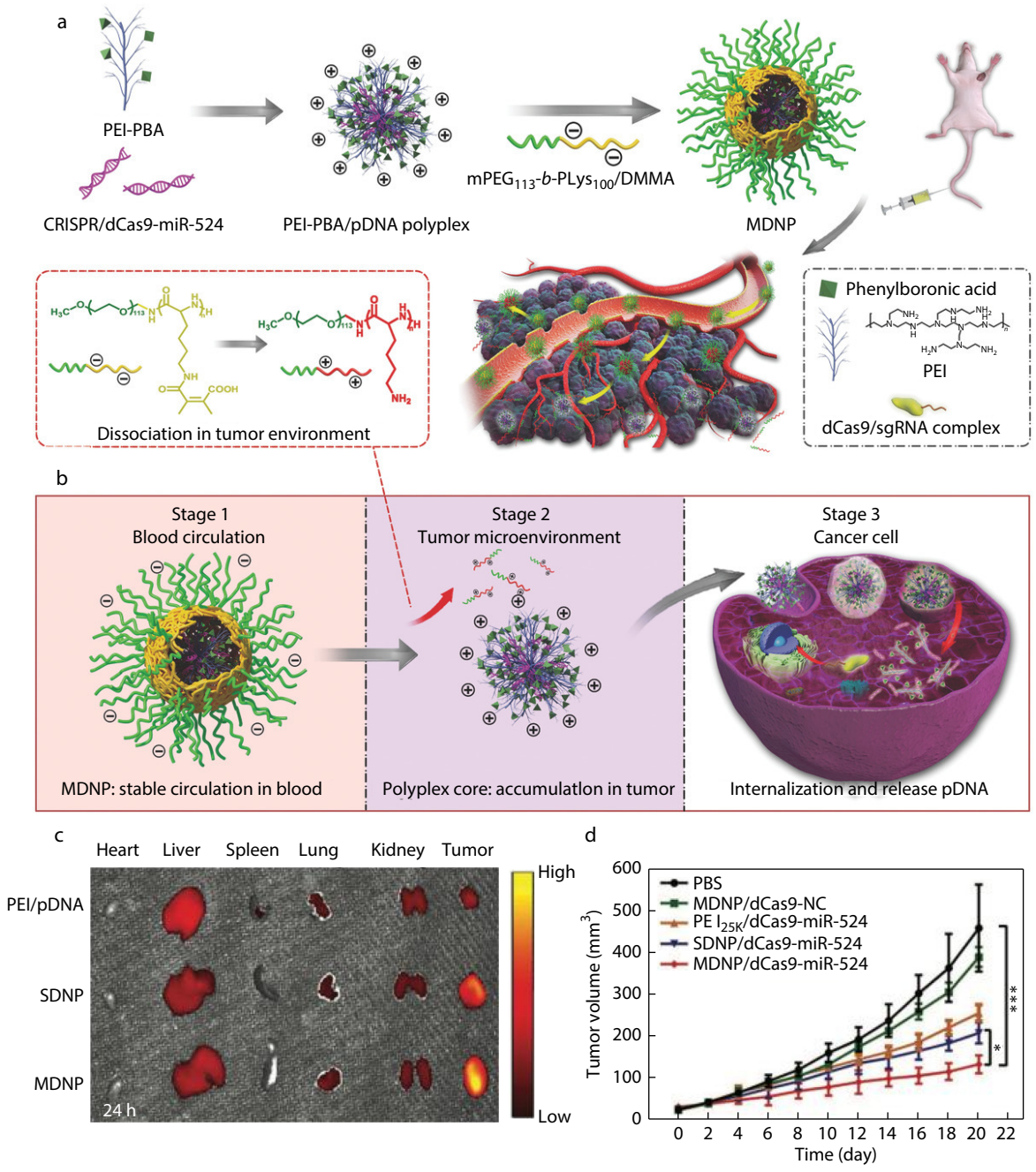

Fig. 2 Multistage delivery nanoparticle (MDNP) facilitates tumor-targeted delivery of CRISPR/dCas9 and efficient tumor suppression. (a) The preparation of MDNP; (b) Multistage delivery of CRISPR/dCas9 system from bloodstream to tumor cells *via* MDNP; (c) *Ex vivo* biodistribution of MDNP; (d) Antitumor efficacy of MDNP in 231-bearing mice. Statistical significance was analyzed by two-way ANOVA with Tukey's multiple comparisons test. *p<0.05 and ***p<0.001. (Reproduced with permission from Ref. [44], Copyright (2018), Wiley) (The online version is colorful.)

(CPT). This strategy significantly enhanced antigen presentation, DC maturation, and activation of T cell-mediated antitumor immunity without causing substantial systemic toxicity.

ANTIGEN-ENGINEERING NANOPLATFORMS TO AMPLIFY TUMOR IMMUNOGENICITY

A major challenge in cancer immunotherapy is the inherently low immunogenicity of tumors, which limits the ability of the immune system to recognize and eliminate cancer cells.[55] This low immunogenicity arises from several factors, including antigenic heterogeneity, where genetic instability generates subpopulations of tumor cells that variably express or completely lack tumor-associated antigens (TAAs).[56] In addition, tumors frequently downregulate antigen-presenting molecules such as major histocompatibility complex (MHC), rendering them invisible to cytotoxic T lymphocytes (CTLs).[57] Consequently, insufficient immune recognition enables tumors to evade immune

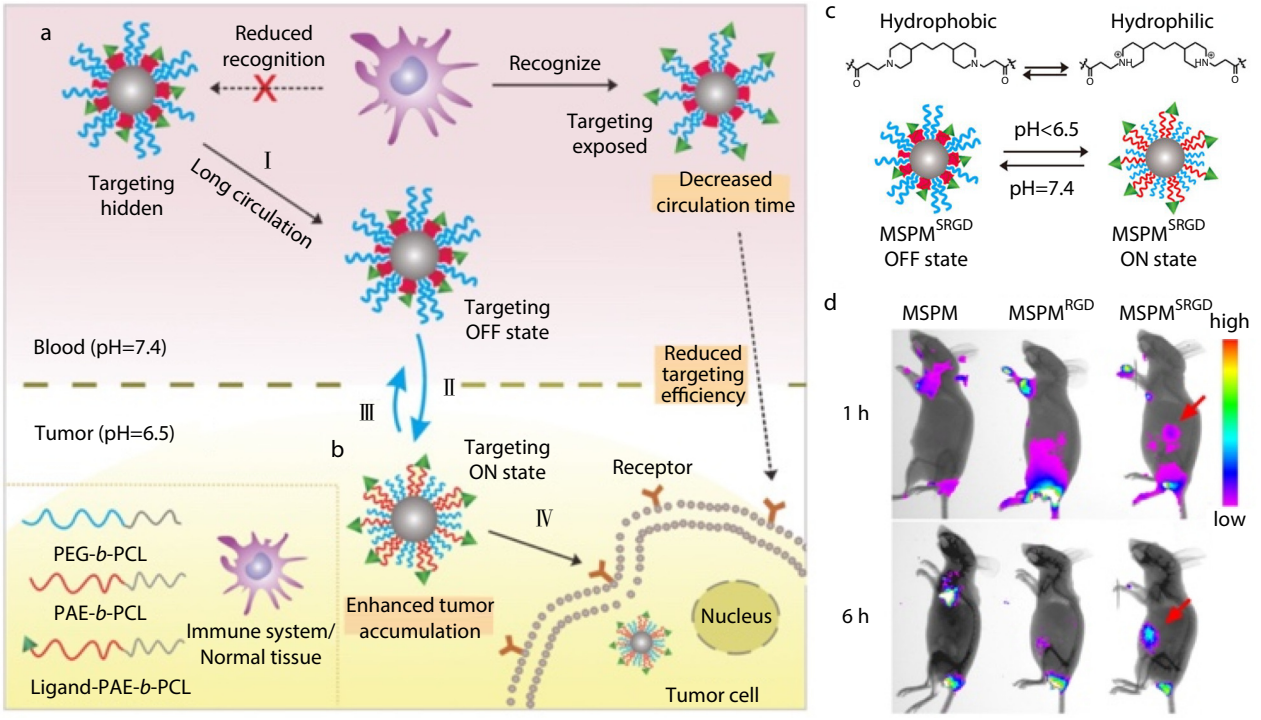

Fig. 3 Mixed-shell polymeric micelles (MSPMs) for prolonged blood circulation and enhanced tumor targeting. (a) MSPMs shielded targeting ligands during blood circulation to avoid undesired immune clearance; (b) MSPMs expose targeting ligand upon reaching tumor tissues to facilitate tumor-targeted drug delivery; (c) Structure transformation of MSPM from pH=6.5 to pH=7.4; (d) Biodistribution of MSPM in HepG2 tumor-bearing nude mice. (Reproduced with permission from Ref. [50], Copyright (2018), ACS) (The online version is colorful.)

surveillance and severely compromises the efficacy of immunotherapies that depend on robust immune activation. To address this challenge, our group developed three complementary strategies aimed at enhancing tumor immunogenicity and overcoming immune evasion: (1) anchoring immunogenic epitopes onto tumor surfaces to restore immune visibility; (2) stimulating tumor cells to re-express or generate immunogenic antigens; and (3) transporting antigens into APCs to promote efficient antigen presentation and T-cell activation. The following sections elaborate the design and mechanisms of these three strategies.

Anchoring Immunogenic Epitopes onto Tumor Surfaces

Inspired by dental implantation, where a missing tooth is replaced with an artificial tooth to restore function, we envisioned an analogous strategy to "seeding" immune-recognizable antigens onto the tumor surface, thereby restoring their visibility to immune cells. To achieve this, the designed nanomaterials must (i) specifically recognize tumor cells, (ii) stably anchor to the tumor cell membrane, and (iii) seed immunogenic epitopes capable of recruiting and activating immune cells for tumor destruction. Fulfilling these requirements necessitates the precise control of nanomaterial surface chemistry. To this end, our group has developed a controllable polymerization method that enables *in situ* polymer growth on protein surfaces, producing nanostructures with uniform size, tunable dimensions, and adjustable interfacial properties. Guided by this strategy, we engineered multifunctional nanomaterials integrating three essential motifs: tumor recognition, anti-endocytosis, and immune-activation domains, thereby achieving effective antigen anchoring and promoting immune-mediated tumor eradication.

Natural killer (NK) cells, as key effectors of the innate immune system, provide rapid and potent antitumor defenses without prior sensitization. They recognize activating ligands on tumor cells *via* receptors such as NKG2D, NKp30, and NKp46, and induce cytotoxicity through perforin and granzyme release.[58,59] However, many solid tumors evade NK cell surveillance by downregulating activating ligands (*e.g.*, MICA/B and ULBPs) or upregulating inhibitory molecules (*e.g.*, PD-L1 and HLA-E).[60] To reestablish NK-tumor cell communication, we rationally designed an NK cell-activating nano-immunomodulator (NK-IMN) through the co-polymerization of phenylboronic acid (PBA), acrylamide (AAm), and immunoglobulin G (IgG) on a bovine serum albumin (BSA) template (Fig. 5).[61] Upon reaching tumor tissues, NK-IMN binds selectively to tumor cells *via* PBA-sialic acid residue (SA) interactions, whereas AAm suppresses endocytosis, ensuring stable membrane anchoring. Surface-anchored IgG acts as an artificial activating ligand "seeded" onto the tumor membrane, engaging CD16 receptors on NK cells to trigger potent NK-mediated cytotoxicity. This strategy effectively reactivated NK cell-mediated antitumor immunity, leading to the marked inhibition of tumor growth, metastasis, and recurrence in 4T1 tumor-bearing mouse models.

In addition to NK cell activation, we sought to enhance antigen presentation by tumor-associated macrophages (TAMs), the dominant immune population in many solid tumors. Although TAMs possess intrinsic antigen-presenting ca-

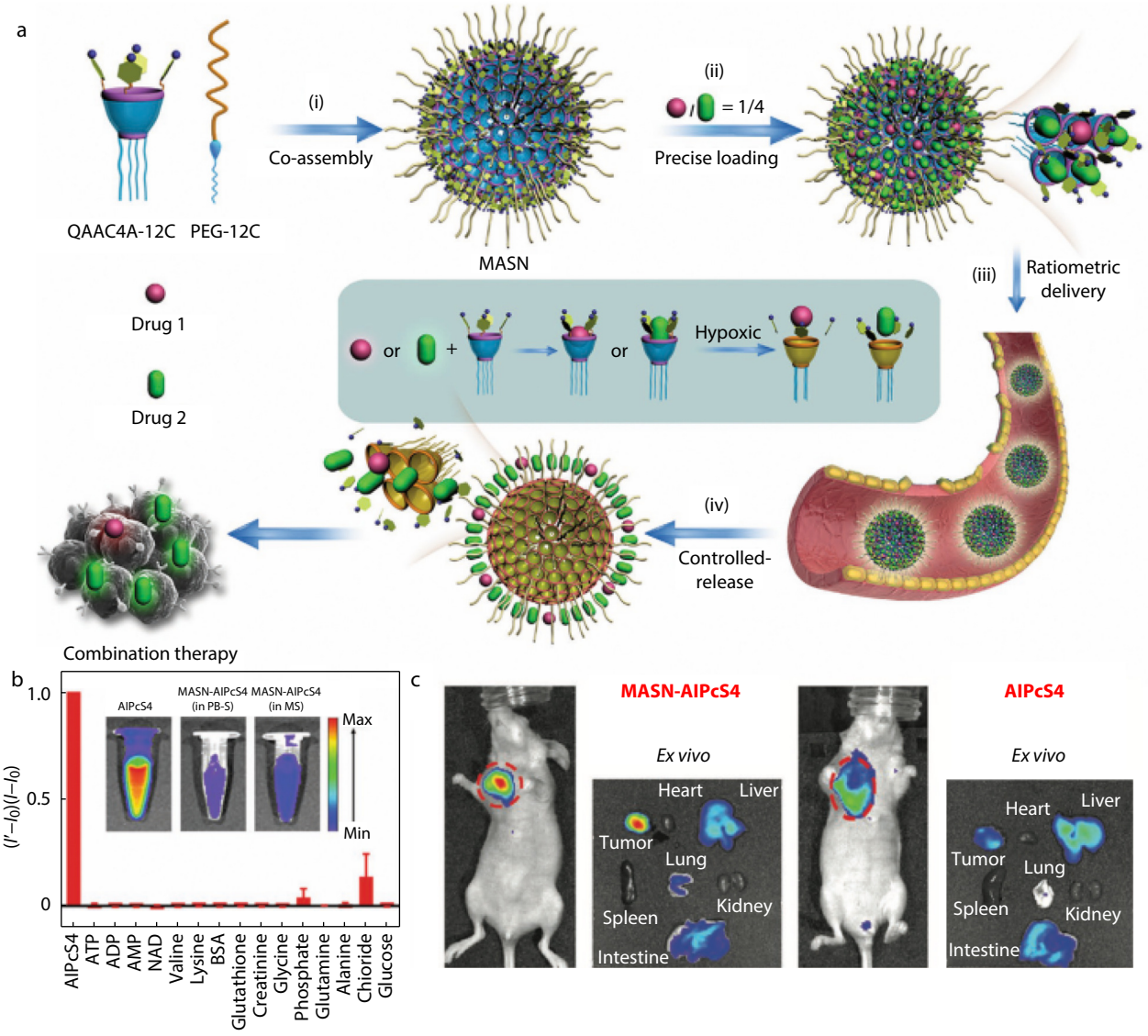

Fig. 4 Hypoxia-responsive quaternary ammonium-modified azocalix[4]arene dodecyloxy ether (QAAC4A-12C) for ratiometric delivery of therapeutic combinations to tumors. (a) Schematic representation of QAAC4A-12C for precise drug loading and ratiometric co-delivery; (b) QAAC4A-12C maintain stability in the presence of various blood components; (c) QAAC4A-12C achieves tumor-targeted delivery of antitumor drugs. (Reproduced with permission from Ref. [52], Copyright (2021), Wiley) (The online version is colorful.)

pacity, tumor cells frequently upregulate "don't-eat-me" signals such as CD47 or PD-L1, thereby suppressing phagocytosis.[62,63] To overcome this, we designed a TAM-activating nano-immunomodulator (TAM-IMN) by co-polymerizing PBA, AAm, and 2-(*α*-d-mannopyranosyloxy)ethyl acrylate (manEA) on a BSA template.[64] Within tumor tissues, TAM-IMN effectively binds to tumor cells through the PBA-SA interaction and stably anchors manEA on the tumor cell membrane. Exposure to manEA facilitates TAMs recognition and phagocytosis through manEA-CD206 interactions, leading to significantly enhanced antigen presentation and robust activation of T cell-mediated antitumor immunity. Similarly, by substituting PBA with c-MET-binding peptides (CMPs) and manEA with Tuftsin-M2 fusion peptides, the resulting TAM-IMN demonstrated comparable antigen seeding efficacy and substantially promoted antigen presentation and immune activation in a B16F10 melanoma mouse model.

Re-express or Re-generate Immunogenic Antigens

Stimulating low-immunogenic tumor cells to re-generate or "grow" antigens represents another effective strategy to counter immune evasion and restore recognition.[65] Under stressful conditions, tumor cells can upregulate or re-express certain antigens. Among the various stress responses, endoplasmic reticulum (ER) stress plays a central role in enhancing tumor immunogenicity. Sustained ER stress can induce immunogenic cell death (ICD), a form of regulated cell death characterized by calreticulin (CRT) translocation to the plasma membrane and release of damage-associated molecular patterns (DAMPs) such as adenosine triphosphate (ATP) and high mobility group box 1 (HMGB-1).[66,67] These immunogenic signals recruit and activate APCs, with CRT serving as an "eat-me" signal recognized by low-density lipoprotein receptors (LDLR) on

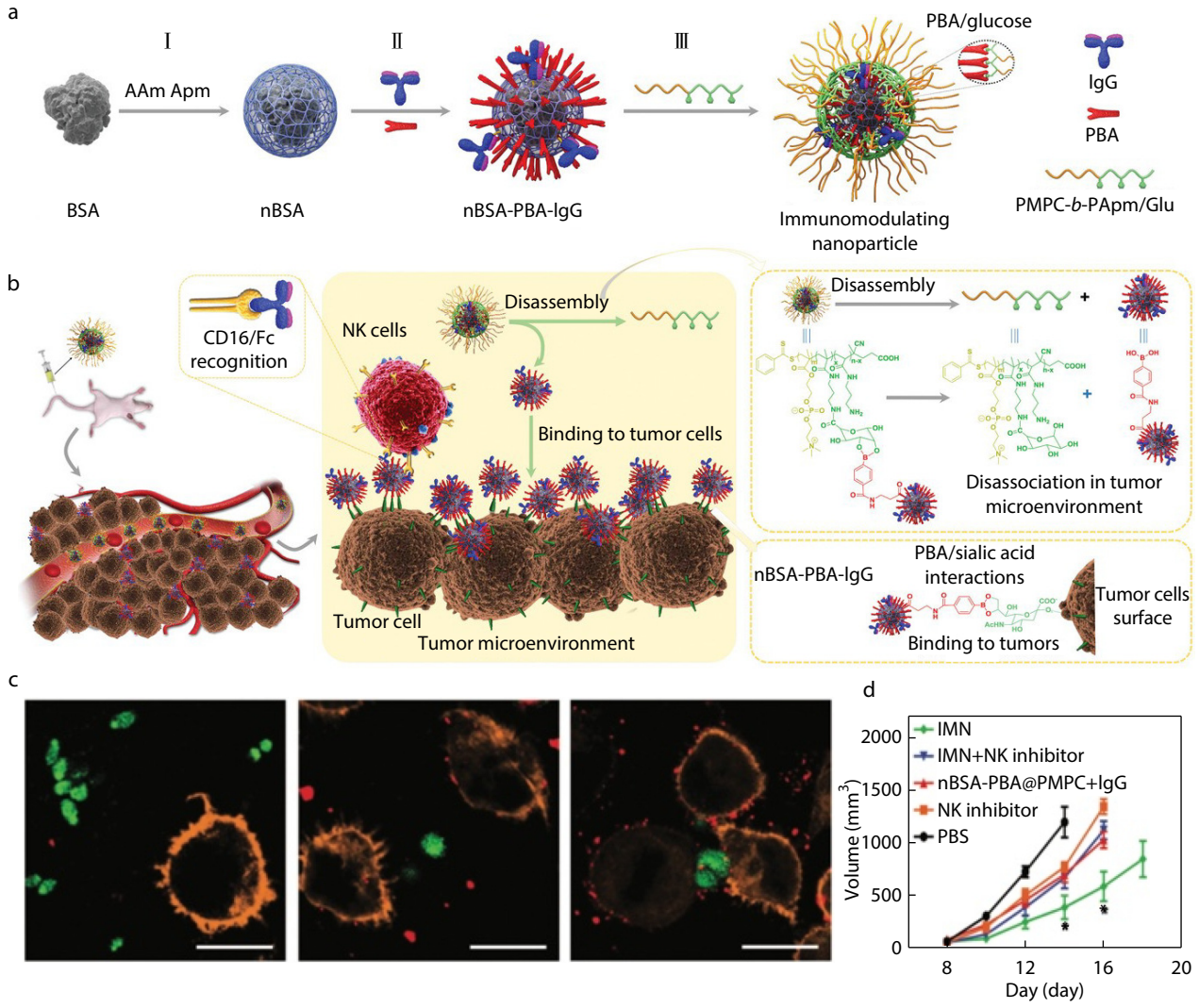

Fig. 5 Natural killer (NK) cells-activating nano-immunomodulator (NK-IMN) facilitate the NK cells-mediated recognition and clearance of tumor cells. (a) The synthesis of NK-IMN; (b) The mechanism of NK-IMN to seeding antigen on tumors to activate NK cells-mediated tumors destruction; (c) CLSM images showing the interaction of NK cells to tumor cells mediated by IMN, scale bar=20 μm; (d) Antitumor effect of IMN in 4T1-bearing mice. Statistical significance was analyzed by two-way ANOVA with Tukey's multiple comparisons test. *p<0.05. (Reproduced with permission from Ref. [61], Copyright (2019), Wiley) (The online version is colorful.)

APCs, thereby promoting efficient antigen capture and T-cell priming.[68] To exploit this mechanism, an effective ICD-inducing nanomaterial must achieve (i) efficient cellular uptake by tumor cells, (ii) rapid endosomal escape, and (iii) precise ER targeting for sustained stress signaling. To meet these criteria, we copolymerized cationic monomer *N*-(3aminopropyl)-methacrylamine (APm) and ER-targeting ligand *N*-(2-((4-methylphenyl) sulfonamido)ethyl)acrylamide (ETL) onto BSA, yielding a nanoformulated ICD inducer (termed nanoICD) (Fig. 6).[69] In tumor tissues, the APm motif facilitates cellular internalization and endosomal escape, whereas the ETL motif ensures ER localization and prolonged retention. This persistent ER interaction elicited pronounced ER stress, resulting in robust CRT exposure, over four times greater than that induced by PTX, and a substantial release of DAMPs. Consequently, the treated tumor cells became potent antigen sources for APCs, promoting antigen presentation and significantly strengthening the T cell-mediated antitumor immunity.

In addition to ER stress induction, targeted organelle disruption can promote antigen regeneration in tumor cells. In particular, induction of lysosomal membrane permeabilization (LMP) has emerged as a potent trigger of ICD.[70] Excessive accumulation of undegraded substances within lysosomes is a critical factor in LMP. Based on this mechanism, we designed a lysosome-targeted aggregation nanoplatform (LTANP) capable of inducing LMP and promoting antigen regrowth.[71] Specifically, two functional monomers were employed: (i) the mannose-6-phosphate ligand (M6PL) for active lysosomal targeting and (ii) 1-vinyl imidazole (VI) for pH-responsive protonation under acidic conditions. These monomers were copolymerized on the surface of BSA to fabricate LTANP. Upon internalization by tumor cells, LTANP was trafficked efficiently to lysosomes, where the acidic environment (about 4.5) triggered charge neutralization and

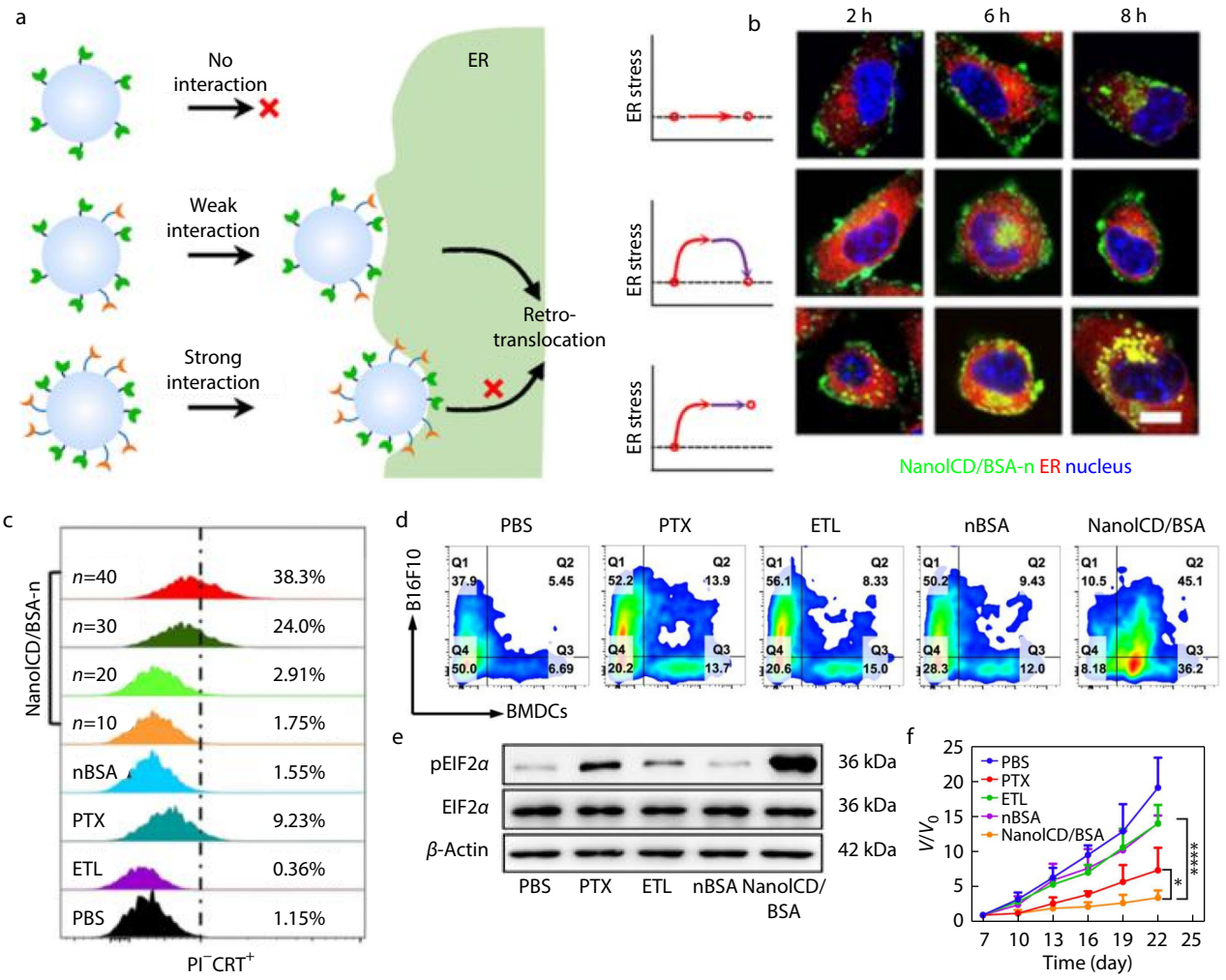

Fig. 6 NanoICD facilitate antigen growing on tumor surface. (a) The mechanism by which nanoICD induces ER stress; (b) Representative confocal images showing the intracellular distribution of nanoICD; (c) Flow cytometric showing the pre-apoptotic exposure of calreticulin (CRT) on cell surface; (d) NanoICD facilitate the phagocytosis of B16F10 cells by BMDCs; (e) Western blot analysis of *β*-actin, EIF2*α*, and pEIF2*α* in B16F10 cells after treated with PBS, PTX, ETL, nBSA, or nanoICD; (f) The growth kinetics of tumors in B16F10-bearing mice following different treatments. Statistical significance was analyzed by two-way ANOVA with Tukey's multiple comparisons test. *p<0.05 and ****p<0.0001. (Reproduced with permission from Ref. [69], Copyright (2024), The American Association for the Advancement of Science) (The online version is colorful.)

nanoparticle aggregation into micron-sized clusters. This aggregation prolonged LTANP retention within the lysosomes, leading to localized swelling and membrane permeabilization. LTANP elicited a cascade of immunogenic events, including robust CRT externalization and DAMPs release, thereby promoting antigen presentation and activating potent antitumor immunity in B16F10 melanoma-bearing mice.

Facilitate Antigens Transport into APCs

In addition to "antigen anchoring" and "antigen re-expression or re-growth, directly delivering TAAs into APCs offers an alternative and complementary strategy to enhance antitumor immunity.[72] For effective antigen delivery, nanomaterials must (i) efficiently encapsulate and protect antigens from premature degradation, (ii) selectively target APCs, particularly DCs, for uptake, and (iii) promote cytosolic antigen release for MHC-I cross-presentation. To fulfill these criteria, we developed a heat shock protein (HSP)-inspired nanochaperone (nChap) based on mannose-modified mixed-shell micelles.[73] nChap self-assembled from PCL-*b*-PAE and mannose-modified PCL-*b*-PEG. The hydrophobic microdomains within the micelles provided confined compartments for encapsulating the model antigen ovalbumin (OVA), whereas the PEG shell protected the loaded antigen from enzymatic degradation following subcutaneous administration. Guided by interstitial flow, nChap/OVA efficiently accumulated in draining lymph nodes and specifically targeted DCs *via* mannose-mannose receptor interactions. Once internalized, the mild proton-buffering capacity of PAE facilitates endosomal escape of the antigen, promoting its cytosolic release and enhancing MHC-I cross-presentation. nChap/OVA elicited potent T cell-mediated antitumor immunity and effectively prevented tumor metastasis and recurrence in mice.

Beyond *ex vivo* antigen loading, an alternative strategy is to capture tumor-released antigens *in situ* and deliver them directly to APCs. During tumor progression or upon therapeutic interventions, such as radiotherapy, large quantities of TAAs are released into the local microenvironment; however,

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these soluble antigens are often rapidly degraded or cleared before efficient uptake by APCs.[74] Therefore, constructing a nanoplatform capable of efficient antigen capture, targeted delivery to APCs, and promotion of antigen cross-presentation is critical for enhancing antitumor immunity. To this end, we developed an antigen-capturing stapled liposome (ACSL) by co-polymerizing maleimide (Mal), folic acid (FA), and 2-(hexamethyleneimino) ethyl methacrylate (C7A-MA) on the liposome surface (Fig. 7).[75] Upon intratumoral injection, ACSL effectively captured TAAs released from irradiated tumor cells *via* Mal-serine coupling, forming stable antigen–liposome conjugates. The FA moieties facilitated selective DC targeting through folate receptor-mediated uptake, ensuring precise delivery of the captured antigens. Within DCs, protonation of C7A triggered endosomal escape and cytosolic translocation of antigens, which were subsequently processed *via* the MHC-I pathway. This sequential process of in situ antigen capture, targeted delivery, and cytosolic cross-presentation robustly activates T cells and elicits systemic antitumor immunity, effectively suppressing both primary and metastatic tumor growth.

TME-MODULATING NANOMATERIALS TO RELIEVE IMMUNE TOLERANCE

Even when tumors are efficiently recognized by the immune system, immune effector cells often remain dysfunctional owing to suppressive signaling pathways, inhibitory cytokines, and immunoregulatory cell populations within the TME.[76] To overcome these barriers, our group developed three nanomaterial-based strategies aimed at alleviating immune tolerance and restoring robust antitumor immunity: (i) tumor-targeted deliv-

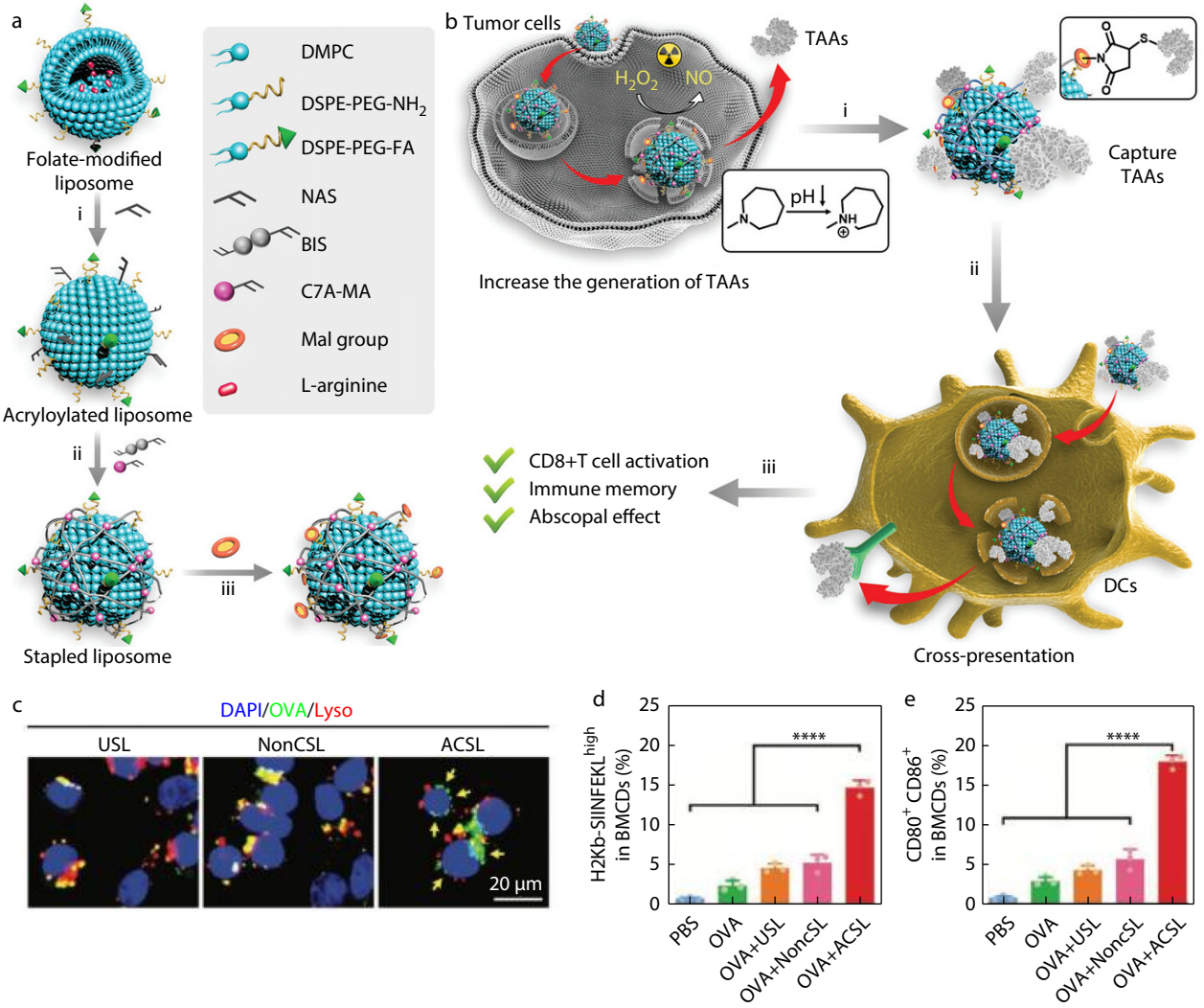

Fig. 7 Antigen-capturing stapled liposome (ACSL) enhanced tumor antigen cross-presentation for radio-immunotherapy. (a) Synthesis of ACSL; (b) Schematic illustration of ACSL for enhanced antigen cross-presentation. (i) Conjugation of *N*-acryloxysuccinimide (NAS) onto the surface of folate-modified liposomes. (ii) Polymerization of *N*,*N*′-methylenebisacrylamide (BIS) and 2-(hexamethyleneimino)ethyl methacrylate (C7A-MA) on the surface of acryloylated liposomes. (iii) Integration of maleimide (Mal) groups onto the surface of stapled liposomes *via* covalent chemistry to obtain the ACSLs; (c) ACSL facilitate cytosolic delivery of antigens; (d) ACSL facilitate antigen cross-presentation; (e) ACSL promotes BMDCs maturation. Statistical significance was analyzed by one-way ANOVA with Tukey's multiple comparisons test. ****p<0.0001. (Reproduced with permission from Ref. [75], Copyright (2021), Wiley) (The online version is colorful.)

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ery of inhibitors that block key immunosuppressive pathways; (ii) neutralization or degradation of suppressive cytokines, metabolites, or proteins that impair immune activation; and (iii) gene-level modulation to silence immunosuppressive signals or amplify immunostimulatory pathways. The following subsections summarize the design principles and mechanisms underlying each strategy.

Tumor-targeted Delivery of Inhibitors

Cytotoxic T lymphocytes (CTLs) are central to antitumor immunity,[77] yet their activity is markedly inhibited within the TME, where multiple suppressive pathways drive T-cell exhaustion.[78] Among these pathways, the PD-1/PD-L1 immune checkpoint axis is the most prominent. Tumors often overexpress PD-L1, and their interaction with PD-1 on T cells induces an anergic state that prevents effective tumor clearance.[79,80] Therefore, blocking PD-1/PD-L1 interactions is a key approach for reactivating T cell function. To achieve selective checkpoint blockade within tumors, we designed a multifunctional nanomodulator (MFNM) by decorating mesoporous silica nanoparticles with anti-PD-L1 antibody.[81] Leveraging the enhanced permeability and retention (EPR) effect, MFNM preferentially accumulates in tumor tissues and efficiently disrupts PD-1/PD-L1 binding. This targeted blockade restored CTL cytotoxicity and substantially strengthened the antitumor immunity. In addition to antibody-mediated checkpoint inhibition, reducing PD-L1 expression at the molecular level is an effective complementary strategy. We used the macrocyclic host SAC4A to encapsulate JQ-1, a bromodomain containing-4 (BRD4) inhibitor known to suppress PD-L1 transcription.[82] The SAC4A–JQ-1 complex exhibited excellent circulation stability in the bloodstream and released JQ-1 in response to tumor hypoxia, leading to marked downregulation of PD-L1 and enhanced T-cell–mediated tumor killing. In addition to checkpoint signaling, tumors also upregulate immunosuppressive factors to inhibit T-cell activation. One example is indoleamine-2,3-dioxygenase 1 (IDO-1), which depletes tryptophan and generates kynurenine metabolites that suppress T cell proliferation.[83] To counter this pathway, we developed nanoscale coordination polymers (NCPs) using 4-phenylimidazole (4PI) as the coordination node.[84] In the acidic TME, the NCPs disassembled and released 4PI, effectively inhibiting IDO-1 activity and restoring T cell function (Fig. 8). Similarly, we leveraged the SAC4A platform to deliver another potent IDO-1 inhibitor, NLG919, achieving targeted intratumoral release, pronounced tumor suppression, and significantly improved survival in 4T1 tumor–bearing mice.

Neutralization or Degradation of Suppressive Cytokines

During tumor progression, cancer and stromal cells secrete

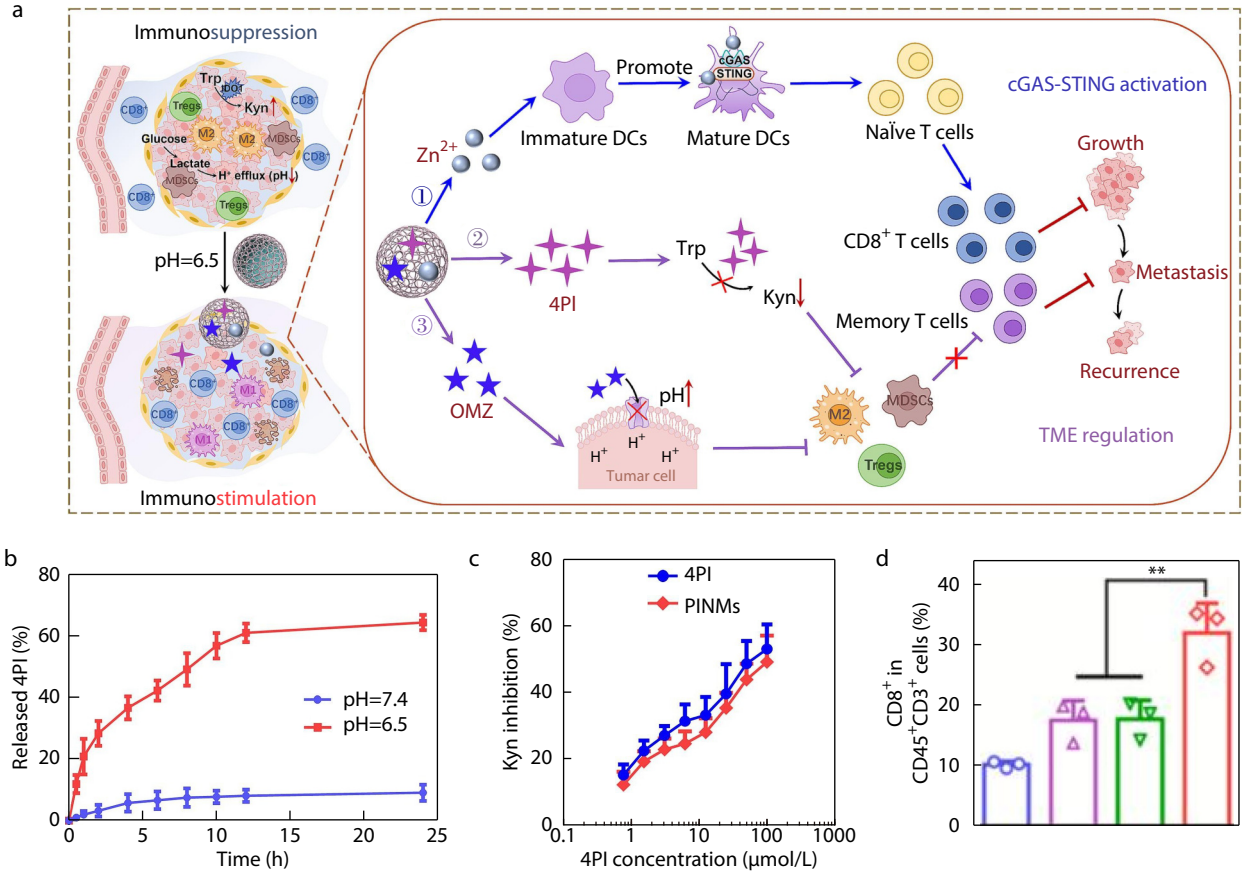

Fig. 8 Nano-immunomodulators (NCPs) inhibiting IDO-1 activity for enhanced cancer immunotherapy. (a) Schematic illustration of NCPs for immune-regulation; (b, d) NCPs effectively released 4-phenylimidazole (4-PI) under acidic conditions (b) to inhibit IDO-1 activity (c) and restore T-cell function (d). Statistical significance was analyzed by one-way ANOVA with Tukey's multiple comparisons test. $^{**}p<0.01$. (Reproduced with permission from Ref. [84], Copyright (2025), Elsevier) (The online version is colorful.)

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large amounts of inflammatory cytokines and immunosuppressive mediators that dampen antitumor immune responses.[85] Neutralizing or degrading these suppressive cytokines using nanomaterials has emerged as a promising strategy for restoring immune activation within the TME. Neutralizing antibodies block cytokine-receptor interactions by binding to specific cytokines and promoting immune clearance. Inspired by this mechanism, we developed an antibody-mimetic nanoplatform by integrating a galectin-1 (Gal-1)-binding ligand, targeting an immunosuppressive factor known to induce T cell apoptosis, together with the macrophage-targeting peptide (TKPR) onto the nanoparticle surface (Fig. 9).[86] This design enables selective binding to Gal-1 in tumor tissues and enhances its macrophage-mediated removal, ultimately reactivating T-cell immunity in the B16F10 melanoma model. In addition to neutralization, directing suppressive cytokines toward intracellular degradation provides an effective alternative. To enable selective cytokine capture and subsequent lysosomal degradation, we designed bifunctional lysosome-targeting chimeras (NLTCs) by incorporating extracellular protein–binding ligands with lysosome-targeting motifs into nanoparticles.[87] Using anti-dinitrophenol (*α*-DNP) as a model protein, NLTCs efficiently mediated lysosomal trafficking and degradation without inducing lysosomal escape. This strategy provides a new conceptual framework for elimi-

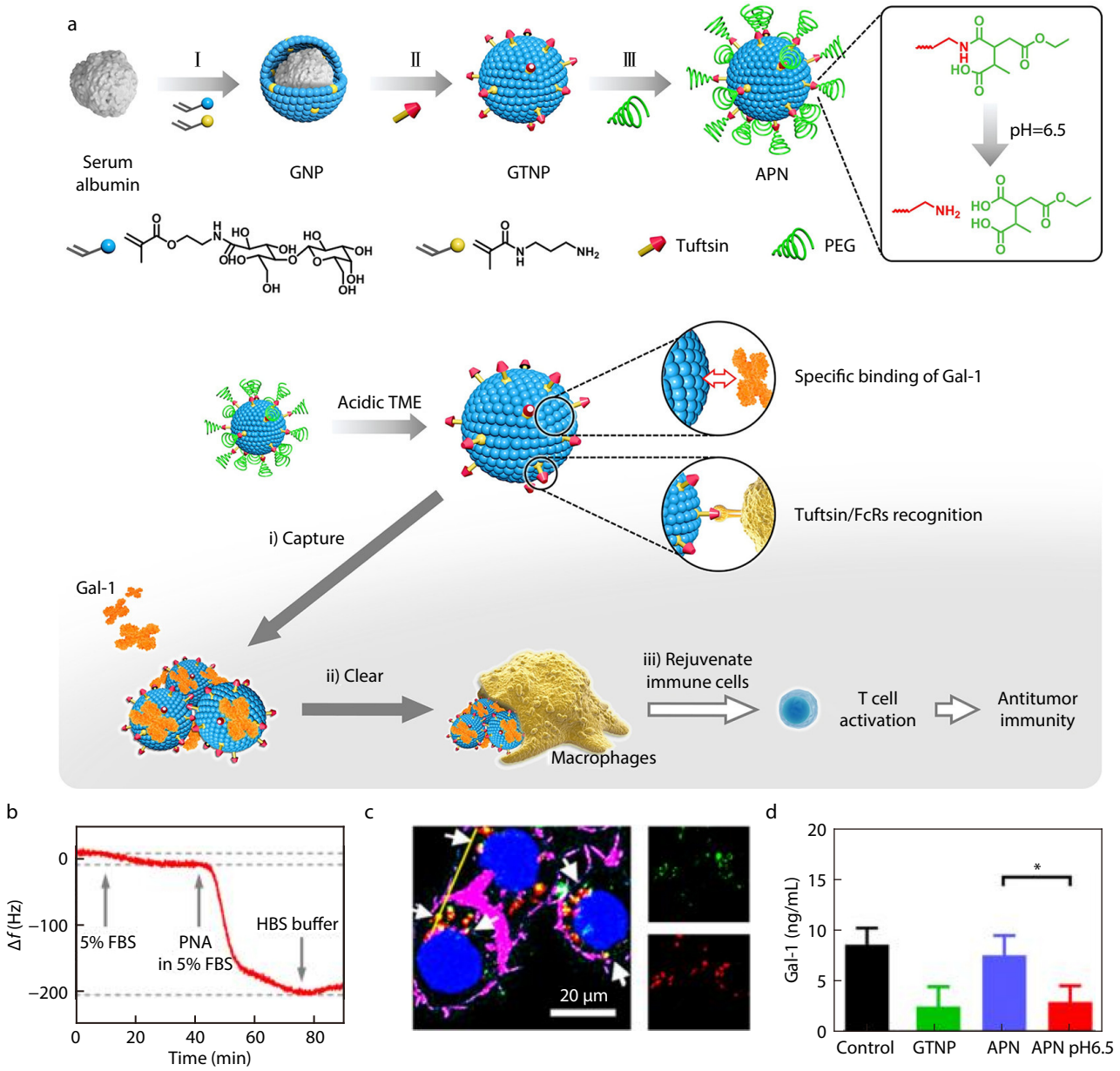

Fig. 9 Antibody-like polymeric nanoparticle (APN) facilitates the removal of intratumoral galectin-1 (Gal-1) for enhanced cancer immunotherapy. (a) Schematic illustration of APN to remove Gal-1 in tumor tissues; (b) Quartz crystal microbalance with dissipation monitoring (QCM-D) demonstrate APN selectively binding Gal-1. (c) APN facilitate the removal of Gal-1 by macrophages; (d) APN effectively reduces the levels of Gal-1 in tumor tissues. Statistical significance was analyzed by one-way ANOVA with Tukey's multiple comparisons test. *p<0.05. (Reproduced with permission from Ref. [86], Copyright (2021), American Chemical Society.) (The online version is colorful.)

nating extracellular immunosuppressive cytokines and reshaping antitumor immunity.

Gene-level Modulation

Although pharmacological inhibition and cytokine neutralization can temporarily alleviate immune tolerance, many immunosuppressive pathways rebound or develop therapeutic resistance as the tumor progresses.[88] Gene-level modulation offers a more durable strategy by directly reprograming the expression of key regulatory genes within the TME.[89] For example, CD47 is a critical "don't eat me" signal overexpressed on tumor cells, enabling them to evade macrophage-mediated phagocytosis. To achieve sustained CD47 suppression, we engineered a clustered, regularly interspaced, short palindromic repeat (CRISPR) and CRISPR-associated 9 (Cas9) ribonucleoprotein (RNP) nanocapsule (Cas9NC), capable of delivering CRISPR/Cas9 systems directly into tumor cells.[90] This platform enabled persistent CD47 knockdown and significantly enhanced macrophage phagocytic activity. We further leveraged the collateral RNase activity of CRISPR-associated 13a (Cas13a), which is activated upon target RNA binding, to design a dual-locking nanoparticle (DLNP) for tumor-specific CRISPR/Cas13a delivery.[91] By selectively targeting PD-L1–overexpressing tumor cells, DLNP simultaneously suppressed PD-L1 expression at the gene level and induced selective killing of PD-L1–high cancer cells through Cas13a-mediated nonspecific RNA degradation. This dual action robustly restored T cell–mediated antitumor immunity. In addition to gene disruption, CRISPR/catalytically inactive Cas9 (CRISPR/dCas9) provides a versatile platform for epigenetically activating immunostimulatory genes.[92] Leveraging this capability, we developed a dual-activatable binary CRISPR nanomedicine (DBCN)[93] in which light irradiation triggers the release and activation of the encapsulated CRISPR/dCas9 system. Upon activation, CRISPR/dCas9 upregulated MHC-I expression, which was frequently downregulated in tumor cells, thereby enhancing immune recognition and cytotoxic T cell killing. This gene activation mechanism markedly suppressed tumor growth, metastasis, and recurrence, underscoring the potential of gene-level modulation as a durable immunotherapy strategy.

CONCLUSIONS AND FUTURE PERSPECTIVES

Over the past decade, rapid advances in nanotechnology have created new opportunities to overcome biological and physicochemical barriers that limit the efficacy of cancer immunotherapy. By engineering materials that can dynamically interact with the complex tumor ecosystem, nanomedicine has demonstrated substantial potential to improve immune activation, enhance tumor recognition, and reshape immunosuppressive TME. In this review, we summarize our group's efforts to establish three representative frameworks—surface-adaptive nanomaterials (SANs), antigen-engineering nanoplatforms, and TME-modulating nanomaterials—as integrated strategies to reinvigorate antitumor immunity. Through the rational design of stimuli-responsive materials, precise modulation of antigen presentation, and targeted intervention in immunosuppressive pathways, these approaches collectively illustrate the transformative potential of bioactive nanomaterials for next-generation cancer immunotherapy.

Surface-adaptive nanomaterials exemplify how intelligent materials can address the contradictory demands of systemic stability and tumor-specific activation. By incorporating pH-, redox-, enzyme-, or hypoxia-responsive motifs into core–shell architectures or molecular containers, these systems achieve prolonged circulation, improved biological barrier penetration, and controlled activation within tumors. Their dynamic adaptability enhances payload delivery, while reducing off-target immune activation and systemic toxicity. In parallel, antigen-engineering nanoplatforms offer an effective means to increase tumor immunogenicity, which remains a major bottleneck in cancer immunotherapy. By "seeding" synthetic immune cues on tumor surfaces, "growing" endogenous antigens *via* organelle-targeted stress signaling, or "delivering" tumor-associated antigens to professional antigen-presenting cells, these platforms reshape antigen processing pathways and convert poorly immunogenic tumors into immune-responsive phenotypes. Complementing these advances, TME-modulating nanomaterials directly intervene in the immunosuppressive landscape, which restrains T-cell activity. By enabling the targeted delivery of immune-checkpoint inhibitors, selective neutralization or degradation of suppressive cytokines, or genetic reprogramming of tumor cells, these systems restore effector immune cell function and disrupt tolerogenic networks within tumors. Together, these three classes of nanotechnologies act synergistically to strengthen antitumor immunity and expand the scope of current immunotherapies.

Despite promising results in preclinical studies, several challenges must be overcome before these strategies can be clinically translated. First, the heterogeneity and dynamic evolution of tumors require nanomaterials capable of multistage adaptivity, real-time sensing, and on-demand responses to complex microenvironmental cues. Therefore, the development of multifunctional and modular platforms that integrate sensing, activation, and feedback regulation is crucial. Second, a deeper mechanistic understanding of nano-bio interactions, such as material-induced immune reprogramming, organelle-specific stress signaling, and establishment of long-term immune memory, is essential for guiding rational design. Advanced imaging, single-cell multiomics, and systems immunology approaches are particularly important for uncovering these mechanisms. From a translational perspective, advancing bioactive nanomaterials for clinical applications require the establishment of standardized and quantitative evaluation criteria. In particular, immune safety profiling should extend beyond conventional toxicity assays to include systematic assessment of systemic cytokine release, complement activation, and off-target immune stimulation, which are critical for minimizing immune-related adverse events. In parallel, durability and immune-memory endpoints, such as long-term tumor protection, memory T cell formation, and resistance to tumor rechallengeshould be incorporated to evaluate the sustainability of antitumor immune responses. Comprehensive pharmacokinetic and biodistribution analyses are essential to ensure predictable *in vivo* behavior, tumor selectivity, and controlled clearance profiles. Finally, translational feasibility depends heavily on good manufacturing practice (GMP)-compatible manufacturability, scalability, and robust quality control (QC) parameters including batch-

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to-batch reproducibility, physicochemical stability, and sterility. Integrating these considerations at an early stage of nanomaterial design is critical for bridging the gap between laboratory innovation and clinical translation. Furthermore, the growing emphasis on personalized immunotherapy suggests that future nanoplatforms need to be rapidly adapted to patient-specific antigenic landscapes and immune profiles.

The convergence of nanotechnology, immunology, and synthetic biology is poised to reshape cancer treatment. Future nanomaterials may incorporate programmable logic gates, enabling autonomous decision making based on real-time biological signals. Hybrid systems that integrate nanomaterials with engineered cells, RNA circuits, or gene editing tools may also generate synergistic immune effects that are unattainable by any single modality. In addition, combining nanomedicine with clinically established treatments, such as radiotherapy, chemotherapy, or targeted inhibitors, may yield synergistic outcomes that widen therapeutic windows and overcome resistance. Continued innovation, interdisciplinary collaboration, and translational research are essential to move these materials from laboratory discovery to clinical application, offering new therapeutic possibilities for patients with immunotherapy-resistant malignancies.

BIOGRAPHY

Yang Liu received his Ph.D. in Polymer Chemistry from Nankai University, China (2011) and his second Ph.D. in Chemical Engineering from University of California, Los Angeles, USA (2016). He is currently a full professor at the College of Chemistry, Nankai University. His research focuses on developing novel polymers and nanomaterials to modulate biological processes for the treatment of chronic diseases, cancers, and neurodegenerative diseases.

Conflict of Interests

The authors declare no interest conflict.

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Graphical Abstract

Bioactive Nanomaterials for Cancer Immunotherapy

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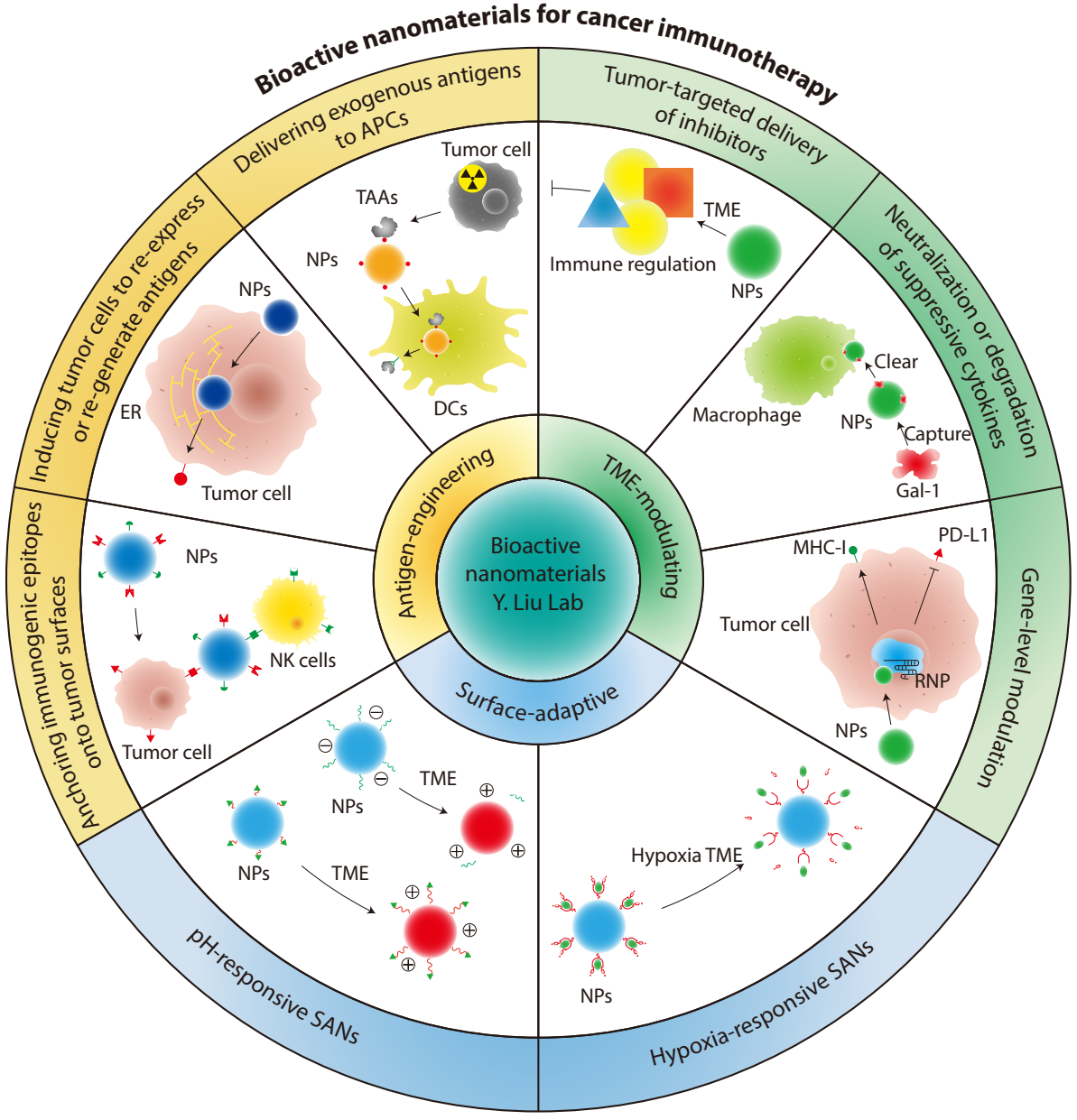
Nankai University; Tianjin Medical University

This review systemically summarizes their studies on bioactive nanomaterials for cancer immunotherapy and highlights three complementary strategies: surface-adaptive nanomaterials to overcome physiological barriers, antigen-engineering nanoplatforms that enhance tumor immunogenicity, and nanomaterials that modulate tumor microenvironment to relieve immune suppression, collectively reinvigorating robust antitumor immune responses.



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