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REVIEW

Nanomaterials Application for STING Pathway-Based Tumor Immunotherapy

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Abstract: The STING pathway has emerged as a therapeutic target in tumor immunotherapy due to its ability to induce interferon responses, enhance antigen presentation and activate T cells. Despite its therapeutic potential, STING pathway-based tumor immunotherapy has been limited by challenges in poor cellular delivery, rapid degradation of STING agonists, and potential systemic toxicity. Recently, advancements in nanotechnology have tried to overcome these limitations by providing platforms for more accurate and efficient targeted delivery of agonists, more moderate sustained STING pathway activation, and more efficient immune presentation and anti-tumor immune response. This review systematically examines the application of nanomaterials in STING pathway-based tumor immunotherapy, focusing on three principal strategies: enhancing tumor vaccine efficacy, modulating the tumor microenvironment, and improving T cell mediated tumor immunotherapy. The challenges to clinical translation, including clinical trial research updates, regulatory hurdles, and biosafety considerations, are also discussed. Overall, STING pathway-based nanomaterials offer promising potential for clinical translation in tumor immunotherapy.

Keywords: STING pathway, STING agonist, nanomaterial, tumor immunotherapy

Introduction

Tumor immunotherapy has emerged as a promising therapeutic strategy, offering considerable potential when combined with typical treatments across various tumor types. However, a substantial proportion of patients respond poorly to tumor immunotherapy. Developing effective strategies to enhance immune responses within the tumor microenvironment has become a promising solution to improve immunotherapeutic effects.[1–4]

The cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS–STING) pathway, abbreviated as the STING pathway, plays a critical role in initiating innate and adaptive immune responses. Activation of the STING pathway can induce the production of type I interferons, enhance antigen presentation, and amplify anti-tumor immunity, positioning it as an important focus in tumor immunotherapy.[5] To date, many types of STING agonists have entered clinical trials, with agents such as ADU-S100, DMXAA, and RBS2418 currently in Phase II.[6] Nevertheless, current strategies directly targeting STING pathway activation encounter several significant challenges, including STING agonists' poor cellular delivery, rapid degradation and potential systemic toxicity, all of which hinder the broader clinical application of STING pathway-based tumor immunotherapy.[7,8]

Advancements in nanotechnology have significantly addressed the aforementioned challenges by enhancing drug stability, improving transmembrane efficiency, enabling targeted tumor delivery, and reducing systemic toxicity.[9–13] Nanomaterial-based delivery systems promote dendritic cell (DCs) maturation and stimulate $CD8^+$ T-cell activation,

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recruitment, and proliferation. These actions enhance antigen presentation and anti-tumor immunity by achieving more efficient, sustained STING pathway activation and remodeling the tumor immune microenvironment.[14,15] However, clinical translation of nanomaterials remains hindered by challenges such as clinical trial research updates, regulatory hurdles and biosafety considerations, despite promising preclinical outcomes.

This article provides a comprehensive review of the nanomaterial application in STING pathway-based tumor immunotherapy, focusing on their application in enhancing the efficacy of tumor vaccines, modulating the tumor immune microenvironment, and improving T cell-based tumor immunotherapy. Utilization of nanomaterials provides new directions and broad prospects for clinical applications.

Overview of STING Pathway and Its Clinical Translation in Tumor Immunotherapy

STING Pathway and Tumor Immunotherapy

The stimulator of interferon genes (STING) protein, a 379 amino acid transmembrane protein, is located in the mammalian endoplasmic reticulum (ER). STING protein comprises an N-terminal transmembrane domain (AA 1–154), a central spherical domain (AA 155–341) and an acidic C-terminal tail (AA 342–379).[16] Human STING and murine STING protein share 68% amino acid sequence homology.[17,18] As shown in Figure 1, STING is localized to the ER through interaction with the calcium sensor stromal interaction molecule 1 (STIM1).[19] When the cyclic GMP-AMP synthase (cGAS) detects intracellular double-stranded DNA (dsDNA) released from necrotic self-cells or foreign pathogens, it can induce the conversion of ATP and GTP into cyclic GMP-AMP (cGAMP), a second messenger for STING activation.[20] After forming the cGAMP–STING complex, it migrates to the perinuclear region, and undergoes post-translational modification in the Golgi apparatus.[21] Modified STING recruits IκB kinase (IKK) and TANK-binding kinase 1 (TBK1) can lead to NF-κB and IRF3 activation and translocation to the nucleus. Activated NF-κB and IRF3 induce the expression of type I interferon (IFN) and inflammatory cytokines.[22] The STING pathway recognizes and eliminates both self and foreign dsDNA, preventing viral and bacterial infections and maintaining immune balance.[23]

The STING pathway has been demonstrated to play a critical role in anti-tumor immune responses, attracting significant attention in tumor immunotherapy. As shown in Figure 2, during anti-tumor treatments, DNA fragments,

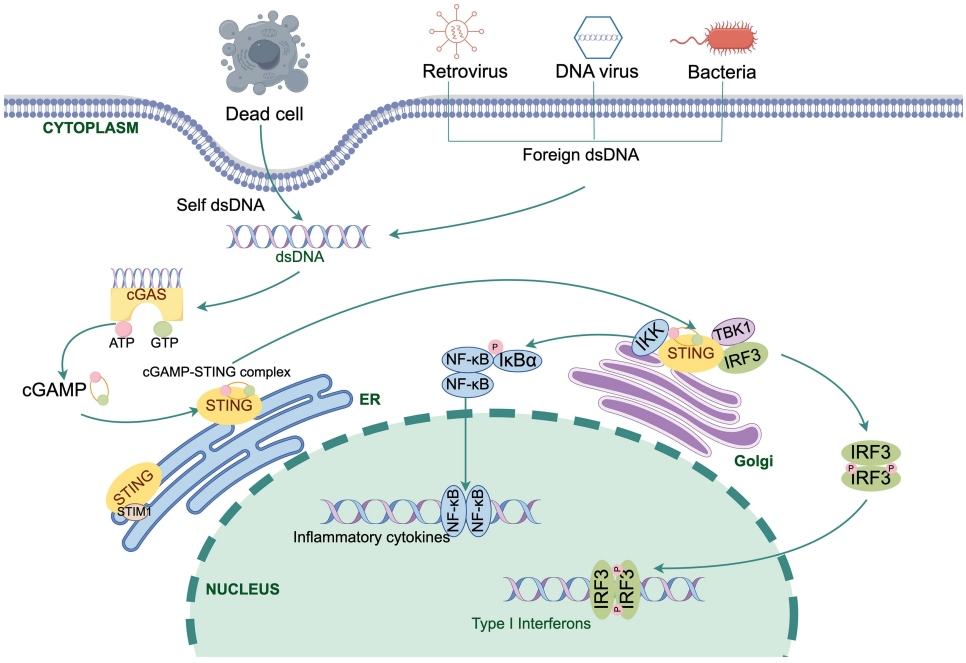

Figure 1 Overview of STING pathway activation. STING is activated by cGAMP synthesized by cGAS upon detection of dsDNA. Activated STING recruits IKK and TBK1, leading to NF-κB and IRF3 phosphorylation and nuclear translocation to induce type I interferons and inflammatory cytokines expression.

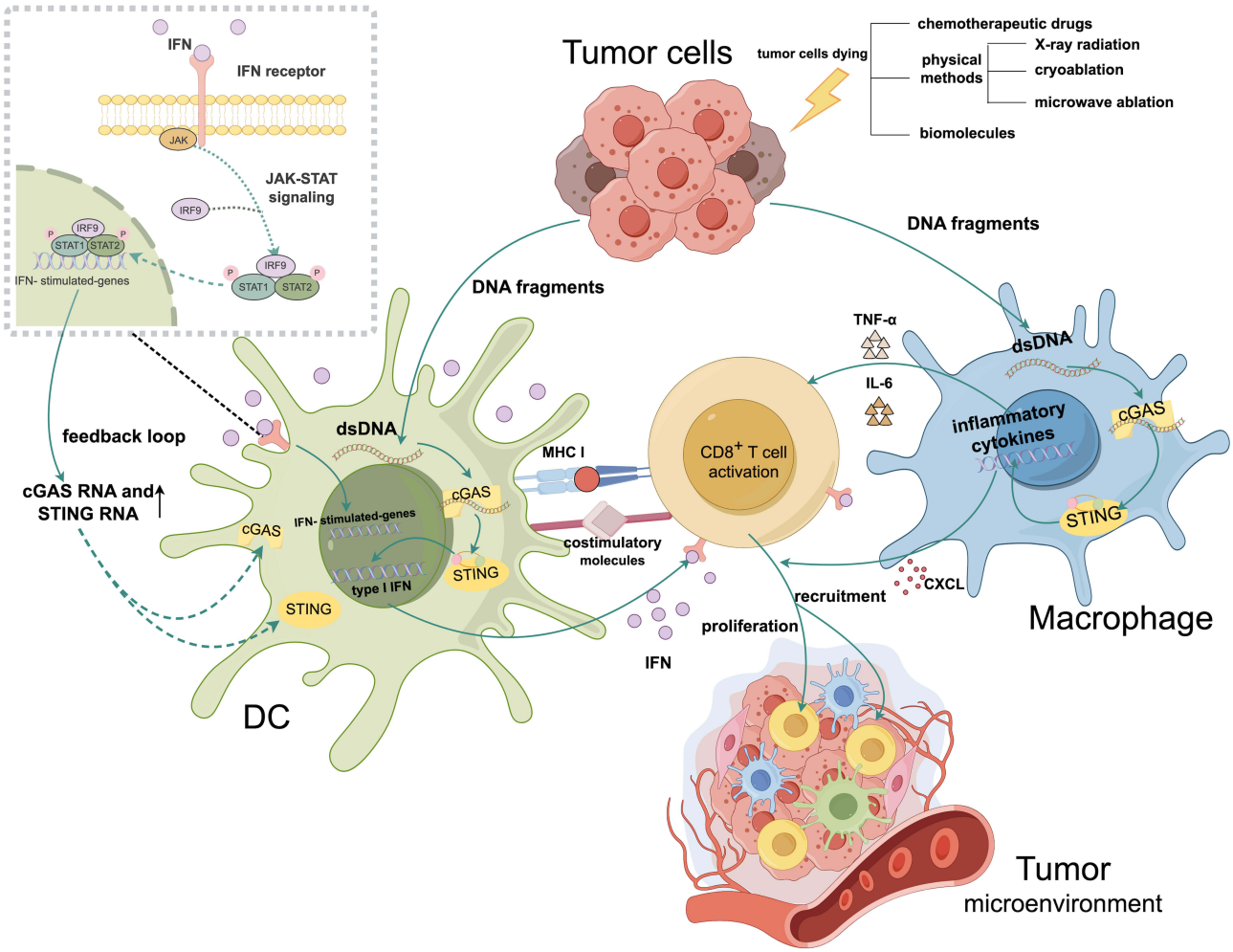

Figure 2 Overview of STING pathway activation that induces the activation of DCs, macrophages and T cells, further augmenting anti-tumor immune responses. DNA fragments released from dying tumor cells activate the STING pathway in APCs (including DCs and macrophages), inducing the expression of type I IFNs and inflammatory cytokines. These cytokines further promote APC maturation and $CD8^+$ T cell activation, recruitment, and proliferation. Subsequent engagement of IFN receptors further up-regulates interferon-stimulated genes, including cGAS and STING, establishing a positive feedback loop that amplifies STING signaling and ultimately enhances anti-tumor immune responses.

which are released from dying tumor cells, are taken up by dendritic cells (DCs) and macrophages. These DNA fragments, a vital form of intracellular dsDNA, can activate the STING pathway in these two cell types, leading to the expression of type I IFNs and inflammatory cytokines (TNF-α, IL-6, etc.).[20,21] Subsequently, type I IFNs activate antigen-presenting cells (APCs, including DCs and macrophages) by binding to IFN receptors, upregulating MHC I and costimulatory molecules to enhance antigen presentation and $CD8^+$ T cell activation. Meanwhile, inflammatory cytokines can create a pro-inflammatory environment and support APC maturation and T cell proliferation. Chemokines CXCL recruit $CD8^+$ T cells to the tumor site and enhance its anti-tumor cytotoxicity.[24,25] Additionally, through IFN receptors of APCs, type I IFNs upregulate cGAS and STING RNA expression, triggering a feedback loop that amplifies IFN production and strengthens anti-tumor immune response.[26,27]

Clinical Translation of STING Pathway-Based Tumor Immunotherapy

STING pathway-based tumor immunotherapy is attracting significant attention for its potential to enhance immune responses and therapeutic outcomes. This section explores its clinical application in tumor vaccines, immune checkpoint inhibitors (ICIs), and chimeric antigen receptor (CAR)-T cell therapy.

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Application in Adjuvant of Tumor Vaccine

Adjuvants are crucial for improving the efficacy of tumor vaccines, which often have low immunogenicity despite targeting specific antigens. As a critical mediator for modulating immune responses, the STING pathway is currently under investigation as a potential vaccine adjuvant.[28] Kinkead et al developed the targeted antigen vaccine PancVAX and combined it with ADU-V16, one STING agonist used as an adjuvant, to induce specific $CD8^+$ T cell responses.[29] Hanson et al also confirmed that liposome c-di-GMP (CDG) significantly enhances antigen accumulation in lymph nodes and $CD8^+$ T cell responses when combined with ovalbumin (OVA) and gp100.[30]

Formulated into lipid nanoparticles, a cationic gemini amphiphile simultaneously activated the STING pathway and enabled robust transfection of plasmid DNA or mRNA into DCs, ultimately significant enhancing tumor vaccine efficacy.[31] When nitro-oleic acid was encapsulated into lipid nanoparticles, it alleviated STING-induced inflammation and minimized systemic toxicity.[32] Strategies that facilitate the efficient and sustain activation of the STING pathway are desirable for improving vaccine efficacy.

Application of STING Pathway-Based Strategy in ICIs Therapy

Another promising clinical application is combining STING pathway-based strategies with ICI therapy. ICIs, targeting the PD-1/PD-L1, can reverse exhausted T-cells to effective T-cells, facilitating anti-tumor responses. When combined with ICIs, STING-based strategies can further sustain the cytotoxic activity of $CD8^+$ T cells by STING pathway activation, ultimately improving its effects.[33–35] Fu et al formulated c-di-AMP (CDA), a common STING agonist, in irradiated GM-CSF-producing cellular tumor vaccines (STINGVAX). When combined with ICIs, STINGVAX enhances tumor eradication by significantly increasing $CD8^+$ T cell proportions and decreasing PD-L1 expression in tumor cells.[36] Additionally, c-di-GMP, another STING agonist, is loaded into lipid nanoparticles to form STING-LNPs, which activate NK cells and induce PD-L1 expression in tumor cells. When used in conjunction with ICIs, this strategy reduces PD-L1 expression, thereby augmenting the overall anti-tumor efficacy.[37] What's more, Hao et al also developed a tumor-penetrating cytopharmaceutical by conjugating STING agonist DMXAA to neutrophils. It promotes DC maturation and enhances T cell infiltration. The combination of this approach with ICIs significantly suppresses tumor growth and extends mouse survival.[38] On another note, by using the ability of IL-12 to restore exhausted T cells' functions, Wang et al utilized lipid nanoparticle DMT7 to encapsulate IL-12 mRNA and developed DMT7-IL12 LNP. DMT7-IL12 LNP markedly increased the secretion of TNF-α and IFN-γ and decreased PD-1 expression on $CD8^+$ T cells, effectively reversing T cell exhaustion. With the assistance of STING agonist MSA-2, these nanoparticles more facilitated $CD8^+$ T cells intratumoral infiltration and improved tumor immunotherapy efficacy.[39] The excessive immune responses induced by the combination of STING agonists and ICIs warrant significant attention, as they may potentially lead to life-threatening adverse effects. It is crucial to address these potential risks through the optimization of the combination strategies.

Application of STING Pathway-Based Strategies in CAR-T Therapy

Moreover, STING pathway-based strategies in CAR-T therapy also hold significant potential for clinical application. CAR-T cell therapy involves genetically modifying T lymphocytes to target and activate against tumor-specific antigens.[40] Accumulating evidences indicated that the STING pathway activation can significantly promote the anti-tumor efficacy of CAR-T therapy. Li et al demonstrated that STING pathway activation promotes the differentiation of cell-like $CD8^+$ T cells through TCF1 regulation, and enhances the anti-tumor efficacy of CAR-T therapy.[41] Xu et al confirmed that DMXAA-induced STING activation enhances CAR-T cell trafficking, persistence, and recruitment in immunosuppressive environments, enhancing anti-tumor efficacy.[42] Conde's studies also showed that combining cGAMP with CAR-T cells induced tumor cell death and inhibited tumor growth.[43] The efficacy of CAR-T therapy can be enhanced by combining STING agonists to overcome immune suppression, improve CAR-T cell expansion, persistence, and tumor infiltration, ultimately boosting therapeutic effectiveness.

Challenges for STING Pathway-Based Tumor Immunotherapy

STING Agonists

Cyclic dinucleotides (CDN), characterized by their cyclic dinucleotide structure, are an intrinsic class of STING agonists, including 2′,3′-cGAMP, 3′,3′-cGAMP, c-di-GMP, and c-di-AMP (CDA). Among these, 2′,3′-cGAMP is produced by

cGAS in mammalian cells, while the others are synthesized by bacterial cGAS.[44] Notably, large-scale production of CDA can be achieved by modulating the expression of diadenylate cyclase in *E. coli* 1917, supporting its broad applicability as a STING agonist.[45] These agonists are characterized by large size, high polarity, poor intracellular delivery, and susceptibility to degradation by ecto-nucleotide phosphodiesterase 1 (ENPP1), presenting considerable challenges to their clinical application.[46,47] Thus, novel, stable STING agonists, including CDN/non-CDN molecules, metal ions, and ENPP1 inhibitors, have been developed and are detailed in Table 1 and Supplementary Figure 1.

Small Molecules

CDN Molecules

Researchers have synthesized a series of CDN class STING agonists based on the intrinsic CDN structure to enhance their anti-hydrolysis of ENPP1 and optimize their degradation resistance. These modified CDN molecules have also shown notable anti-tumor efficacy through expeditious STING pathway activation. A series of CDN class STING agonists (including ADU-S100, MK-1454, MK-2118, etc.[48–55,68–70]) and their clinical status are listed in Table 1. Among these, ADU-S100, stabilized by thiophosphate substitution in the intrinsic CDN structure, was the first CDN class STING agonist to advance to clinical trials,[71] although its safety and efficacy still require further improvement. Another novel CDN class STING agonist, disulfide phosphate analog 2′3′-cCsAsMP, was designed for anti-hydrolysis of ENPP1 and degradation resistance. Compared to intrinsic cGAMP, 2′3′-cCsAsMP can achieve 10 times more effective in stimulating IFN secretion in human THP1 cells.[72] Similarly, MK-1454 exhibited a high affinity for STING and a significant type I IFN induction. When MK-1454 was injected intratumorally into tumor-bearing mice, it was

Table 1 List of STING Agonists Under Development

Drug Name	Year	Developer	Highest Status	Immune Activation Effect	Limitation
CDN molecules					
ADU-S100[48]	2015	Novartis (Aduro Biotech)	Phase II	Induce type I IFN response, promote TAAs presentation	1. Large molecular size and high polarity hinder membrane permeability and cellular uptake 2. Rapid degradation by ENPP1 reduces pharmacological stability and efficacy 3. Intratumoral injection limits clinical applicability
MK-1454[49]	2017	Merck & Co.	Phase II	Activate STING pathway, upregulate pro-inflammatory cytokines	
MK-2118[50]	2017	Merck & Co.	Phase I	Trigger systemic immune activation, support anti-tumor response	
IMSA-101[51]	2019	Immune Sensor Therapeutics Inc.	Phase II	Enhance $CD8^+$ T cell infiltration, stimulate innate immunity	
BMS-986301[50]	2019	Bristol-Myers Squibb	Phase I	Induce tumor-specific immune memory, augment adaptive immunity	
SB-11285[52]	2019	F-star Therapeutics	Phase I	Promote immune cell recruitment, activate DCs	
BI-1387446[53]	2020	Boehringer Ingelheim	Phase I	Enhance type I IFN production, facilitate tumor regression	
TAK-676[54]	2020	Takeda Oncology	Phase II	Strengthen STING-based immune priming, enhance therapeutic synergy	
E-7766[50]	2020	Eisai Inc.	Phase I	Modulate TIME, increase T cell mediated cytotoxicity	
DN-015089[55]	2021	Shanghai De Novo	Phase I	Induce IFN-stimulated-genes expression, enhance anti-tumor responses	
VB-85247[55]	2021	VENENUM Biodesign	Preclinical Study	Activate innate immunity, suppress tumor growth	

(*Continued*)

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Table 1 (Continued).

Drug Name	Year	Developer	Highest Status	Immune Activation Effect	Limitation
Non-CDN molecules					
DMXAA[18]	2001	Antisoma, Novartis	Phase II	Stimulate type I IFN production, enhance anti-tumor immunity	1. Systemic inflammation and narrow therapeutic window limit safe dosing 2. Non-specific distribution causes off-target immune activation 3. Sustained activation risks immune exhaustion and lacks long-term safety data.
PC7A[56]	2017	UT Southwestern Medical Center	Preclinical Study	Activate STING pathway, induce IFN production and increase $CD8^+$ T cell activity	
ABZI[57]	2018	–	Phase II	Trigger STING pathway activation, induce immune responses	
MSA-2[58]	2018	Merck & Co.	Phase I	Enhance STING pathway signaling, amplify T cell immune responses	
GSK-3745417[50]	2019	GlaxoSmithKline	Phase I	Trigger type I IFN and cytokine release, enhance $CD8^+$ T cell infiltration	
CRD-5500[55]	2019	Curadev	Preclinical Study	Stimulate pro-inflammatory signaling, support tumor suppression	
HG-381[55]	2021	HitGen, Inc.	Phase I	Induce STING activation, enhance innate immune defense	
ONO-7914[55]	2022	Ono pharmaceutical	Phase I	Amplify immune signaling, support tumor-specific immune response	
SNX-281[59]	2022	Silicon therapeutics	Phase I	Induce cytokine production, facilitate T cell activation	
KL340399[55]	2022	Kelun-Biotech	Phase I	Promote TAAs presentation, augment adaptive immunity	
Metal ions					
Mn2+[60]	–	–	–	Enhance dsDNA sensitivity, improve cGAMP-STING binding	1. Systemic toxicity limits safety 2. Poor targeting causes overactivation
Zn2+[61]	–	–	–	Facilitate DNA phase transition, boost cGAS activation	
ENPP1 Inhibiter					
MV-626[62]	2018	Mavupharma	Preclinical Study	Boost type I IFN production and immune activation	1. Low bioavailability limits efficacy 2. Off-target effects cause immune toxicity
RBS2418[63]	2019	Riboscience LLC	Phase II	Activate antigen presenting cells and increase T cell infiltration	
SR-8314[64]	2019	Stingray Therapeutics	Preclinical Study	Enhance STING activation, promote anti-tumor immunity	
SR-8541A[65]	2020	Stingray Therapeutics	Phase II	Enhance APCs activation and increase T cell infiltration	
ZX-8177[66]	2022	Zenshine Pharma	Phase I	Activate STING pathway, support T cell activation	
Pyrido[2,3-d] pyrimidin-7-one derivatives[67]	2024	Pfizer Inc.	Preclinical Study	Enhance tumor-specific immune response	

demonstrated to induce complete tumor regression and enhance the efficacy of ICI therapy and entered Phase II clinical trials.[73] Unfortunately, CDN class STING agonists still require intratumoral injection to achieve therapeutic effects, limiting their broader clinical translation.

Non-CDN Molecules

Novel STING agonists, suitable for intravenous injection, oral, and subcutaneous administration, were developed to address the limitations of existing intratumoral injection delivery methods for CDN class STING agonists. DMXAA, the first intravenous injection non-CDN class STING agonist, showed significant anti-tumor effects in mouse models. However, its poor binding to human STING led to suboptimal results in a Phase II clinical trial of non-small cell lung cancer.[17,74,75] Thus, as a way to address the need for a high binding affinity of human STING, aminobenzoimidazole (ABZI), another novel non-CDN class STING agonist, exhibited superior efficacy in binding both mouse and human STING.[57] Compared to cGAMP, ABZI achieved a 400-fold greater STING pathway activation in human PBMCs. Intravenous injection of ABZI exhibited powerful tumor growth inhibition and extend survival in mouse models.[76]

Apart from intravenous injection of ABZI, MSA-2, a novel non-CDN STING agonist for oral and subcutaneous administration, induces elevated IFN expression in plasma and tumors, resulting in durable anti-tumor immune responses.[58] By conjugating the triggering receptor expressed on myeloid cells 2 (TREM2) inhibitor artesunate to MSA-2, Deng et al developed the novel STING agonist prodrug named GB2. Intravenous injection of GB2 promoted M1 polarization of tumor-associated macrophages (TAMs), enhanced immune response and induced tumor regression.[77] Several novel non-CDN class STING agonists (including SNX-281, GSK-3745417, ONO-7914, etc.[50,55,56,59]) and their clinical status are listed in Table 1. More multi-center clinical trials are encouraged to evaluate its clinical biosafety and efficacy.

Metal Ions

Metal ions, due to their superior chemical stability, effectively address the challenge of insufficient stability often observed in STING agonists. Manganese ions (Mn^{2+}), released from cellular organelles like the Golgi apparatus and mitochondria, can accumulate cytoplasmically and enhance sensitivity to dsDNA, improving cGAMP-STING binding and pathway activation.[60] Similarly, zinc ions (Zn^{2+}), primarily stored in mitochondria and the ER, promote cGAS activation by facilitating intracellular DNA phase transition.[61] However, the systemic toxicity of metal ions has gained increasing attention. It has been reported that excessive exposure to Mn^{2+} led to manganism, displaying serious central nervous system damage and an elevated risk of Parkinson's disease.[78] In addition, excessive exposure to Zn^{2+} resulted in multi-system damage, including neurological suppression, immune system dysfunction, digestive systems injury, etc.[79] Nanomaterials are expected to minimize their systemic toxicity by means of metal ions control release and targeted delivery.

ENPP1 Inhibitors

ENPP1 inhibitors can reduce the hydrolysis and degradation of extracellular cGAMP, thereby elevating its concentration and facilitating STING pathway activation.[80] For instance, through inhibition of extracellular cGAMP degradation and subsequent STING pathway activation, ZX-8177 can increase the infiltration of $CD8^+$ T cells and NK cells into the tumor microenvironment (TME) and improve tumor immunotherapy efficacy.[66] MV-626, another highly potent and selective ENPP1 inhibitor, showed completely oral bioavailability in mouse models. When combined with radiation or ICIs, MV-626 can effectively block cGAMP hydrolysis, delay tumor growth, and significantly prolong overall survival.[62] Several ENPP1 inhibitors, such as SR-8541A[65] and RBS2418,[63] have significantly improved $CD8^+$ T cells intratumoral infiltration in mouse models and progressed to Phase II clinical research. While SR-8314 and Pyrido[2,3-d]pyrimidine-7-one derivatives[64,67] remain in preclinical study stages (Table 1). More efficient inhibition of cGAMP degradation and better oral bioavailability of ENPP1 inhibitors needed to be explored. Moreover, the combined application of ENPP1 inhibitors with radiotherapy and ICIs is expected to further enhance the anti-tumor effect.

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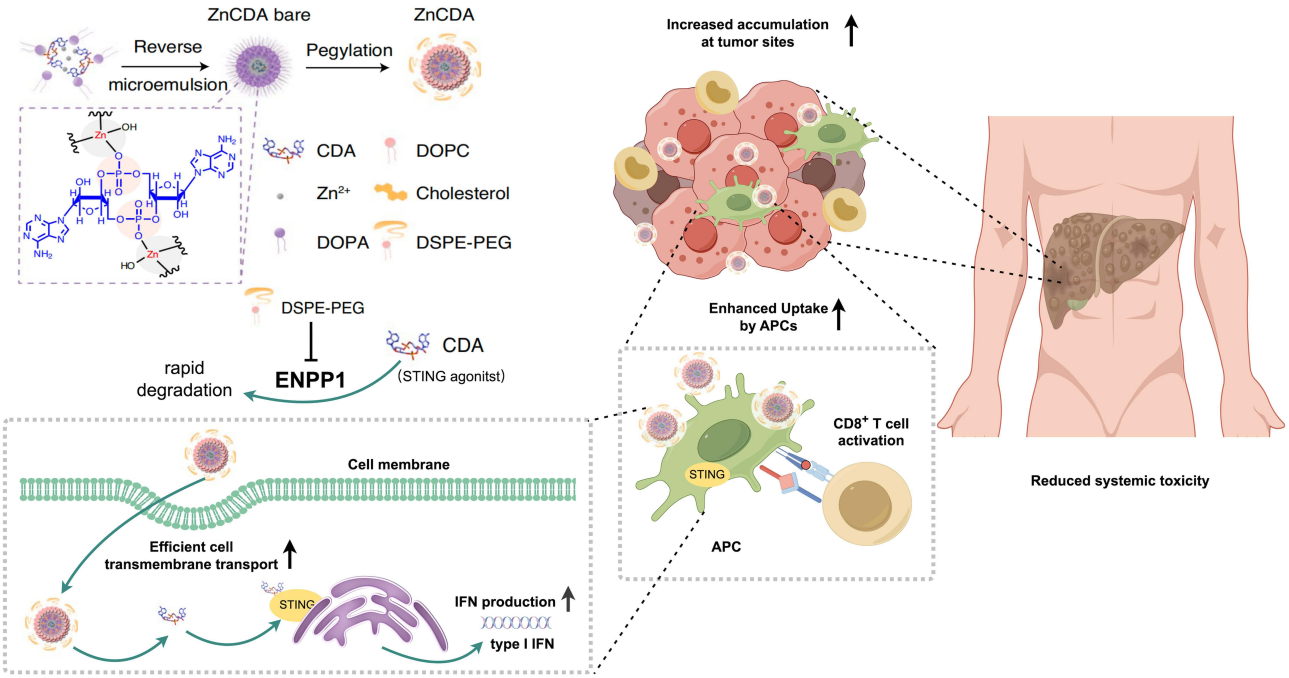

Figure 3 Application of nanotechnology in addressing challenges of STING pathway-based tumor immunotherapy. Application of nanotechnology, as exemplified by c-di-AMP (CDA) formulated as ZnCDA with a zinc phosphate core and PEG-lipid shell, can reduce STING agonist degradation, promote transmembrane transport, enhance APC uptake, and increase IFN production. It also increases accumulation at tumor sites and eventually reduces systemic toxicity. Reprinted with permission from Yang K, Han W, Jiang X, et al. Zinc cyclic di-AMP nanoparticles target and suppress tumours via endothelial STING activation and tumour-associated macrophage reinvigoration. Nat Nanotechnol. 2022;17(12):1322–1331. Copyright © 2022, Springer Nature.[83]

Delivery Challenges and Solutions

There are several critical delivery challenges of STING agonists, which primarily manifest in low cell transmembrane transport efficiency, rapid degradation, and systemic toxicity. As illustrated in Figure 3, recent advances in nanotechnology, especially in the development of novel delivery systems, have partially addressed these challenges.[81,82]

Cell Transmembrane Transport and Rapid Degradation

Efficient transmembrane transport is crucial for the STING pathway activation due to STING's localization in ER. Nevertheless, large molecular size, high polarity, and susceptibility to hydrolysis of STING agonists significantly impede their delivery, reducing bioavailability and therapeutic efficacy.[7,8] These problems also potentially increase the requirement for higher doses or more frequent injections.[84] Wilson et al employed cationic poly(beta-amino ester) nanoparticles to deliver CDNs to the cytoplasm, achieving significant STING and IRF3 activation. Notably, the dosage required was 100-fold lower than that needed without the use of nanoparticles.[85] Similarly, Webb et al utilized polymeric vesicles to synthesize STING-NPs, which can significantly enhance cGAMP uptake and cytoplasmic delivery. After intravenous injection, this approach resulted in a 40-fold increase in the half-life of cGAMP and significantly elevated serum levels of IFN, TNF-α, IL-12, etc.[86] Additionally, Ariosa et al synthesized one pre-formed loadable lipid nanoparticle aimed at reducing ENPP1 activity and achieved the result of inhibition of 2′3′-cGAMP rapid degradation.[87,88]

Systemic Toxicity

Overactivated STING pathway and heightened immune responses pose a risk of excessive inflammatory cytokine secretion and cytokine storms, which can lead to systemic toxicity.[58]

Dou et al developed and synthesized high-mesoporous Mn-based nanomaterials with metformin nanoparticles named Mn-MSN@Met-M NPs. Through retaining tumor cell membrane proteins and adhesion molecules, these nanocarriers

can facilitate homologous binding to tumor cells, and reduce accumulation in other organs and systemic toxicity.[89] In addition, Yang et al encapsulated bacterial-derived CDA in nanoscale coordination polymers with a zinc phosphate core and PEG-conjugated phospholipid bilayer. This nanoparticle enhances CDA tumor accumulation and penetration by disrupting endothelial cell vasculature, as well as reducing systemic toxicity.[83] Furthermore, Cui et al combined the photosensitizer BODTPE and the targeting ligand dibenzocyclooctyne to design nanoparticles. This nanoparticle specifically target tumor cells via a click chemistry reaction with azide receptors of the cell membrane, improving drug accumulation and stability while maintaining minimal systemic toxicity.[90]

STING Pathway-Based Nanomaterial for Tumor Vaccine

Tumor vaccine was designed to trigger anti-tumor immune responses by targeting tumor-specific antigens, activating and amplifying corresponding immune cell responses.[91] Recent nanomaterial applications, such as metal ion-loaded, pH-sensitive, and biologically or chemically modified nanoparticles, significantly enhance STING pathway activation, promote MHC I antigen presentation and upregulate costimulatory molecule expression. These approaches also preserve vaccine integrity, extend duration, and regulate release, further enhancing their therapeutic potential and tumor vaccine efficacy.[92,93]

Metal-Based Nano-Tumor Vaccine

Metal nanoparticles, including Fe_2O_3, α-Al_2O_3, and MnO_2, possess properties of enhanced membrane penetration, streamlined synthesis and robust stability. These properties render them particularly suitable as carriers for the precise delivery of STING agonists.[94,95] Notably, apart from serving as carriers, MnO_2 nanoparticles also act as potent STING agonists.

Using metal iron nanoparticles as carriers, a PEIM@Mem iron nano-tumor vaccine, engineered by loading the STING agonist MSA-2 and an acidic copolymer, significantly enhanced antigen uptake and presentation by APCs, leading to a marked $CD8^+$ T cell response and effective tumor regression.[96] In the same way, an α-Al_2O_3-UPs-4T1/EPB nano-tumor vaccine was developed using α-Al_2O_3 nanoparticles as carriers via the covalent conjugation of ubiquitin-binding proteins. This innovative vaccine improved $CD8^+$ T cell responses and tumor-infiltrating lymphocyte receptor diversity. Notably, the incorporation of the STING agonist DMXAA, this vaccine further enhanced DCs migration to lymph nodes and lymphocyte infiltration into tumors, resulting in a significant anti-tumor effect in mouse model.[97] Unlike merely serving as carriers, the dual function of MnO_2 nanoparticles plays a unique efficacy when developing a MnP-PEG nano-tumor vaccine. This vaccine efficiently delivers Mn^{2+} via endocytosis, and activates STING pathway, further inducing IFN and inflammatory cytokine expression, enhancing $CD8^+$ T cell-mediated anti-tumor activity.[98]

To further stimulate DCs maturation and upregulate co-stimulatory molecules, OVA, a model antigen to enhance immunogenicity, was integrated into nanoparticles.[99] Zhao et al incorporated MnO_2 nanoparticles and cationic polymers to construct the MPO nano-tumor vaccine. Upon draining to the lymph nodes, Mn^{2+} activated the STING pathway and induced the generation of tumor-associated antigens (TAAs). The MPO nano-vaccine promoted DCs maturation, ultimately enhancing anti-tumor immune responses by utilizing the synergy of OVA and TAAs.[100] Qiao et al further improved vaccine efficacy by incorporating Mn^{2+} and Al^{3+} into their MnO_2-Al-OVA nano-vaccine system. This delivery platform effectively directs the vaccine to lymph nodes, facilitates efficient endocytic uptake by DCs and significantly amplifies the antigen-specific anti-tumor immune response.[101] To target the overexpressed mannose receptors on TAMs and DCs, Gu et al synthesized mannose-modified, OVA-coated MnO_2 nanoparticles. This nano-tumor vaccine released Mn^{2+}, activated the STING pathway, induced M2 to M1 phenotype switch and upregulated CD80/CD86 on DCs, and enhanced $CD8^+$ T cell activation.[102] Nevertheless, the cytotoxicity of metal nanoparticles (including their potential to disrupt cellular membranes, affect cytoskeletal components, and damage DNA, etc.) remains a concern.[103] Recently, several strategies have been employed to address this issue. PEGylation was used in MnP-PEG nanoparticles to improve endocytic drug delivery, confining STING pathway activation to the tumor microenvironment rather than acting systemically.[98] The MnO_2-Al-OVA platform utilizes TME-responsive release and dual-metal coordination, enabling dose reduction, minimizing systemic metal ion exposure and potential neurotoxicity.[101] Another novel mannose-modified MnO_2 nanoparticles achieve selective targeting of immune cells via receptor-mediated uptake, enhancing delivery

specificity and reducing off-target effects.[102] Although these strategies have been explored, additional approaches are still encouraged to improve the biosafety of metal-based nano-tumor vaccine.

PH-Sensitive Nano-Tumor Vaccine

PH-sensitive nanoparticles, which exhibit the ability to undergo structural changes in response to specific pH environments, have been engineered to facilitate the precision and efficacy of STING agonist delivery.

Using reversible addition-fragmentation chain transfer (RAFT) polymerization, Zhou et al synthesized a PEG-b-PDPA copolymer that can be activated at pH5.9–6.2. The PEG-b-PDPA copolymer was conjugated with DMXAA and tumor-specific antigens to develop a nano-tumor vaccine. This vaccine enhanced DC's endocytosis, facilitated rapid antigen release into the cytoplasm, and achieved a better $CD8^+$ T cell response in the mouse model of subcutaneous administration.[104] Unfortunately, poor binding to human STING of DMXAA hinders its clinical application. In a related study, Su et al developed another pH-sensitive nano-tumor vaccine incorporating cGAMP and tumor-specific antigens with multivesicular nanoparticles. This vaccine can self-assemble at physiological pH and disassemble in acidic conditions, which precisely delivered cGAMP to DCs and induced a robust $CD8^+$ T cell response upon subcutaneous administration.[105]

Meanwhile, pH-sensitive nanoparticles with the capacity to activate the STING pathway have also been explored. A series of ultra-pH-sensitive (UPS) nanoparticles were developed from copolymers with linear or cyclic tertiary amines, tunable across physiological pH (4–7.4), and had greater ability to activate the STING pathway simultaneously. Among these, PC7A was selected for its ability to induce the highest CTL responses through STING pathway activation, resulting in significant anti-tumor effects in mouse models. Gradual degradation of PC7A in acidic environments can also prolong STING pathway activation, enabling a more sustained and controlled immune response compared to cGAMP, highlighting its promising clinical potential.[56,106] Intratumoral injection of the PC7A nano-vaccine effectively promoted T cell proliferation and infiltration within tumors, facilitated the IFN-γ-expressing $CD8^+$ T cell recruitment, and enhanced the efficacy of anti-tumor immune response.[107] Although significant progression of targeting precision and delivery methods has been made in PH-sensitive nano-tumor vaccine, their clinical effectiveness and safety are needed more improvement and validation. For instance, instead of intratumoral injection, oral or subcutaneous administration of the PC7A may indicate a promise prospect for clinical application.

Biologically/Chemically Modified Nano-Tumor Vaccine

Biologically/chemically modified nanoparticles are emerging as novel tools for delivering STING agonists and activating STING pathway. Guo et al utilized bio-inspired tumor cell membrane technology to modify poly(lactic-co-glycolic acid) nanoparticles with the CBP-12 peptide. These biologically modified nano-tumor vaccine can precisely deliver cGAMP and tumor-specific antigens to $Clec9a^+$ DCs, induced STING pathway activation, markedly improved antigen presentation and the key immunoregulatory factor production.[108,109] Additionally, using self-degradable poly(beta-amino esters), Liu et al engineered a chemically modified nano-tumor vaccine to deliver cGAMP and the protein antigen OVA to APCs. This vaccine effectively enhanced MHC I-mediated antigen presentation of APCs, increased IFN production and improved tumor vaccine efficacy.[110] Moreover, Chen et al designed cGAMP-loaded lipidoid nanoparticles (LNPs/cGAMP). LNPs/cGAMP were injected to the apoptotic site of tumor induced by a low dose of DOX. These nanoparticles can capture TAAs and develop as LNP/cGAMP/TAAs. This lipidoid-based nanosystem tumor vaccine promoted the presentation of tumor antigens, activated the STING pathway, promoted T cell activation, and significantly enhanced the anti-tumor immune response.[111] Different from the direct STING pathway activation, Zhao et al developed chitosan-derived composite nanoparticles to promote intracellular DNA release and subsequently activate the STING pathway. By means of these nanoparticles as adjuvants, this tumor vaccine facilitated DC maturation, stimulated macrophage activation, and enhanced overall immune responses.[112,113] However, it should be concerned that complex synthetic technology of these biologically/chemically modified nano-tumor vaccine may impede their mass production and clinical translation.

While recent nanomaterials have significantly enhanced tumor vaccine efficacy via improved STING activation and targeted antigen delivery, each strategy presents unique advantages and critical limitations. Specifically, metal-based nano-tumor vaccine exhibits robust delivery and potent immune activation, yet raise biosafety concerns due to inherent cytotoxicity and systemic toxicity risks. Conversely, pH-sensitive nano-tumor vaccine enables precise antigen release responsive to tumor acidity but faces ongoing challenges in clinical validation and systemic administration feasibility. Biologically or chemically modified nano-tumor vaccine, despite their superior targeting specificity and immunogenicity, encounter substantial hurdles related to complex synthesis, regulatory standards, and scalable manufacturing.

STING Pathway-Based Nanomaterial for Modulating Tumor Immune Microenvironment

The tumor immune microenvironment (TIME), characterized by polarization of TAM toward the M2 phenotype, accumulation of regulatory T (Treg) cells, and secretion of cytokines inhibiting T cell activation, plays a pivotal role in tumor cell immune evasion and metastasis.[114–116] In addition to single STING pathway activation, the application of nanomaterial can more effectively modulate the immunosuppressive TIME by integrating multiple synergistic effects (such as oxidative stress, radiotherapy, and TLR pathway activation) with STING pathway activation.[117]

Single STING Pathway Activation

Various STING agonists-loaded nanoparticle can independently modulate the TIME. By encapsulating c-di-GMP in lipid nanoparticles, Nakamura et al developed targeted lipid nanoparticle formulations (STING-LNP). STING-LNP was verified to activate immune cells infiltrating the TIME and induce anti-tumor immune responses in various types of malignant tumors.[118] Luo et al constructed Ln-GAMP-NPs through the self-assembly of lanthanides with AMP/GMP (1:1 M ratio) in aqueous solutions. These nanoparticles effectively activated the STING pathway, upregulated $CD8^+$ T cell proportion, and remodeled the TIME.[119] Additionally, Xu et al developed a supramolecular CDN nanoparticle composed of oleic acid, deoxycytidine-derived CDG, and the hydrophobic ligand 3′,5′-diOA-dC. This nanoparticle markedly improved intracellular CDG transport and facilitated STING pathway activation. It also modified the ratio of Treg cells and M2 macrophages, leading to the remodeling of the immunosuppressive TIME.[120] Furthermore, by incorporating STING agonist cGAMP into polymeric vesicles, Wang et al synthesized STING-activated nanoparticles (STANs) using the RAFT method. The result indicated that intravenous injection of STANs promoted T cell recruitment and activation and normalized the TIME in mouse models.[121] Unlike direct agonist for STING pathway, Liu et al encapsulated a STING mutant with strong IFN-inducing capabilities ($STING^{R284S}$) in lipid nanoparticles. This approach can deliver $STING^{R284S}$ to STING-deficient tumor cells, stimulate anti-tumor cytokines production, and effectively activate T cells while remodeling the TIME.[122] Compared with single STING agonist delivery systems, novel nanoparticles, which can induce both STING pathway activation and other synergistic biological effects (including oxidative stress and TLR pathway activation), are expected to modulate the immunosuppressive TIME more effectively.

Synergy of Oxidative Stress Inducing and STING Pathway Activation

Oxidative stress resulting from cellular damage can effectively enhance the expression of TAAs, activate immune cells, and markedly modulate immunosuppressive TIME. Utilizing ultrasound and the polycarbonate membrane extrusion method, Bao et al developed membrane fusion lipid-encapsulated Fe-STING nanoparticles containing Fe^{2+} ions and cGAMP. Fe^{2+} ions can generate reactive hydroxyl radicals and induce oxidative stress, while cGAMP activates the STING pathway. The synergy between oxidative stress and STING pathway activation transformed the TIME from "cold" to "hot", characterized by intratumoral infiltration of $CD8^+$ T cells and reprogramming of macrophages from the M2 to M1 phenotype.[123] Additionally, using the combination of the STING agonist SR-717 and the photosensitizer TCPP, Zhou et al developed a novel nanoparticle named SR@PMOF. Following intravenous injection and subsequent irradiation at the tumor site, light activation of TCPP within SR@PMOF induced reactive oxygen species (ROS) generation, and promoted TAAs and tumor DNA fragments release. In synergy with SR-717-mediated STING pathway

activation, SR@PMOF can significantly promote DCs and $CD8^+$ T cell maturation, reversing the immunosuppressive TIME.[124] Similarly, Li et al constructed a near-infrared-responsive nanoenzyme by doping Mn^{2+} into OVA-templated Prussian blue nanoparticles. These nanoparticles induced oxidative stress through photothermal conversion and simultaneously released Mn^{2+} to activate the STING pathway and promote DCs maturation and antigen presentation, resulting in significant T cell activation and the TIME modulation.[125] Moreover, Zhou et al synthesized Mn_3O_4@Au-dsDNA/DOX nanoparticles, which integrated chemotherapy with STING pathway activation functions. The synergy between DOX-mediated oxidative stress and STING pathway activation by dsDNA and Mn^{2+} enhanced $CD8^+$ T cell activity and intratumoral infiltration. Notably, through the enhanced permeability and retention effect, Mn_3O_4@Au-dsDNA/DOX nanoparticles can accumulate at tumor sites and significantly improve immunosuppressive TIME.[126] Excessive oxidative stress was known to induce cellular damage and DNA mutations.[127] Although synergy of oxidative stress inducing and STING pathway activation can better modulate the immunosuppressive TIME, nanotechnology application in the future is expected to balance efficiency and safety of oxidative stress response.

Synergy of TLRs and STING Pathway Activation

Toll-like receptors (TLRs), one of the key innate immune receptors, detect pathogens and damage and activate anti-tumor immune responses.[128] The combined activation of TLRs and the STING pathway can produce synergistic effects for more effective immune system activation and immunosuppressive TIME reversal.[129] Zhang et al developed multi-component nano-vaccines (McNVs) by conjugating TLR7/8 agonist 522 and STING agonist CDG^{SF}. TLR7/8 pathway activation can promote a series of inflammatory and immune cytokine production. When synergized with STING pathway activation, these McNVs nanoparticles effectively enhanced APCs presentation and increased lymphocyte intratumoral infiltration, reversing the immunosuppressive TIME.[130] Similarly, Liu et al developed TME-targeting nanoparticles (PMM NPs) by conjugating TLR4 agonists and Mn_3O_4. In synergy with TLR4-mediated NF-κB activation, the PMM NPs can amplify STING-mediated immune response and increase IFN and pro-inflammatory cytokine secretion. PMM NPs can also reprogram macrophages from the M2 to M1 phenotype, alleviating immunosuppressive TIME.[131] However, co-activation of these pathways may trigger excessive cytokine release or cytokine storms.[132] Therefore, optimizing therapeutic parameters (including dosage, timing, administration sequence, and route of administration) represents an effective strategy to balance efficacy and safety. Additionally, novel TME-responsive nanomaterials capable of precise spatiotemporal modulation of immune activation are expected to facilitate controlled regulation of immune responses.[133]

Synergy of Radiotherapy and STING Pathway Activation

Radiotherapy, a classical anti-tumor therapy, induces tumor cell death through DNA damage and immunogenic cell death (ICD). Radiotherapy can release damage-associated molecular patterns and TAAs and subsequently activate immune cells. When combined with STING pathway activation, it can further promote APC maturation and T cell activation, thereby modifying the immunosuppressive TIME.[134] By conjugating cGAMP to nanoscale metal-organic layers (MOLs), Luo et al developed cGAMP/MOL nanoparticles. These MOLs effectively penetrated and were retained within the TIME, exhibited strong radiosensitizing effects, and promoted tumor ICD. The incorporation of STING pathway activation by cGAMP. This dual effect resulted in increased radiosensitivity, facilitated the intratumoral infiltration of APCs, and enhanced antigen presentation, ultimately promoting anti-tumor responses.[135] In the same way, Deng et al synthesized MnO_2 nanoparticles using biomimetic mineralization techniques. Mn^{2+} ions released from nanoparticles not only activated the STING pathway but also overcame hypoxia-induced radioresistance in tumor cells and enhanced ICD, ultimately reversing the immunosuppressive TIME.[136] As illustrated in Figure 4, these STING-centric nanomaterials synergistically enhance tumor-vaccine efficacy and modulate the immunosuppressive microenvironment.

Despite significant progress in nanomaterials for TIME modulation, distinct strategies exhibit varied therapeutic efficacy and safety profiles. Single STING pathway activation provides controlled immune stimulation yet is insufficient against complex immunosuppressive environments. Combining oxidative stress markedly enhances antigen release and immune cell infiltration but poses potential cytotoxic risks. Similarly, combined activation of TLR and STING pathways strongly reverses immunosuppression but requires careful management of cytokine release. Additionally, integrating

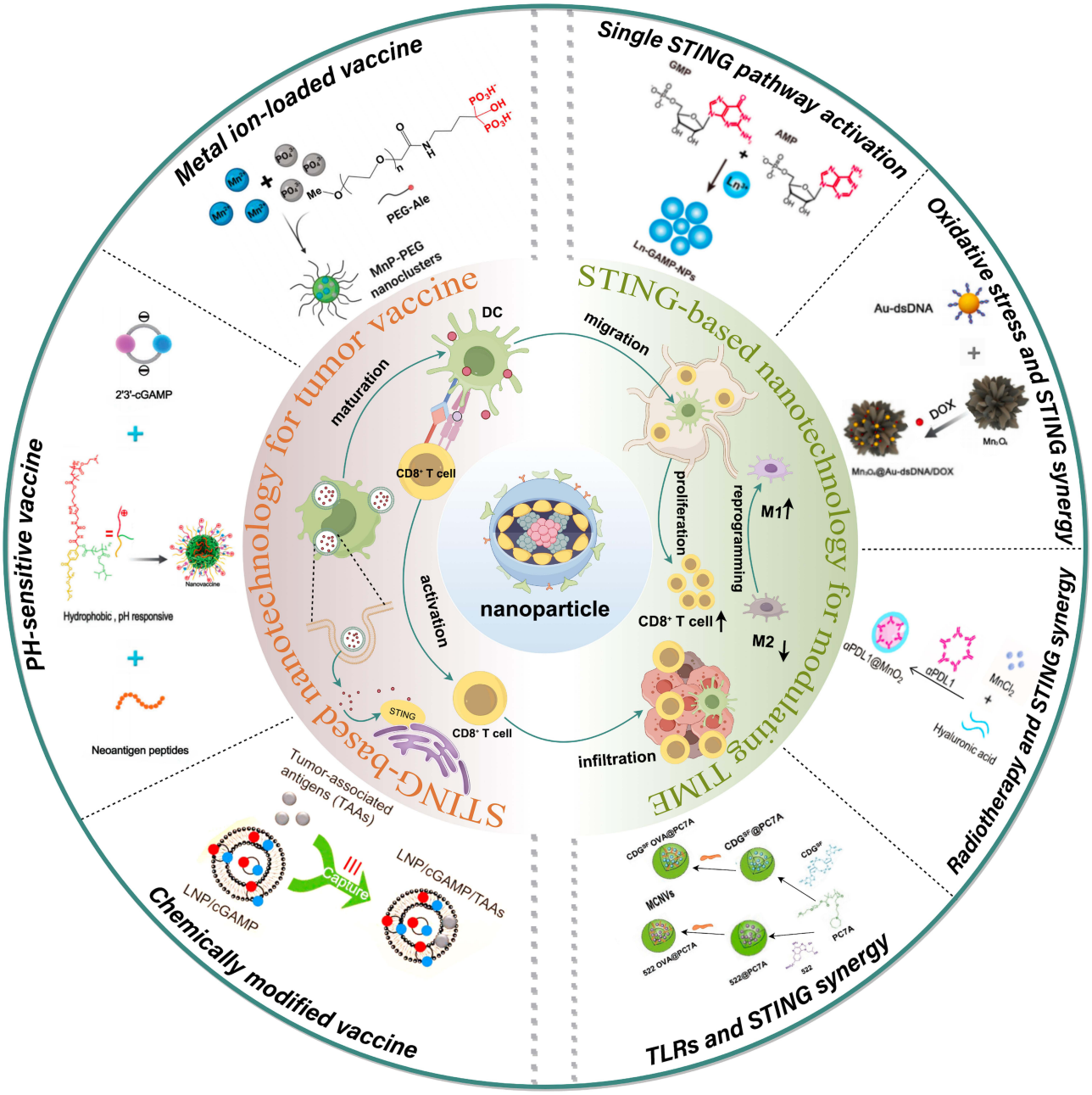

Figure 4 STING pathway-based nanomaterial in tumor vaccines and immune microenvironment modulation. The application of nanomaterials to enhance tumor vaccine efficacy and modulate the immune microenvironment, focusing on strategies to activate the STING pathway and integrate multiple synergistic effects (such as oxidative stress, radiotherapy, and TLR pathway activation), results in enhanced $CD8^+$ T cell proliferation and an M2-to-M1 macrophage phenotype switch. Reproduced from Gao M, Xie YQ, Lei K, et al. A Manganese Phosphate Nanocluster Activates the cGAS-STING Pathway for Enhanced Cancer Immunotherapy. Advanced Therapeutics 2021;4(8). © 2021 The Authors. Advanced Therapeutics published by Wiley-VCH GmbH. Creative Commons CC-BY-NC license.[98] Su T, Cheng F, Qi J, et al. Responsive Multivesicular Polymeric Nanovaccines that Codeliver STING Agonists and Neoantigens for Combination Tumor Immunotherapy. Adv Sci (Weinh) 2022;9(23):e2201895. © 2022 The Authors. Advanced Science published by Wiley-VCH GmbH. Creative Commons CC BY license.[105] Chen J, Qiu M, Ye Z, et al. In situ cancer vaccination using lipidoid nanoparticles. Sci Adv 2021;7(19). Copyright © 2021 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original US Government Works. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC).[111] Luo Z, Liang X, He T, et al. Lanthanide-Nucleotide Coordination Nanoparticles for STING Activation. J Am Chem Soc 2022;144(36):16366–16377. Copyright © 2022 American Chemical Society.[119] Zhou M, Wang X, Lin S, et al. Multifunctional STING-Activating Mn(3) O(4) @Au-dsDNA/DOX Nanoparticle for Antitumor Immunotherapy. Adv Healthc Mater 2020;9(13):e2000064. © 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[126] Zhang B-D, Wu J-J, Li W-H, et al. STING and TLR7/8 agonists-based nanovaccines for synergistic antitumor immune activation. Nano Research 2022;15(7):6328–6339. © Tsinghua University Press 2022. This article is made available via the PMC Open Access Subset for unrestricted research re-use and secondary analysis in any form or by any means with acknowledgement of the original source. These permissions are granted for the duration of the World Health Organization (WHO) declaration of COVID-19 as a global pandemic.[130] Deng Z, Xi M, Zhang C, et al. Biomineralized MnO(2) Nanoplatforms Mediated Delivery of Immune Checkpoint Inhibitors with STING Pathway Activation to Potentiate Cancer Radio-Immunotherapy. ACS Nano 2023;17(5):-4495–4506. Copyright © 2023 American Chemical Society.[136]

radiotherapy amplifies immune activation and antigen presentation, though further clinical validation of safety and optimal dosage is required.

STING Pathway-Based Nanomaterial for T Cell Tumor Immunotherapy

T cell tumor immunotherapy aims to enhance T cell responses for effective tumor recognition and elimination by targeting tumor-specific antigens.[137] Developments in nanomaterial have demonstrated the ability to enhance DC antigen presentation and promote T cell activity, holding substantial potential in improving T cell tumor immunotherapy effects. This potential is especially significant in CAR-T cell therapy, where STING pathway activation markedly amplifies CAR-T cell proliferation and cytotoxicity.[138,139]

Enhancing DC Antigen-Presentation Ability and T Cell Tumor Immunotherapy

By means of chemically modified and mesoporous nanoparticles, nanotechnology optimizes STING agonist delivery to DCs, promoting their antigen-presentation ability and T cell activation.

Chemically Modified Nanoparticles

It is reported that chemically modified nanoparticles with mannan can enhance their recognition by DCs, induce mannan-associated antigens phagocytosis, and promote DCs maturation and antigen-presentation ability.[140,141] Stearic acid (SA) was grafted onto chitosan and subsequently modified with mannose to form M-CS-SA micelles. These micelles can effectively target DCs through interaction with the mannose receptor and adsorb TAAs released from Oxaliplatin-induced ICD, creating an autologous tumor vaccine. By activating the STING pathway and promoting DCs maturation and antigen-presentation ability, these micelles increased $CD8^+$ T cells intratumoral infiltration, effectively inhibiting tumor growth.[142] Similarly, bovine serum albumin (BSA) was grafted onto mannose to construct BSA-Man@Mn^{2+}. This nanoparticle also effectively facilitates DC-targeting through interaction with the mannose receptors on DCs. Concurrently, ferritin-encapsulated β-lapachone (Lap) released from BSA-Man@Mn^{2+} induced tumor cells ICD and released abundant dsDNA for STING pathway activation. In combination with STING agonist Mn^{2+}, BSA-Man@Mn^{2+} ultimately promoted $CD8^+$ T cell activation, significantly enhanced T cell tumor immunotherapy effects.[143] Additionally, Li et al developed nanoparticles, ONc-Mn-A-malF127, with antigen-capturing capabilities through chemically grafting the protein capture groups malF127. By prolonging the retention of antigens released through the photosensitizer ONc-induced ICD at tumor sites, the malF127 component enhanced their phagocytic uptake by DCs. Concurrently, the incorporation of STING agonist Mn^{2+} and ABZI collectively promoted DC maturation, ultimately inducing $CD8^+$ T cells to mediate anti-tumor immune responses.[144]

Mesoporous Nanoparticles

Mesoporous nanoparticles, novel nanoparticles featuring a large surface area and easy functionalization for loading drugs such as cisplatin, are a promising drug delivery platform for tumor treatment.[145,146] By utilizing mesoporous silica nanoparticles functionalized with PEG and loaded with c-di-GMP, Chen et al developed novel nanoparticles named cdG@RMSN-PEG-TA. Through prolonging antigen retention time and modulating immune cell interactions in tumor sites, these nanoparticles significantly enhanced DC antigen presentation and co-stimulatory molecule expression, resulting in the recruitment of $CD8^+$ T cells, amplifying T cell tumor immunotherapy effects.[147] Another mesoporous nanoparticles are composed of polymerized alginate porous scaffolds, exhibiting high porosity and controlled degradability.[148] Smith et al utilized porous scaffolds loaded with c-di-GMP and CAR-T cells. When these implants were subsequently placed at solid tumor sites, the CAR-T cells effectively eradicated tumor cells and released TAAs. Concurrently, c-di-GMP activated DCs and enhanced antigen presentation, providing immunological support for CAR-T cells and improving the efficacy of CAR-T cell-mediated tumor immunotherapy.[149] By means of simple structure and high loading capacity, mesoporous nanoparticles are expected to address the complex synthetic technology of chemically modified nanoparticles.

Enhancing Drug Tumor Accumulation and T Cell Tumor Immunotherapy

Nanomaterials can be engineered to prolong the circulation time of STING agonists, enable their sustained release within the TME, enhance agonist accumulation in tumors, promote $CD8^+$ T cell infiltration, and ultimately augment the T cell immunotherapy effects.[150]

Prolonged Drug Circulation Time

Given the irregular and complex structure of tumor vasculature, a prolonged drug circulation time can significantly enhance the concentration of drugs within tumor sites.[151] A novel highly hydrophobic nanoparticle composed of ROS-sensitive polymer (P1) and mPEG2k-DSPE can significantly enhance the stability of the loaded drugs, prolong their circulation time, and increase their accumulation within tumor sites. These nanoparticles, loaded with cisplatin and camptothecin, induced DNA damage and activated the STING pathway, increasing $CD8^+$ T cells infiltration and enhancing T cell tumor immunotherapy effects.[152] Additionally, red blood cell (RBC) membranes were used to develop novel nanoparticles to extend the circulation time and elevate their concentration in tumor sites. Building on this approach, Li et al synthesized nanoparticles named m-PUNCs by integrating ultrasmall iron oxide nanoparticles with the STING agonist PHMA diblock copolymer. These nanoparticles were significantly uptaken by TAMs, activated the STING pathway, increased $CD8^+$ T cell populations and enhanced T cell tumor immunotherapy.[153] Prolonged drug circulation time has a trend to increase systemic toxicity, suggesting the critical need for precisely targeted delivery to minimize the systemic toxicity.

Precisely Targeted Drug Delivery at Tumor Sites

Precisely targeted drug delivery strategies can enhance drug accumulation at tumor sites, reduce systemic toxicity and improve T cell tumor immunotherapy. Intratumoral injection is the simplest way to distribute drug in tumors.[154] Cheng et al encapsulated cGAMP in a silk fibroin (SF) hydrogel and injected it into the tumor site. Hydrogel, characterized with the thermoresponsive properties, can transition from a liquid to a solid state at physiological temperatures (37 °C). The hydrogel's stable properties ensured their retention at tumor site and facilitated the sustained delivery of the STING agonist cGAMP to DCs, promoting $CD8^+$ T cell proliferation within both the tumor and associated lymph nodes, ultimately inducing a robust anti-tumor immune response.[155]

Under common subcutaneous or intravenous administration, achieving precisely targeted drug delivery at tumor sites remains to be addressed. Novel magnetic iron oxide nanoparticles can achieve highly precise, drug delivery to tumor site through directional guidance under an externally magnetic field.[156] Huang et al utilized magnetic iron oxide nanoparticles loaded with Mn^{2+} and Ca^{2+} to synthesize Fe_3O_4@Ca/$MnCO_3$. Under an external magnetic field, the nanoparticles upon subcutaneous administration were directed to the tumor sites and interacted with DCs, facilitating TAAs internalization. Mn^{2+} significantly activated immune responses via the STING pathway activation, while Ca^{2+} induced autophagy in DCs, enhanced antigen presentation, ultimately promoted $CD8^+$ T cell activation and improved T cell tumor immunotherapy effects.[157] It is expected to conduct further clinical applications to evaluate its efficacy and safety. As shown in Figure 5, these targeted delivery strategies enhance T cell tumor immunotherapy by improving antigen presentation, prolonging in-vivo exposure of STING agonists, and achieving precise tumor-site accumulation.

Nanomaterial-based strategies have markedly improved DC antigen presentation and STING agonist accumulation at tumor sites, though notable limitations persist. Chemically modified nanoparticles effectively enhance DC targeting, but their complex synthetic process impedes large-scale production. Mesoporous nanoparticles offer simple structures and high loading capacity yet raise biodegradability concerns. Approaches prolonging drug circulation time significantly increase tumor accumulation but concurrently heighten systemic toxicity. In contrast, precise targeted drug delivery effectively reduces off-target effects, yet clinical effectiveness and feasibility remain to be confirmed.

Challenges in Clinical Translation

Despite extensive research on improving the therapeutic outcomes with STING pathway-based nanomaterials, clinical translation remains limited. Some drawbacks and challenges should be considered.

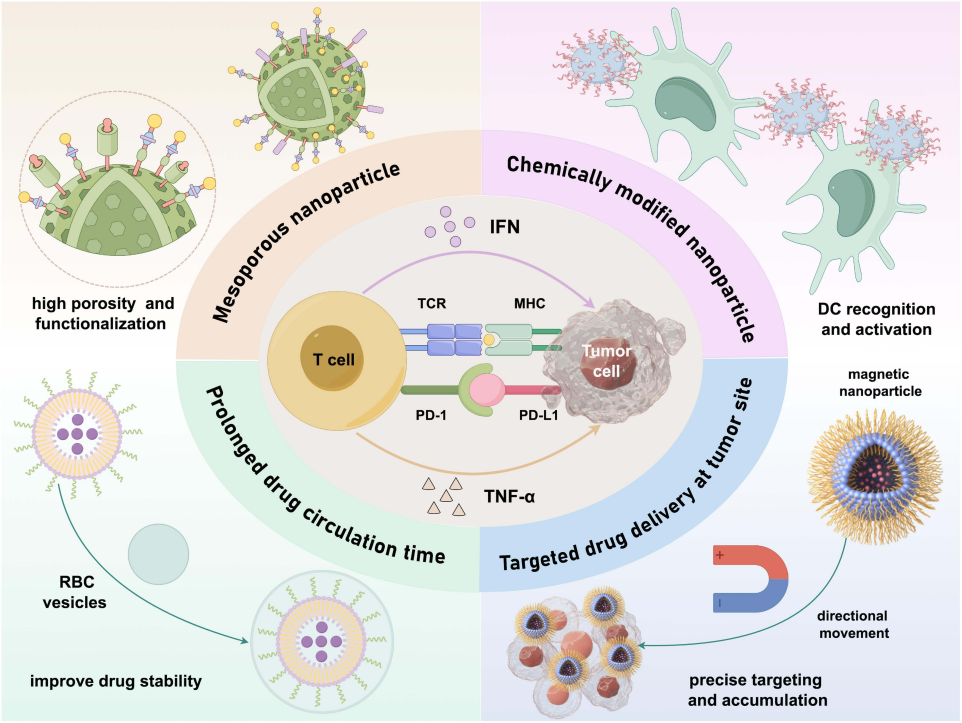

Figure 5 STING pathway-based nanomaterial for enhancing T cell tumor immunotherapy. Application of nanomaterial in enhancing T cell tumor immunotherapy, focusing on improving tumor-associated antigen presentation, prolonging drug (STING agonist etc) circulation, and achieving targeted drug delivery at tumor sites.

Clinical Trial Research Updates

Most nanomaterial-based delivery systems are still assessed in murine tumor models, especially melanoma,[56,96,119] that inadequately reflect human biological heterogeneity and immune diversity,[158–160] leaving their efficacy in other tumors uncertain and impeding clinical translation. Therefore, exploring animal models that can better recapitulate human immune microenvironments is expected to generate reliable efficacy data and accelerate clinical translation. In this regard, patient-derived xenografts or humanized mouse models, which successfully recreate patient-specific tumor-immune interactions,[161–163] can bring new insights for this challenge.

Regulatory Hurdles

The complex synthesis process of nanomaterials, especially those incorporating biological or chemical modifications, increasingly presents regulatory challenges that impede clinical translation.[164,165] Researchers are encouraged to identify robust formulations through systematic evaluation and the establishment of Good Manufacturing Practice standards for nanomaterial synthesis,[166,167] aiming to ensure batch consistency and scalable production for clinical translation.[168,169]

Biosafety Considerations

Clinical biosafety considerations primarily arise from immune hyperactivation induced by STING pathway activation, as well as nanomaterial-induced systemic toxicity, exemplified by Mn^{2+}- and Zn^{2+}-related neurotoxicity.[58,103] Recently, surface modifications like PEGylation, ligand decoration and TME-responsive activation enhance targeting of nano-delivery and reduce dosing, effectively alleviating immune hyperactivation and systemic toxicity. PEGylated MnP-PEG nanoparticles significantly enhanced intratumoral STING activation by improving endocytic drug delivery into APCs.[98] Mannose-modified MnO_2 nanoparticles improved delivery specificity to immune cells via receptor-mediated uptake.[102] A series of TME-responsive nanomaterials can be activated under tumor-specific acidic pH, enabling controlled drug release and enhanced targeting of nano-delivery.[104,105,107] Nevertheless, the long-term biosafety of these approaches requires further investigation, including comprehensive evaluation of pharmacokinetics and biodistribution.[86,170]

Outlook

The integration of nanomaterial with STING pathway modulation opens a new prospect for tumor immunotherapy, characterized by improved efficacy, precision, and adaptability.

It has been reported that basal activation of the STING pathway varies across tumor types, with patient genetic backgrounds and tumor immune statuses further affecting tumor immunotherapeutic effects.[21,171–173] In particular, the latter, characterized by differences in immune cell infiltration and activation within the tumor immune microenvironment, represents a key challenge for effective STING pathway-based immunotherapy. Hence, the assessment of tumor mutational burden, neoantigen levels, and cytokine expression using genomic and proteomic data can support the design of STING pathway-based nanomaterial and personalized treatment. Additionally, combining ICI therapy to restore exhausted T cells helps enhance immune cell infiltration and activation in the tumor microenvironment, offering a promising approach to modulate immune status.

In summary, the future of STING pathway-based nanomaterial in tumor immunotherapy lies in refining nanocarrier systems for optimized delivery of STING agonist. Innovations in biocompatible, multifunctional nanoparticles and biodegradable, TME-responsive materials will enhance the targeting of nano-delivery and minimize systemic toxicity.

Abbreviations

STING, stimulator of interferon genes; ER, endoplasmic reticulum; STIM1, stromal interaction molecule 1; cGAS, cyclic GMP-AMP synthase; dsDNA, double-stranded DNA; cGAMP, cyclic GMP-AMP; IKK, IκB kinase; TBK1, TANK-binding kinase 1; IFN, interferon; DCs, dendritic cells; APCs, antigen-presenting cells; ICIs, immune checkpoint inhibitors; CAR, chimeric antigen receptor; CDG, c-di-GMP; OVA, ovalbumin; CDA, c-di-AMP; CDN, cyclic dinucleotide; ENPP1, ecto-nucleotide phosphodiesterase 1; ABZI, aminobenzoimidazole; TREM2, triggering receptor expressed on myeloid cells 2; TAMs, tumor-associated macrophages; TME, tumor microenvironment; TAAs, tumor-associated antigens; RAFT, reversible addition-fragmentation chain transfer; UPS, ultra-pH-sensitive; TIME, tumor immune microenvironment; Treg, regulatory T; ROS, reactive oxygen species; TLRs, Toll-like receptors; ICD, immunogenic cell death; MOLs, metal-organic layers; SA, stearic acid; BSA, bovine serum albumin; RBC, red blood cell; SF, silk fibroin.

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Author Contributions

All authors made a significant contribution to the work reported. ZWR took part in drafting and revising the article. TXL, QYC, WXC, and ZKQ contributed to the critical review and editing of the manuscript. LT and GNQ conceived the study, supervised its execution, approved the final version for publication, and agree to be accountable for all aspects of the work. All authors have agreed on submission to the International Journal of Nanomedicine.

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Disclosure

The authors report no conflicts of interest in this work.

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