Background Activating the innate immune pathway of stimulator of interferon genes (STING) can elicit potent anti-tumor immunity via the production of type-I interferons (IFN-I). However, cyclic-dinucleotide (CDN) STING agonists have undesirable pharmacological properties. Most CDNs in clinical development are administered intratumorally, thus precluding their utility against advanced cancer. Here, we report the development of a new nanoparticle system for the systemic delivery of CDN STING agonists with potent efficacy, favorable pharmaceutical properties, and acceptable safety profiles.

Methods Various metal ions were screened for synergy with CDNs for IFN-I response from bone marrow-derived dendritic cells. Lipid nanoparticles carrying CDN and manganese ions (termed SNP) were synthesized. Mice bearing syngeneic tumors (including CT26 and B16F10) as well as genetically engineered mouse models were treated by intravenous administration of SNP, followed by tumor monitoring and immune profiling of the tumor microenvironment. White New Zealand rabbits bearing VX2 tumors as well as healthy mongrel dogs were treated with SNP and evaluated. Lastly, human tumor biopsies derived from head and neck squamous cell carcinoma (HNSCC) patients were incubated with SNP or soluble STING agonists and analyzed for immune activation.

Results We identified that Mn$^{2+}$ achieved strong synergy with CDN STING agonists for inducing IFN-I production. SNP carrying CDN and Mn$^{2+}$ was dosed intravenously in mice, leading to robust IFN-I response, remodeling of the immunosuppressive tumor microenvironment, and expansion of anti-tumor CD8$^+$ T cells. Intravenous SNP therapy resulted in robust anti-tumor efficacy in multiple murine tumor models, including CT26, B16F10, and a genetically engineered mouse model of MMTV-PyMT triple-negative breast cancer. We have also observed robust anti-tumor efficacy of SNP against VX2 squamous carcinomas in rabbits and have demonstrated the safety of intravenous SNP therapy in healthy dogs. Mechanistically, the efficacy of SNP therapy was dependent on the host STING expression but independent of the tumor STING expression. In addition, the anti-tumor efficacy of SNP was decreased in mice lacking Ifnar1 or Ifngr1 expression in the B16F10 melanoma model, showing the crucial effects of IFN-I and IFN-II responses. Moreover, SNP treatment led to robust IFN-I responses from fresh human tumor biopsies derived from HNSCC patients.

Conclusions SNP empowers highly effective systemic cancer immunotherapy via nanotechnology. It also underscores the potential of utilizing metal ions for immune-mediated disease treatment.

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Ethics Approval All work conducted on animals was in accordance with and approved by the University of Michigan Institutional Review Board (IRB).

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