International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

# Novel Modifications and Delivery Modes of Cyclic Dinucleotides for STING Activation in Cancer Treatment

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**Abstract:** The microenvironment tends to be immunosuppressive during tumor growth and proliferation. Immunotherapy has attracted much attention because of its ability to activate tumor-specific immune responses for tumor killing. The cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway is an innate immune pathway that activates antitumor immunity by producing type I interferons. Cyclic dinucleotides (CDNs), produced by cGAS sensing cytoplasmic abnormal DNA, are major intermediate activating molecules in the STING pathway. Nowadays, CDNs and their derivatives have widely worked as powerful STING agonists in tumor immunotherapy. However, their clinical translation is hindered by the negative electrical properties, sensitivity to hydrolytic enzymes, and systemic toxicity. Recently, various CDN delivery systems have made significant progress in addressing these issues, either through monotherapy or in combination with other treatment modalities. This review details recent advances in CDNs-based pharmaceutical development or delivery strategies for enriching CDNs at tumor sites and activating the STING pathway.

**Keywords:** cyclic dinucleotides, stimulator of interferon genes pathway, immunotherapy

## Introduction

As one of the biggest dangers threatening human life and health safety, tumors cause nearly 10 million deaths each year.[1] The treatment of tumors has always been faced with poor prognosis and unsatisfactory eradication.[2,3] In recent years, the strength of immunotherapy has brought new hope for tumor treatment. This emerging treatment has unique advantages in that it precisely attacks tumor cells by the personal immune system, increasing patient tolerance and producing long-lasting anti-tumor effects.[4] More than that, combining immunotherapy with other anti-tumor tactics may not only enhance therapeutic efficacy but also reduce tumor recurrence.[5] These remarkable superiorities make immunotherapy one of the important development directions of cancer therapy.

The cyclic GMP-AMP synthase(cGAS)-stimulator of interferon genes (STING) pathway is an evolutionarily conserved immune pathway widespread in living organisms.[6] After interacting with double-stranded DNA (dsDNA), cGAS catalyzes the formation of 2′, 3′-cyclic guanosine monophosphate (GMP) - adenosine monophosphate (AMP) (2′, 3′-cGAMP).[7–9] The generated cGAMP subsequently activates the stimulator of interferon genes (STING) on the endoplasmic reticulum (ER).[9,10] Activated STING induces downstream production of the type I interferon and strongly upregulates interferon-driven anti-tumor effects.[11] Given that the STING pathway activation is an important link in the anti-tumor responses of multiple immune cell types, many studies have been devoted to exploiting the anti-tumor potential of the STING pathway.[12,13]

Received: 30 October 2024
Accepted: 28 December 2024
Published: 6 January 2025

Cyclic dinucleotides (CDNs), as natural STING agonists, have thus entered the public eye.[14,15] CDNs are cyclic structures consisting of two nucleotides linked by phosphodiester bonds, including cyclic diadenosine monophosphate (c-di-AMP, CDA), cyclic diguanosine monophosphate (c-di-GMP, CDG), and cyclic GMP-AMP (cGAMP).[16,17] Given the natural STING agonistic function of CDNs, many STING agonists based on them come into being, which activate the STING pathway by mimicking the structures and functions of CDNs.[18,19]

Though showing distinct potency in vitro experiments, CDNs have certain limitations in activating the STING pathway in the clinic.[20] First, CDNs suffer from degradation by nucleotide hydrolases because of their high sensitivity to phosphodiesterases (PDEs).[21] Second, anionic phosphate groups enriched on CDNs make it difficult for them to penetrate through the negatively charged cell membrane surface to the cytoplasm. This prevents CDNs from effectively activating STING in the cytosol and exerting downstream anti-tumor immune functions.[16] Besides, owing to their hydrophilicity, CDNs are highly prone to systemic dissemination and trigger extensive inflammatory cytokine responses, resulting in uncontrollable inflammatory damage.[22] Consequently, exogenously dosed CDNs showed poor efficacy as well as serious toxic side effects in clinical trials.[23,24] To resolve these issues, emerging drugs and delivery materials have been constructed to increase the accumulation of CDNs at tumor sites and enhance their STING activation abilities.

Here, we summarize the new progress in drug discovery or nano delivery policies centered on CDNs. The new opportunities for its combination with other treatment modalities are also described. With the gradual understanding of the mechanisms of CDNs in STING activation and cell-cell signal transduction,[25] many novel medications, such as artificially synthesized CDN analogs, have been developed to enhance the STING activation efficacy by enhancing CDN retention in tumor microenvironment (TME).[22,26] Meanwhile, with the rapid development of nano-assisted therapy technology, multiple nanomaterial systems have been used to reform the in vivo delivery of exogenous CDNs. Along with improving the delivery efficiency of CDNs, these nanomaterials reduced systemic toxicity by specifically targeting tumor tissues using their surface modifiers.[27,28] Furthermore, certain special delivery systems, such as hydrogels, bacterial carriers, and metal materials have been widely explored to actualize CDNs-based STING activation. These novel modes compensate for the shortcomings of traditional direct administration of CDN drugs and inject new vitality into anti-tumor immunotherapy.

## Mechanisms of CDNs-Based STING Agonists

Tumor cells are characterized by genomic instability, susceptibility to oxidative stress, and exuberant metabolism,[29,30] which result in micronucleus formation and chromatin fragment leakage, leaving dsDNA naked in the cytoplasm.[31,32] Moreover, nuclear and mitochondrial DNA damage will be induced by exogenous stimuli, such as chemotherapy or radiotherapy (RT).[32,33] DsDNA activates cGAS to synthesize 2 “, 3” -cGAMP, one form of CDNs, which can be transferred and spread between cells. In diversified organisms, CDA and CDG were first found to directly target STING.[34] With the in-depth study of the STING pathway, 2′, 3′ -cGAMP was confirmed to be the more effective molecule that targets STING activation in mammals.[35] The endoplasmic reticulum (ER) - transmembrane receptor STING protein in tumor or immune cells binds to 2 “, 3” -cGAMP, oligomerizing and transporting to trans-Golgi vesicles.[11] In the Golgi apparatus, STING integrates downstream TANK binding kinase 1 (TBK1) through its C-terminal tail (CTT). TBK1 undergoes conformational changes upon binding to STING, triggering its autophosphorylation and the phosphorylation of STING. Phosphorylated STING unites interferon regulatory factor 3 (IRF3), making it close enough to be phosphorylated by TBK1.[36] Then phosphorylated IRF3 forms a dimer and translocates to the nucleus and exerts its transcriptional function, expressing immunostimulatory genes (ISGs) and type 1 interferons (IFNs), including IFN-β.[37,38] IFN-β promotes the recruitment and activation of tumor-associated inflammatory cells, as well as the activation and maturation of dendritic cells (DCs). Furthermore, it facilitates the cross-activation of $CD8^+$ T cells, infiltrating and killing primary and metastatic tumors, and forming immune memory (Figure 1).[39,40]

Since being reported, the STING pathway has rapidly become a hotspot for research, followed by the appearance of numerous drugs and material systems for STING activation. Many drugs targeting the accumulated endogenous CDNs have been studied for elevating the 2′, 3′ -cGAMP distribution in TME to decline their hydrolysis by extracellular hydrolases.[22,41] Simultaneously, various strategies for CDN delivery are being explored, including polymer particles,[42,43] liposomes,[44,45] hydrogels,[46,47] and engineered bacteria.[48,49] Given its inherent characteristics, nanotechnology effectively

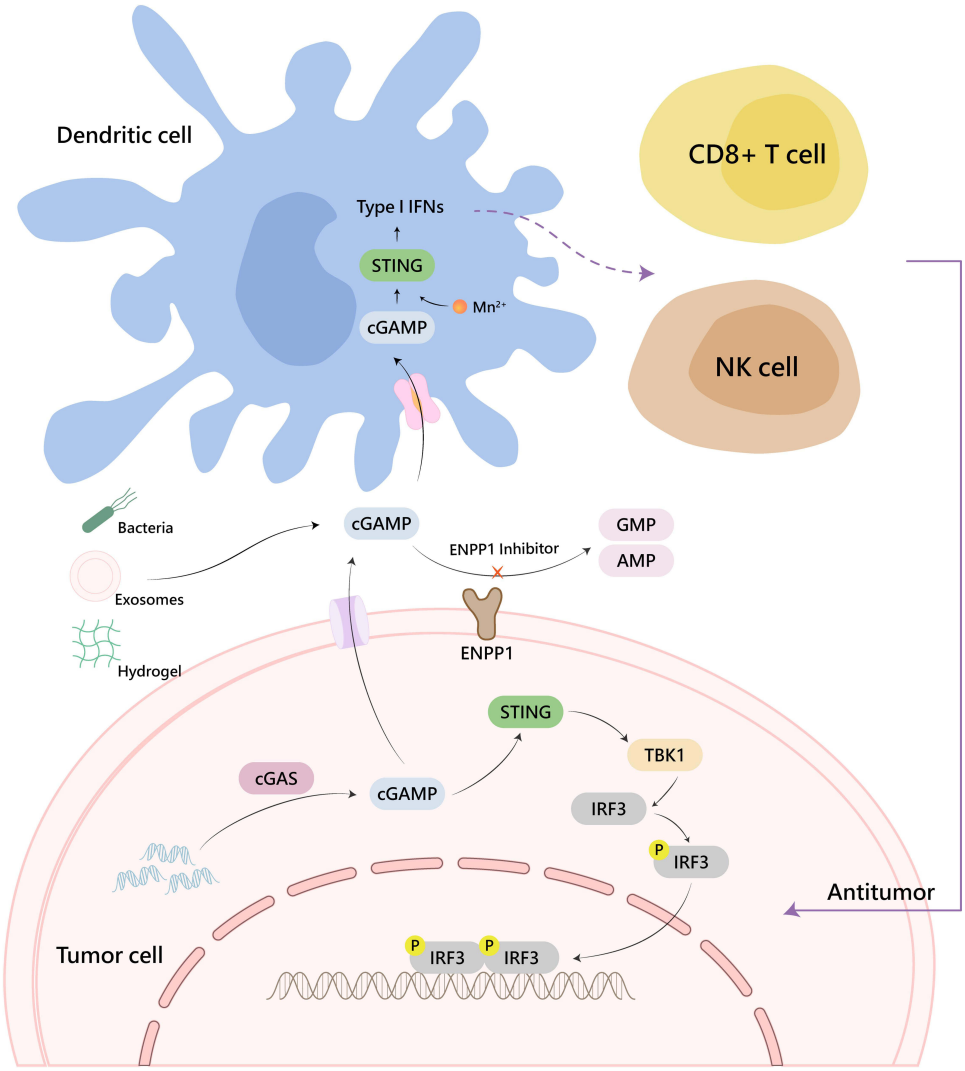


**Figure 1** Schematic representation of CDNs-mediated STING activation.

achieves synergistic treatment of STING pathway activation with other therapies. For example, the combination of immune checkpoint blockade (ICB),[50] photothermal therapy (PTT),[51] photodynamic therapy (PDT),[52] chemodynamic therapy (CDT),[53] etc. further enhances its anti-tumor efficacy.

In summary, the agents that activate the cGAS-STING pathway have flourished in the field (Table 1).

## CDNs and Their Analogues

Many studies have demonstrated that cGAMP will directly activate the STING pathway after transferring to immune cells.[37] CDNs have turned into universal STING agonists nowadays.[91,92] However, the negative charge and high susceptibility to hydrolysis by extracellular nucleases make CDNs not meet the requirements for becoming a drug molecule.[93,94] With the intention of creating STING-targeting medications with enhanced pharmacokinetics and efficacy, kinds of cGAMP analogs have emerged.[95]

Loads of CDN analogues and their modified derivatives have been synthesized, which demonstrate higher drug activity, tolerance to hydrolytic enzymes, and cell penetration rate. Since CDNs are formed by two nucleotides connected by two phosphodiester bonds, the main modification sites of CDNs are located in the base, ribose, and phosphate backbone.[91]


https://doi.org/10.2147/IJN.S503780

**Table 1** Cyclic Dinucleotide-Mediated STING Activation

| Type | Ingredients for STING Activation | Target Tumor Cells/Tumor Type | Co-treatment | Reference |
|---|---|---|---|---|
| CDNs and CDNs analogs | E7766 | BCG, NMIBC | - | [54] |
| | ADU-S100 | Advanced/Metastatic Solid Tumors, Lymphomas | Anti-CTAL-4, Anti-PD-1 | [55] |
| | MK-1454 | B16-F10, MC38 | Anti-PD-1 | [56] |
| | MK-2118 | Advanced/Metastatic Solid Tumors, Lymphomas | Anti-PD-1 | [57] |
| | IMSA-101 | Solid Tumors | Anti-PD-1 | [58] |
| | BI-1387446 | EMT6 | Anti-PD-1 | [59] |
| | BMS-986301 | MC38, CT26 | Anti-PD-1 | NCT03956680 |
| | TAK-676 | Advanced/Metastatic Solid Tumors | Anti-PD-1 | [60] |
| | SB-11285 | 4T1, CT26 | Anti-PD-1, cyclophosphamide | [61] |
| | VB-85247 | BCG, NMIBC, MB49 | Anti-PD-1 | [62] |
| | 2′, 3′-GAMP | SCC-VII, Pan02, KPC | C-REV | [63] |
| Polymer particles | CDG | B16-F10 | - | [19] |
| | CDG | 4T1 | - | [64] |
| | CDG | CT26 | Melanin+NIR | [65] |
| | CDG | B16-F10, CT26, 4T1 | Anti-PD-1 | [66] |
| | 2′, 3′-GAMP | MC38, TC-1 | - | [67] |
| | 2′, 3′-GAMP | B16-F10 | Anti-PD-L1 | [68] |
| | 2′, 3′-GAMP | B16-F10 | Anti-CTAL-4, Anti-PD-1 | [69] |
| | 2′, 3′-GAMP | B16-F10 | siRNA | [70] |
| | $Mn^{2+}$, 2′, 3′-GAMP | B16-F10 | Anti-PD-L1 | [71] |
| | CDA, $Mn^{2+}$ | CT26 | - | [22] |
| | CDA, $Mn^{2+}$, $Zn^{2+}$ | CT26 | - | [72] |
| | CDA, $Mn^{2+}$ | 4T1 | RT | [73] |
| | ADU-S100 | B16-F10 | RT | [74] |
| Lipid nanoparticles | 2′, 3′-GAMP | B16-F10 | - | [75] |
| | 2′, 3′-GAMP | MC38, TC-1 | - | [76] |
| | 2′, 3′-GAMP | B16-F10 | TAAs, OVA, DOX | [77] |
| | 2′, 3′-GAMP | B16F10, MC38 | TLR4 agonists, OVA, Anti-PD-1 | [78] |
| | CDG | B16-F10 | Anti-PD-1 | [44] |
| | CDG | B16-F10 | CpG-ODNs, TLR9 agonists | [79] |
| | CDA, $Zn^{2+}$ | MC38, B16-F10, LLC | OVA, Anti-PD-L1 | [80] |
| | CDA, $Mn^{2+}$ | C1498 | Anti-CTLA-4 | [81] |
| | ADU-S100 | MC38, B16-F10 | - | [82] |
| Hydrogel | 2′, 3′-GAMP | 4T1 | Surgery, $CuO_2$, DOX | [83] |
| | CDA | CT26, 4T1, GL-261-luc | CPT | [46] |
| | 2′, 3′-GAMP, 3′, 3′-GAMP | RAW264.7, L929 | OVA | [84] |
| | 2′, 3′-c-di-AM(PS)2 (Rp, Rp) | 4T1, LLC | Surgery | [85] |
| | 2′, 3′-c-di-AM(PS)2 (Rp, Rp) | Panc02 | Surgery | [86] |
| | 2′, 3′-c-di-AM(PS)2 (Rp, Rp) | GL-261-luc | Anti-PD-1, IL-15 | [87] |
| AuNPs | 2′, 3′-GAMP | K7 | GNR-PEI+NIR, Anti-PD-L1 | [88] |
| hNVs | 2′, 3′-GAMP | 4T1 | - | [89] |
| Engineered bacteria | CDA | B16-F10, EL4, A20, 4T1, CT26 | EcN | [46] |
| Virus-like particles | 2′, 3′-GAMP | B16-OVA | Anti-PD-1 | [90] |

**Abbreviations**: STING, stimulator of interferon genes; BCG, Bacillus Calmette-Guerin; NMIBC, unresponsive non-muscle invasive bladder cancer; Anti-CTAL-4, anti-cytotoxic T lymphocyte-associated antigen-4, Anti-PD-1, anti-programmed death receptor 1 monoclonal antibody; C-REV, canerpaturev; CDG, c-di-GMP; NIR, Near-Infrared Spectroscopy; 2′3′-cGAMP, 2′3′-cyclic GMP-AMP; Anti-PD-L1, anti-programmed death ligand 1 monoclonal antibody; CDA, c-di-AMP; RT, radiotherapy; TAAs, tumor associated antigens; OVA, Ovalbumin; Dox, doxorubicin; TLR4, Toll-like receptor 4; CpG-ODN, cytosine-phosphorothioate-guanine oligodeoxynucleotides; TLR9, Toll-like receptor 9; CPT, camptoth-ecin; IL-15, interleukin −15; AuNPs, Plasmonic Gold Nanoparticles; GNR-PEI, Polyethyleimine modified golden nanorod; hNVs, hybrid cell membrane nanovesicles; EcN, Nissle1917.

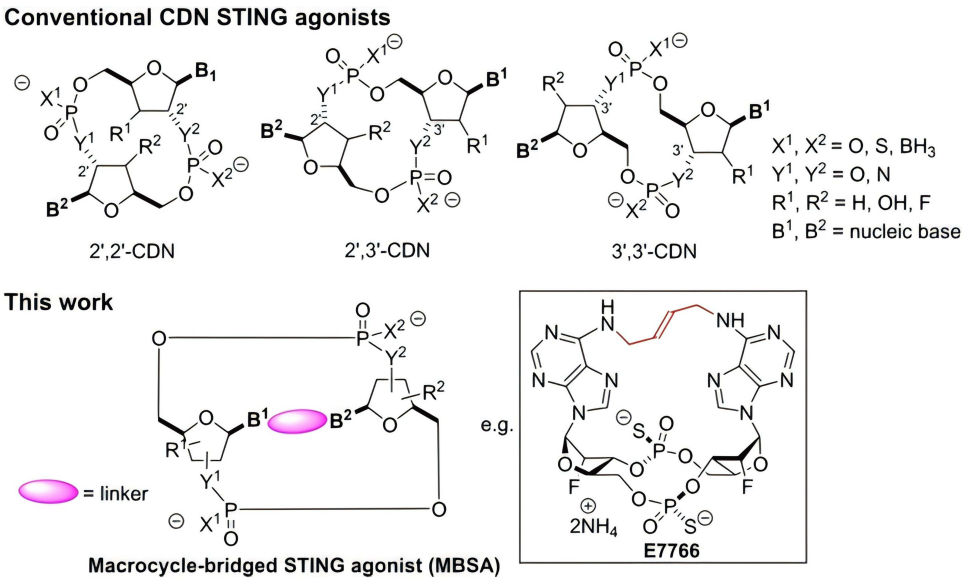


**Figure 2** Structures of conventional CDN STING agonists and macrocycle-bridged STING agonist (MBSA). Reproduced with permission from Kim DS, Endo A, Fang FG et al. E7766, a Macrocycle-Bridged Stimulator of Interferon Genes (STING) Agonist with Potent Pan-Genotypic Activity. *ChemMedChem*. 2021;16(11):1741–1744.[96] © 2021 Wiley-VCH GmbH.

Some earlier CDNs are now entering clinical trials. Kim et al reported a macrocycle-bridged STING agonist (MBSA),[96] which locked the bioactive u-shaped conformation of the CDNs by injecting a trans cyclic macrocyclic bridge between nucleic acid bases. MBSA exhibited extensive pan-genotypic activity in major human STING variants. E7766, possessing this conformation, has entered clinical trials. During this trial, E7766 exhibited antitumor activity and immune memory response in the bacillus Calmette-Guerin (BCG) unresponsive non-muscle-invasive bladder cancer (NMIBC) model (Figure 2).[54] Phosphorothioate modification is the most classical one among the phosphoric acid backbone of oligonucleotides,[97] which improves the immunoreactive activity and stability against nucleases degrading CDNs.[98] More importantly, phosphorothioate analogs can increase the hydrophobicity of CDNs, making them more easily to be taken up.[99] Many drugs approved for clinical trials, such as ADU-S100,[55] MK-1454,[56,100] BI-1387446,[59] are modified in this way. In a Phase I dose-escalation trial, Meric-Bernstam et al reported that ADU-S100 caused significant increases in inflammatory cytokine levels and peripheral blood T cell counts in patients with advanced or metastatic solid tumors or lymphomas, suggesting systemic immune activation. Also, 94% of evaluable injected lesions were stable or reduced in size. However, there existed a certain proportion of treatment-related adverse events, such as pyrexia (17%), chills (15%), and injection site pain (15%).[55]

Monotherapy with CDNs and their derivatives has mostly been upgraded and updated because of their insignificant clinical efficacy and non-negligible side effects.[55,101] In the bargain, combining with other treatment modalities or being the payload agents for novel delivery systems provides new ideas for CDN drugs to activate the STING pathway and related cancer immunotherapy.[102,103]

## Emerging Patterns for CDN Delivery

In recent years, diversified material systems have been explored and utilized to optimize drug delivery efficiency and healing efficacy. Apart from enhancing the targeting potency to reduce medical toxicity, these delivery systems prolonged the half-life of drugs by increasing their clearance resistance.[104,105] Besides, these new modes assisted in the combination of CDNs-mediated STING activation with various immunotherapy strategies for tumor killing.[106]

### Polymeric Microparticle

Polymer particles are widely used in nanomedicine synthesis as a classical nano-delivery material.[107,108] Polymer nanoparticles (PNPs) are typically constructed through spontaneous complex self-assembly employing biocompatible

and biodegradable polymers such as pectin, chitosan, cyclodextrin, etc.[109,110] In this process, therapeutic drugs are encapsulated in the core of PNPs. To achieve higher targeting and increase uptake efficiency, PNPs selectively interact with certain cells or tissues via surface functional groups modified by specific proteins, peptides, monoclonal antibodies, etc.[111,112] Some PNPs can even achieve lysosomal escape during the process of intracellular acidification maturation, diminishing the destruction of loaded pharmaceuticals.[110] Considering the characteristics aforementioned, polymer particles are currently being actively developed for the delivery of CDNs.[45]

Polymer particles can increase tumor-site retention and fulfill intracellular delivery of unmodified native CDNs, such as CDG and cGAMP.[64,67,69] Recently, Xu et al reported an amphiphilic supermolecular drug-drug conjugate (ASDD) (Figure 3). Through hydrogen bonds and hydrophobic interactions, ASDD used nucleotide lipid ligand hydrophobic 3′, 5′ -dioleic acid-deoxycytidine (3′, 5′ -diOA-dC), which was synthesized by oleic acid and deoxycytidine, to assemble with hydrophilic CDG into uniformly stable supramolecular CDG-nanoparticles (CDG-nps).[19] CDG-nps were proved to enhance CDG uptake by APC cells at the tumor site, promoting STING activation and immune activation in TME. Their another decomposition product, 3′, 5′ – dioA-dC, was degraded by esterases into oleic acid and deoxycytidine, arising with no negative impact on the organism.

Interestingly, CDNs can undergo covalent modifications to alter their pharmacological properties. After polymerizing with other substances and forming polymer particles, their anti-tumor effect may be directly strengthened.[65] Dosta et al designed a highly potent poly-drug-conjugated (β-amino ester) (pBAE) nanoparticle formulation (CDN-NP). They

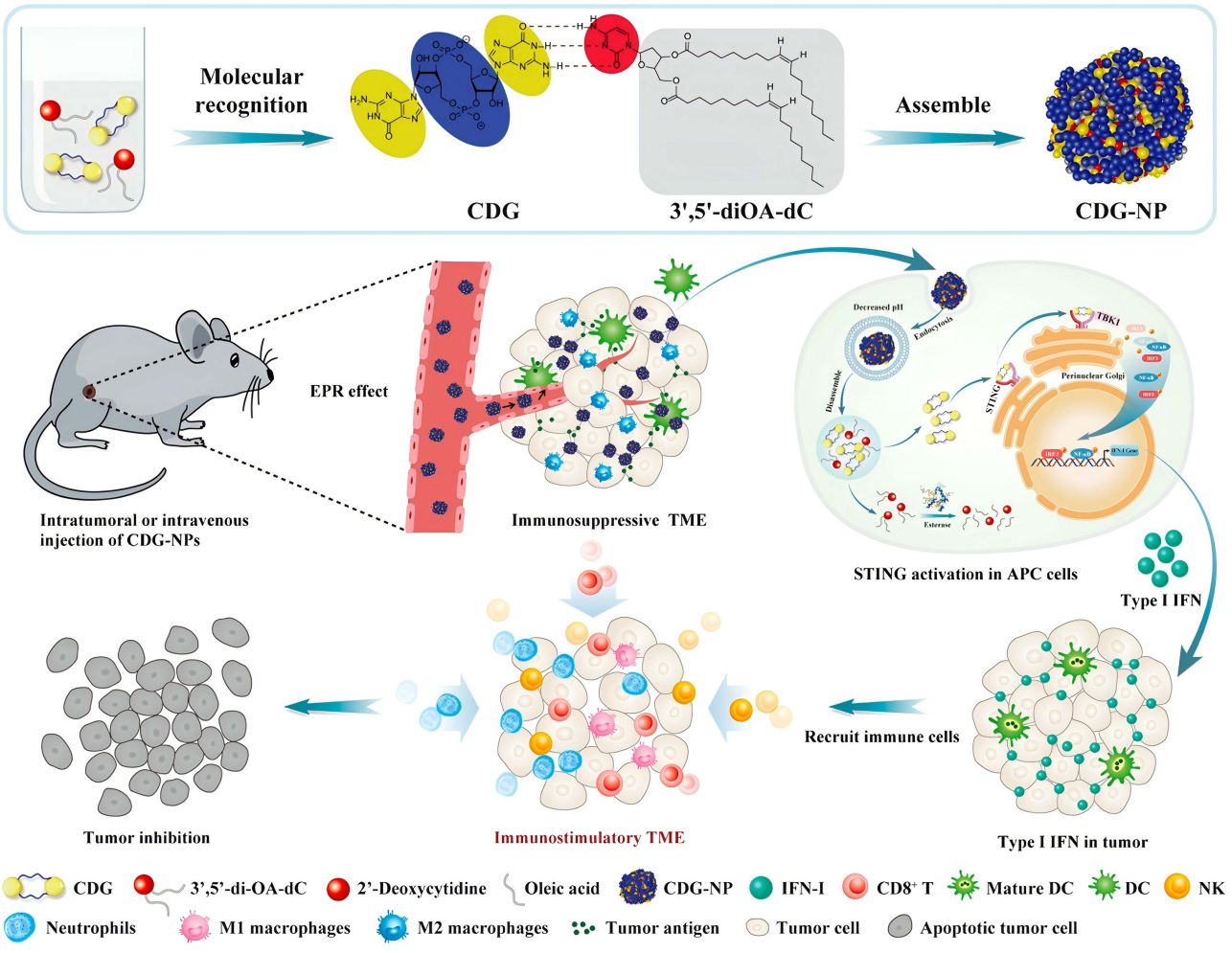


**Figure 3** Formation of Supramolecular Cyclic Dinucleotide Nanoparticle Delivery System CDG-NPs and Their Application in STING-Mediated Cancer Immunotherapy. Reproduced with permission from Xu L, Deng H, Wu L et al. Supramolecular Cyclic Dinucleotide Nanoparticles for STING-Mediated Cancer Immunotherapy. *ACS Nano*. 2023;17(11):10,090–10,103.[19] Copyright 2023, American Chemical Society.

employed maleimide-modified ML-317 conjugate with pBAE to form ML-317-linker-pBAE and acrylate-terminated pBAEs polymer mix with arginine oligopeptide (C6-CR3) to form cationic pBAEs. The CDN-NP was born by means of electrostatic complexation between CDNs and C6-CR3, shaping an intravenous STING agonist.[66] CDN-NPs internalized by tumor cells were released over time and taken up by immune cells in TME and secondary lymphoid organs. Whereupon CDNs would be cleaved by cathepsins in the cytoplasm and released from CDN-NPs, thereby inducing STING activation for tumor growth inhibition. In multiple syngeneic mouse tumor models, low-dose CDN-NPs combined with immune checkpoint blockade (ICB) treatment induced robust tumor killing and immune memory.

In addition to delivering CDNs agents alone, the polymer system easily achieves the combination of CDNs with other medications.[70,74] For example, Wang et al established a combined anti-tumor pattern by integrating CDA and $Mn^{2+}$ into tannic acid nanostructure (TMA-NPs).[73] Magnetic resonance imaging (MRI) displayed that under X-ray irradiation, TMA NPs significantly alleviated hypoxia caused by the oxygenation of $Mn^{2+}$ in the large tumors, bringing about excessive production of ROS and DNA damage. Accordingly, CDNs released from TMA-NPs, $Mn^{2+}$ released from phenolic carriers, and DNA fragments released from cell debris worked together to amplify STING activation. The combination of TMA-NPs and RT activated the cascaded STING pathway and fulfilled a remarkable radioimmune therapeutic effect on primary and distant tumors, paving the way for the clinical application of $Mn^{2+}$-CDN nano-modulators in multimodal tumor treatment.

## Lipid Nanoparticles

Nanoliposomes are spherical vesicles composed of one or more phospholipid bilayers. The hydrophilic head of phospholipid molecules is inserted into water, and the hydrophobic tails aggregate with each other to form spherical liposomes with bilayer lipid molecules.[113,114] At this point, hydrophobic drugs are encapsulated in lipophilic bilayer shells while hydrophilic drugs are enclosed in the aqueous interior region of liposomes. After administration, liposomes fuse with biofilms by their strong affinity, thereby releasing the loaded active ingredients into the cells.[115] Liposomes therefore protect the active drug from degradation in body fluids and overcome barriers to cellular and tissue absorption.[116,117] In the bargain, via modifying with different ligands or combining with diverse delivery platforms, lipid nanoparticles upgrade drug targeting and diminish toxic side effects on nontarget organs.[118]

Cationic nanoliposomes have been widely investigated for CDN delivery.[119] Encapsulating CDNs in the aqueous phase of the nanoliposome core is the most classical mode of encapsulation. Koshy et al encapsulated cGAMP in cationic liposomes at different polyethylene glycol (PEG) levels to assess their enzymatic resistance, STING activation, and systemic immune activation ability.[75] In both orthotopic melanoma models and invasive lung metastases, pegylated cGAMP liposomes showed definite therapeutic efficacy. By adjusting the surface structure of liposomes, many liposome material models strengthened their stability in body fluids and made for stronger STING activation. For example, Doshi et al prepared a $CD103^+$ DC-targeted cGAMP liposome using a Clec9a-targeting peptide called WH peptide to selectively deliver cGAMP into DCs. Clec9a/DNGR-1 is a type C lectin receptor that highly expressed on $CD8^+$ and $CD103^+$ DCs yet not on any other hematopoietic cells. This resulted in far more encapsulated cGAMP being ingested by DC, lowering fluid clearance and systemic side effects. In MC38 and B16F10 tumor-bearing mouse models, only 0.1 mg/kg intravenous injection of the cGAMP liposomes would induce a strong antitumor immune effect.[82]

Due to the toxicity issues and insufficient in vivo efficacy of cationic lipids, other forms of lipid nanocarrier systems are being developed vigorously.[120,121] For instance, pH-responsive ionizable lipids are neutral at physiological pH, and positively charged only in the acidic environment of the endosome. This feature largely ameliorated the shortcomings of cationic lipids in terms of potency and toxicity.[122] Nakamura et al designed a PEGylated CDG ionizable lipid STING-LNPs based on YSK12-C4.[44] YSK12-C4 is an ionizable cationic lipid (CLD) with a high affinity for immune cells, which can effectively deliver core drugs into the cytoplasm of cells. In the B16-F10 lung metastasis model, STING-LNPs activated NK cells, transforming the tumor immuno-cold state into the immuno-hot state for innate immune responses. In addition, it has been shown that the shape and property of nanocarriers significantly affect their abilities to be transported in vivo and assimilated by target cells. Non-spherical nanoparticles displayed longer blood circulation half-life and higher cellular internalization efficiency than spherical ones.[123] Consequently, Dane et al designed a lipid nanodisc formed by self-assembly of mercapto PEGylated lipids and high melting temperature phospholipids, containing CDN prodrug with

 https://doi.org/10.2147/IJN.S503780 

a diamine peptide linker (Figure 4a and b).[76] They conducted coarse-grained molecular dynamics simulations on the LND model (diameter 40 nm). When passing through a rigid pore (diameter 20 nm) under moderate tension of approximately 330 pN (200 kJ $mol^{-1}$ $nm^{-1}$), LND could deform and enter pores smaller than its equilibrium diameter, while traditional liposomes with similar lipid composition and the same diameter could not deform enough to enter the pore. This result indicated that an elliptical flexible disk may diffuse faster than a hard object of the same size. What's more, it exhibited the same trend in the absence of external forces or airflow interference. In a 24h biodistribution model in MC38 tumor-bearing mice, LND-CDNs showed higher tumor accumulation (7.4%: 1.1%) and lower absorption in other tissues (less than 0.5%) than CDN-encapsulated liposomal formulations (LipoCDN).

The application of lipid nanocarriers is a canonical pathway for achieving the conjunction of STING activation with other therapeutic approaches. Classical cancer treatment modalities, including chemotherapy or radiotherapy, have been certificated to produce tumor-specific antigens, which are considered the tumor orthotopic vaccine.[124,125] Chen et al designed a lipid nanoparticle (LNP) to simultaneously reach cross-presentation of antigens and activation of the STING pathway. Firstly, immune genetic death and tumor-associated antigens (TAAs) release were induced by intratumoral injection of low doses of doxorubicin (DOX). Subsequently, lipid nanoparticles LNP/cGAMP captured TAAs in situ through electrostatic interactions, promoting antigen presentation of APCs. Then, cGAMP released in the cytoplasm activated the STING pathway, which led to type I IFN generation and T cell activation, thereby producing a strong anti-tumor immune response and forming immune memory in the B16F10 tumor model.[77]

The combination of lipid nano delivery systems with other delivery modalities is also being developed by researchers for CDN delivery. Lipid polymer hybrid nanoparticles (LPHNPs) are advanced core-shell nanostructures composed of liposomes and polymer nano units. Its polymer core region is ordinarily surrounded by a lipid layer. Because of their dual structural characteristics, LPHNPs have the advantages of high stability, high load capacity, high biocompatibility, rate-limiting controlled release, long half-life, and superior therapeutic effect.[126] Yang et al reported a hybrid delivery system of lipid polymers. In this system, bacteria-derived CDA was encapsulated into nanoscale coordination polymers (NCP) consisting of a non-toxic zinc phosphate hydrophilic core and PEG-conjugated phospholipids (ZnP). Compared with the half-life of CDA encapsulated liposomes (3.30 hours), ZnCDA-NCP greatly reduced CDA degradation in serum, prolonging its circulation half-life to 12.63 hours in vivo. The increasing half-life naturally led to a significant slowdown in the growth rate of the tumor model.[80]

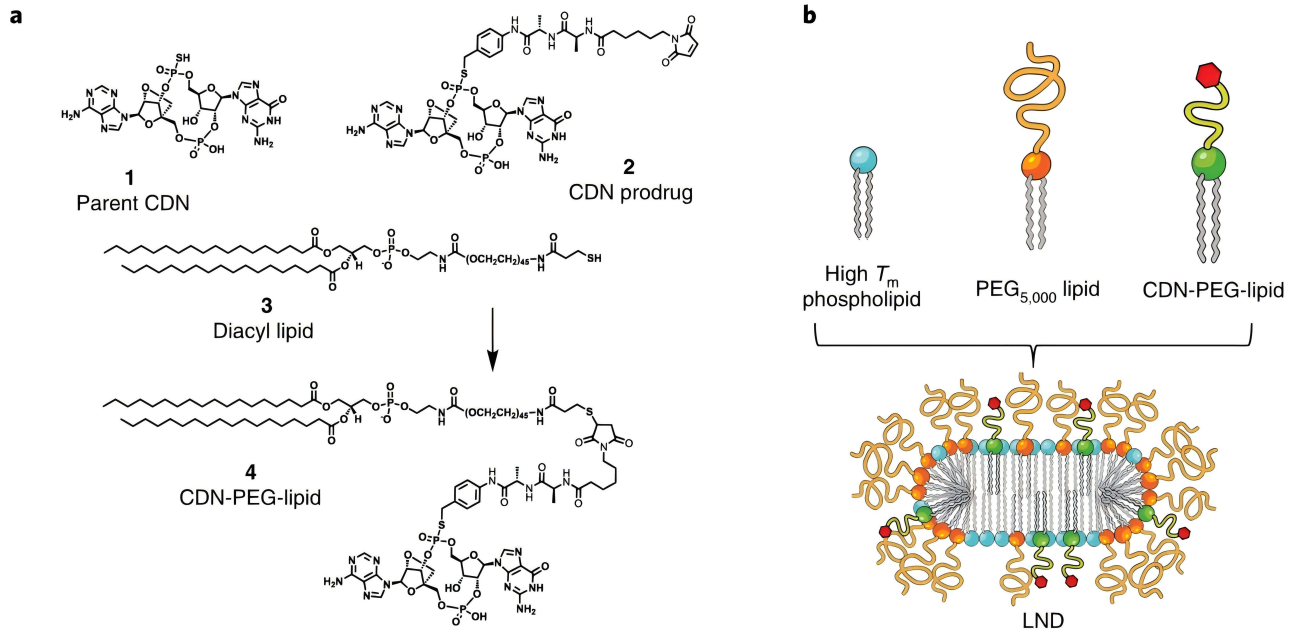


**Figure 4** Design and characterization of nanoparticles for STING agonist delivery. (**a**), Chemical structures of the parent CDN STING agonist (1), CDN prodrug (2), diacyl lipid (3) and CDN-PEG-lipid (4). (**b**), Schematic of LND containing CDN-PEG-lipid. Reproduced with permission from Dane EL, Belessiotis-Richards A, Backlund C et al. STING agonist delivery by tumour-penetrating PEG-lipid nanodiscs primes robust anticancer immunity. Nat Mater. 2022;21(6):710–720.[76] © The Author(s) 2022. Creative Commons Attribution 4.0 International License.

## Hydrogel

The majority of current STING agonists in clinical trials are administered intratumorally.[127] However, drug leakage resulting from intratumoral injection easily reduces curative efficacy and brings about serious toxic damage to surrounding tissues.[128] Therefore, controlled-release delivery systems, such as hydrogels formed in situ, become the potential CDN delivery platform.[129,130] Hydrogel is a polymer system with excellent biocompatibility and biodegradability.[131] Its three-dimensional network structure is composed of one or more hydrophilic polymers, containing abundant water. Besides, there is evidence that hydrogel formulations are mostly prepared under mild conditions, which is more conducive to maintaining the activity of CDNs than that of nano formulations.[132]

Shortly after cGAMP was proved to have the capacity of STING activation, Lee et al designed a cationic linear polyethyleneimine (LPEI)/hyaluronic acid (HA) hydrogel (LH gel) to load cGAMP which was specifically delivered CDNs to phagocytic macrophages.[84] Compared with traditional cationic liposomes, LH/cGAMP gel prompted a prominent 2.5-fold increase in the amount of IFN-β released by immune cells. Recently, Wang et al exploited a supramolecular hydrogel system, which chemically coupled the hydrophilic peptide fragment iRGD with the hydrophobic anticancer medicine camptothecin (CPT) to form a peptide-drug conjugate (diCPT-iRGD).[46] In water, self-assembled DiCPT iRGD shaped supramolecular nanotubes (NTs) with positive surface changes, loading negatively charged CDA. After local injection, the CDA-NT solution shaped hydrogel instantly as a repository for internal expansion and discharge of CDA and CPT. In C57BL/6 tumor-bearing mice, the CDA loaded by the hydrogel system represented a sustainable secular liberation, which could still be detected 35 days after in vivo injection.

Considering that hydrogel systems are amenable to local injection, surgery has opened up a unique channel for hydrogel delivery systems. The application of medicine-carried hydrogel to postoperative tumor resection margins has become a reasonable means to induce tumor immunity and prevent local tumor recurrence.[86,133] Park et al pioneered the attempt to encapsulate cGAMP by a conventional hyaluronic acid hydrogel 3D scaffold, which was utilized at the tumor resection site after surgery.[85] Experiments indicated that hydrogel-encapsulated STING activators had a slower diffusion rate and longer-lasting liberation in vivo, contributing to eliminating residual tumor cells in the immunosuppressive microenvironment. Apart from regulating medicine release through grid size, some stress-responsive hydrogels can even actively respond to changes in light, heat, magnetic field, or pH value to obtain conditional drug release.[134] Lately, Fang et al designed a pH-responsive hydrogel system for in situ drug delivery in postoperative tumors.[83] The hydrogel system Gel@M/CuO2/DOX/STING was formed by self-assembly of polysulfoxide betaine methacrylate (PSBMA) in saline, encapsulating 2′, 3′ -cGAMP and M/$CuO_2$/DOX nanoparticles (doxorubicin(DOX)-loaded copper peroxide nanoparticles encapsulated by macrophage membrane). After the hydrogel was injected at the tumor site after breast cancer resection, the body fluid pH in TME drove hydrogel backbone ion interaction to degrade, loosing cGAMP and M/CuO2/DOX. Following closely behind were DNA damage induced by DOX, ROS generated by $Cu^{2+}$-catalyzed Fenton reaction, and activation of the STING pathway, accurately removing residual tumor cells and preventing postoperative tumor recurrence. In addition to the combination with traditional chemotherapy as well as chemodynamic therapy described above, hydrogel delivery systems are also commonly used to combine with other antitumor therapies. For instance, Wang et al combined multiple modalities of antitumor immunotherapy to synthesize a peptide-based supramolecular filament (SF) hydrogel, which was made up of three separated immunomodulators, including α-PD-1 antibody, il-15 cytokine, and CDA (Figure 5a).[87] Under the action of matrix metalloproteinase-2 (mmp-2) in tumor tissue, the hydrogel continuously discharged these pharmacological components, which played a synergistic role (Figure 5b).

## Other Delivery Methods

### Metallic Carriers

Metallic materials, such as gold nanoparticles (AuNPs), have been extensively investigated to exploit their biomedical applications, including pharmaceutical delivery, photoacoustic imaging, and photothermal therapy.[135] AuNPs have good biocompatibility and efficient targeting towards tumor tissues in the systemic circulation.[136] Surface modification of gold nanoparticles easily assist them in conjugating with other drugs or proteins, making them an ideal carrier for CDNs delivery.[137] Zhao et al prepared a polyethyleneimine-modified gold nanorod (GNR-PEI), in which positively charged GNR-PEI can complex with cGAMP through electrostatic interactions, forming a GNR-PEI/cGAMP complex.[88] GNR-

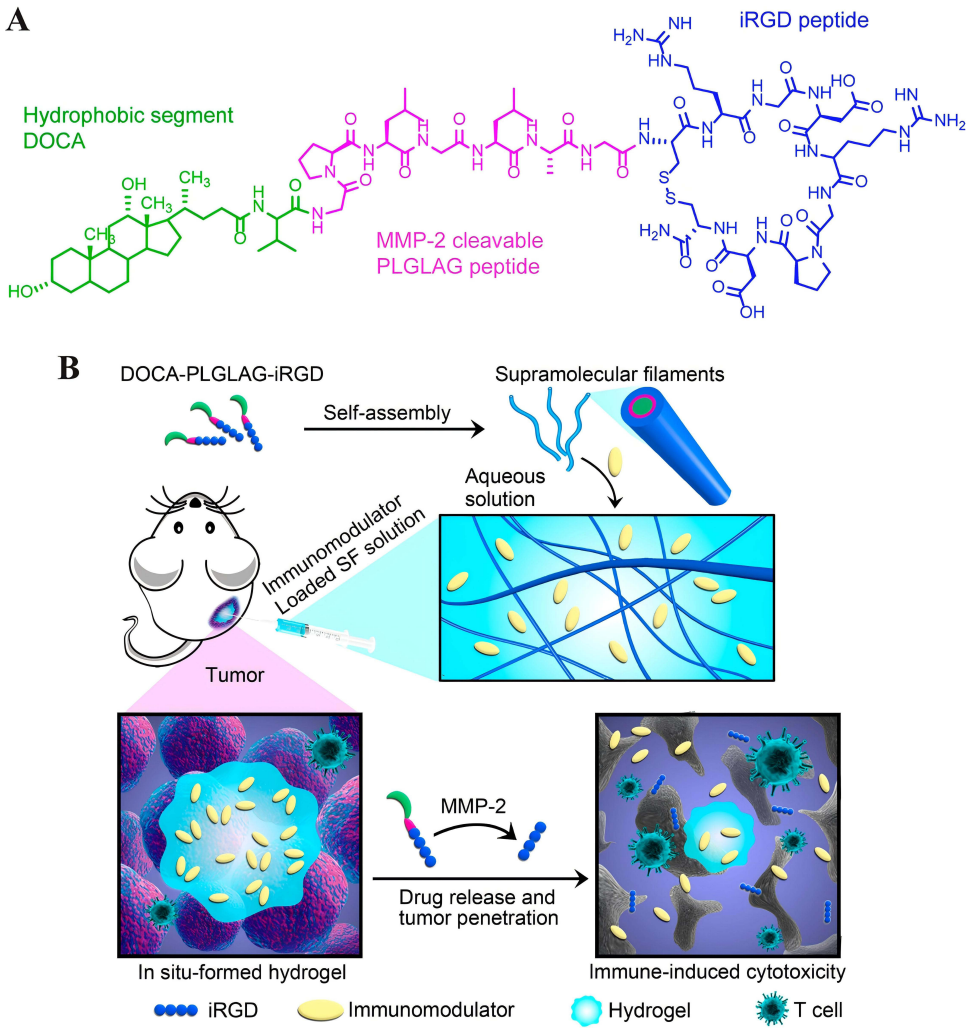


**Figure 5** Schematic illustration of the designed and studied immunotherapeutic supramolecular filament (SF) hydrogels. (**A**), Chemical structure of the designed DOCA-PLGLAG-iRGD peptide amphiphile (PA). (**B**), Schematic illustration of localized immunomodulator delivery using a DOCA-PLGLAG-iRGD supramolecular hydrogel for MMP-2-responsive drug release and tumor microenvironment regulation. Reproduced with permission from Wang F, Su H, Wang Z et al. Supramolecular Filament Hydrogel as a Universal Immunomodulator Carrier for Immunotherapy Combinations. ACS Nano. 2023;17(11):10,651–10,664.[87] Copyright 2023, American Chemical Society.

PEI/cGAMP triggered tumor ablation and in situ TAA generation under near-infrared light irradiation, recruiting antigen-presenting cells at the tumor site. Thereafter, STING activation induced by cGAMP stimulated the proliferation and activation of DCs, sensitizing the anti-tumor immune effect produced by tumor vaccines.

## Biomimetic Membranes

The low immunogenicity and tumor-targeting properties of biomimetic membranes make them safe, efficient, precise, and controllable drug delivery platforms.[138,139] Rao et al reported a hybrid biofilm nanovesicle (hNV) for the delivery of cGAMP to prevent tumor recurrence and metastasis after surgery.[89] The hNV was composed of platelet-derived NVs (P-NVs), M1 macrophage-derived NVs (M1-NVs), and tumor cell-derived NVs overexpressing high-affinity SIRPα variants (SαV-C-NVs) (Figure 6a). Platelet-derived NVs (P-NVs) made hNV effectively accumulated at the surgical wound site by binding to damaged blood vessels and tissues, enriching cGAMP at the postoperative tumor site. Meanwhile, M1 macrophage derived NVs (M1 NVs) repolarized TAM into an M1-like phenotype(Figure 6b). The overexpression of the SIRPα variant on the HNV surface greatly increased its affinity for CD47, competitively blocking the CD47-SIRP signaling axis of tumor cells. Through their synergistic effect, hNV reprogrammed the “cold” tumor to an immunogenic state, prominently inhibiting postoperative tumor recurrence and metastasis.

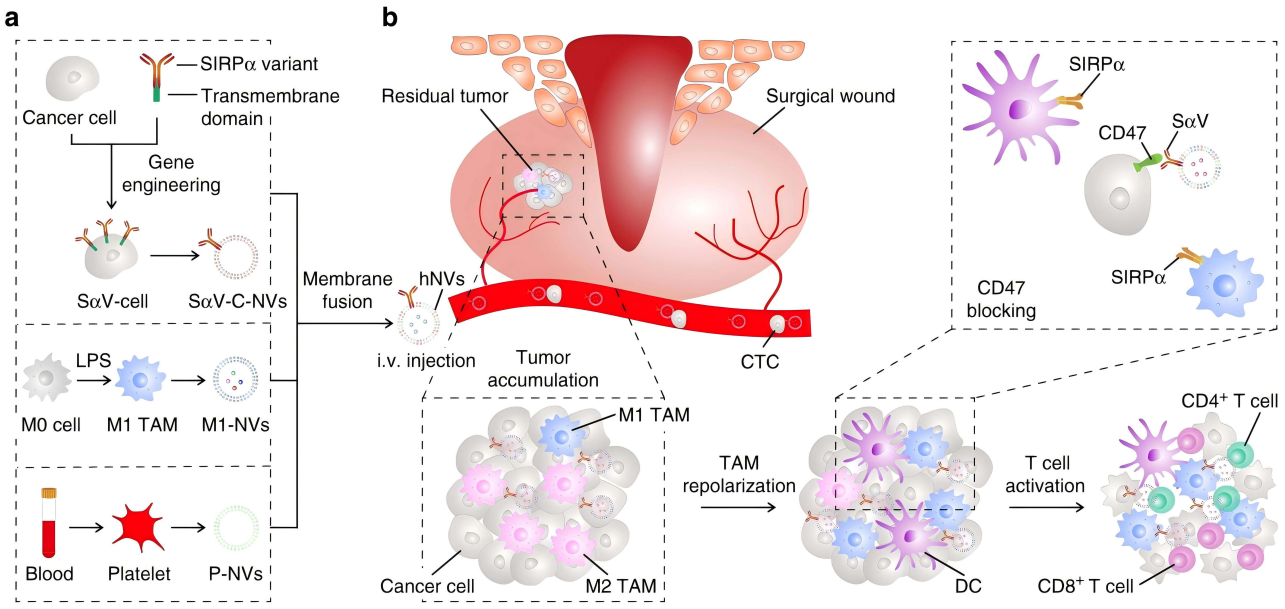


**Figure 6** Schematic and characterization of hNVs. a, Schematic showing the hNVs consist of engineered SαV-C-NVs, M1-NVs, and P-NVs. b, Schematic showing the hNVs efficiently interact with CTCs in the blood, accumulate in the post-surgical tumor bed, repolarize TAMs towards M1 phenotype, and block the CD47-SIRPα "don't eat me" pathway, thus promoting macrophage phagocytosis of cancer cells, as well as boosting antitumor Tcell immunity. Reproduced with permission from Rao L, Wu L, Liu Z et al. Hybrid cellular membrane nanovesicles amplify macrophage immune responses against cancer recurrence and metastasis. Nat Commun. 2020;11:4909.[89] Copyright © 2020, This is a US government work and not under copyright protection in the US; foreign copyright protection may applyCreative Commons CC BY license.

### Bacteria

Bacteria, as a particular delivery carrier, have attracted great attention because of their unique tumor-targeting properties and active phagocytosis by various immune cells.[140,141] Due to the fact that CDNs can be produced by invading bacterial cGAS, engineered bacteria with genetically modified characteristics are ideal carriers for STING agonism.[142] Leventhal et al designed an EcN strain SYNB1891 that expressed CDA at the tumor site. SYNB1891 used the hypoxia promoter pfnrs loop with dacA of Listeria monocytogenes to constitute the PfnrS-dacA circuit, initiating CDA expression in the anaerobic environment of tumor tissue.[48] SYNB1891 dramatically enhanced the expression of IFN-β1 and decreased tumor growth in B16/F10 tumor-bearing mice model. Apart from bacterial vectors, virus-like nanoparticles, such as cGAMP-VLPs formed from cGAMP coated with HIV-1 structural protein and vesicular stomatitis virus glycoprotein (VSV-G) also exhibited significant STING-based anti-tumor T cell responses.[90]

## Conclusion

The immune reversal capability induced by the STING pathway activation in tumor cells or APCs has made STING agonists a boom in tumor treatment.[142] Moreover, conclusive clues demonstrated that anti-tumor immune responses mediated by STING activation play important roles in conventional therapies. Therefore, STING agonists have rapidly evolved today as a potential complementary cure to other treatments.[143] Whereas CDNs are the natural upstream STING activating signaling molecules in organisms, an increasing number of novel molecules and delivery systems targeting enriching CDNs at tumor sites are being developed in laboratories and explored in clinical trials.[144] Unfortunately, direct systemic administrations of CDNs tended to show severe systemic toxicity. Their therapeutic efficacy failed to meet expectations, which remains to be further explored.[145,146]

Emerging CDNs-based STING activation strategies have upgraded their targeted efficacy through accurate medicinal action, avoiding harmful side effects. They largely address the shortcomings of direct systemic administration of STING agonists, making STING-mediated anti-tumor immune activation more precise and bringing less impact on other organs.[147] Simultaneously, combining with STING activation, RT therapy, chemotherapy, immune checkpoint inhibitors, and metal immunotherapy tend to display superior therapeutic effects.[148,149] In this review, we summarize the momentous advances in CDNs-based STING activation, including exploiting new CDN analogues and their derivatives, as well as developing multimodal novel CDN delivery systems.


https://doi.org/10.2147/IJN.S503780

However, heaps of CDN-targeted STING pathway activation strategies are still in their infancy. Before entering clinical applications, there are still many potential challenges. Firstly, there has been evidence that mouse STING (mSTING) and human STING (hSTING) do not respond consistently to various STING agonists. Regretfully, under the same degree of stimulation, mSTING reacts much more strongly to produce IFN-β or other corresponding cytokines than hSTING. Accordingly, a variety of therapeutic tactics with considerable efficacy in animal experiments may not necessarily be directly extrapolated to clinical patients.[150,151] Secondly, it has not been confirmed whether the specific staging of cancer patients (such as whether metastasis occurs) will affect the overall anti-cancer efficacy of STING agonists. Research into this issue may contribute to developing accurate clinical medication guidelines for STING agonists. Additionally, in recent years, many newly developed pharmaceuticals or delivery systems have complex synthesis processes and high heterogeneity, whose cost is extremely huge. It makes it difficult for them to achieve mass production, let alone clinical translation.[152]

Furthermore, there is much to be investigated regarding the STING pathway. In addition to the anti-tumor immune effects associated with type I IFNs, STING activation has been associated with glucose metabolism,[153,154] protein metabolism,[155] lipid metabolism,[156] and specific apoptosis.[157] Nevertheless, a majority of these theories have just been proposed recently and there is still a lack of in-depth understanding of their mechanisms. With the clarification of the framework of STING-related substance metabolism, new metabolic therapeutic agents or regimens will be discovered to optimally combine with STING agonists, promoting anti-tumor activity and minimizing toxicity. It can be foreseen that more pharmaceuticals and delivery patterns will be exploited to facilitate STING activation-dependent tumor treatments in the future.

## Abbreviations

cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; IFNs, interferons; CDNs, Cyclic dinucleotides; 2′, 3′-cGAMP, 2′, 3′-cyclic GMP-AMP; dsDNA, double-stranded DNA; ATP, adenosine triphosphate; GTP, guanosine triphosphate; ER, endoplasmic reticulum; TBK1, TANK binding kinase 1; IRF3, interferon regulatory factor 3; ISGs, immunostimulatory genes; GMP, guanosine monophosphate; AMP, adenosine monophosphate; PDEs, phosphodiesterases; ENPP1, exonucleotide pyrophosphatase/phosphodiesterase 1; EMT, epithelial-mesenchymal transition; QD, quaque die; DSPM, NaGdF4, Nd@NaLuF4@PEG-polyphenol/Mn; MBSA, macrocycle-bridged STING agonist; BCG, bacillus Calmette-Guerin; NMIBC, non-muscle-invasive bladder cancer; PNPs, Polymer nanoparticles; ASDD, amphiphilic supermolecular drug- drug conjugate; 3 ′, 5′ -diOA-dC, 3 ′, 5′ -dioleic acid-deoxycytidine; CDG-nps, CDG-nanoparticles; ICB, immune checkpoint blockade; RT, Radiotherapy; PEG, polyethylene glycol; APCs, antigen presenting cells; LPHNPs, Lipid polymer hybrid nanoparticles; CDA, cyclic diadenosine monophosphate (c-di-AMP); CDG, cyclic diguanosine monophosphate (c-di-GMP); NCP, nanoscale coordination polymers; LipoCDNs, CDNs encapsulated liposomal formulations; LipoCDA, CDA encapsulated liposomal formulations; CPT, camptothecin; SF, supramolecular filament; PEI, Polyethylenimine; hNV, hybrid biofilm nanovesicle; Tregs, tumor regulatory T cells; TME, tumor microenvironment; MRI, Magnetic resonance imaging; CLD, cationic lipid; TAAs, tumor-associated antigens; NTs, nanotubes; mmp-2, matrix metalloproteinase-2; AuNPs, gold nanoparticles.

## Data Sharing Statement

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

## Funding

This work was supported by the National Natural Science Foundation of China (82172645, 82372805 to W.G.; 82403433 to X.Z.), Key Research and Development Program of Jiangsu Province (BE2022667, BE2022753 to W.G.), Key Project of Nanjing Health Commission (ZKX21013 to W.G.; ZKX24013 to S.L.), Nanjing Drum Tower Hospital Cultivation Program for Outstanding Youth Science Fund of National Natural Science Foundation of China (2023-JCYJ-YP-02 to S.L.).

## Disclosure

The authors report no conflicts of interest in this work.

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