Background The cGAS-STING pathway, which is crucial in antitumor immunotherapy, has been a research focus in developing STING agonists for cancer immunotherapy. However, the use of these agonists in clinical applications has been hindered by their instability, low bioactivity, and severe side effects. In this study, we created a new class of 'self-oxygenated' polymeric nanoparticles with redox-responsive properties that can deliver STING agonists while enhancing sonodynamic therapy (SDT). This approach aimed to efficiently activate the cGAS-STING pathway and achieve a synergistic effect between SDT and immunotherapy for pancreatic cancer.

Methods The nanosystem diABZI-ITPF@O2 was obtained using the polycondensation reaction and thin-film method. The hypoxia relief and sonodynamic therapeutic effects of this oxygen-carrying nanosystem on human and murine pancreatic cancer cell lines were studied. The tumor growth inhibition of the STING-activating nanosystem was evaluated in both subcutaneous and orthotopic pancreatic cancer mouse models. For mechanistic analysis, the study investigated the induction of immunogenic cell death (ICD), dendritic cell maturation, and T cell activation using immunofluorescence, flow cytometry, and RT-qPCR.

Results The spherical nanoparticles (diABZI-ITPF@O2) were formed by the amphiphilic fluoropolymer, with an average size of approximately 105.0 ± 3.6 nm. These nanoparticles could penetrate cancer cells, escape from lysosomes, generate reactive oxygen species (ROS) when exposed to ultrasound, and release drugs triggered by ROS. Moreover, this nanosystem exhibited a specific accumulation in tumor sites, alleviated tumor hypoxia, and induced an abscessal response. Consequently, it demonstrated a synergistic efficacy in SDT-immunotherapy, while minimizing immune-associated toxicity in both subcutaneous and orthotopic pancreatic cancer models. Mechanically, the ICD triggered by SDT would enhance the expression of co-stimulators on dendritic cells (DCs), while the activation of STING would stimulate the production of IFN-β, CCL5, CCL10, and CCL11, thereby facilitating the recruitment and activation of cytotoxic T cells (figure 1). This process would ultimately transform the pancreatic tumor microenvironment from poor immunogenicity to T cell inflammation.

Conclusions We have demonstrated that the diABZI-ITPF@O2 nanosystem successfully targeted tumor sites, alleviated tumor hypoxia, improved SDT efficiency, and effectively triggered the activation of the STING pathway. This activation then promoted the recruitment and activation of DCs and T cells, ultimately leading to a more powerful and effective antitumor immune response. These findings may offer new perspectives on the creation of a highly effective SDT-immunotherapy nanosystem, with the potential to enhance the effectiveness of immunotherapy.

Ethics Approval All animal experiments were performed in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) guidelines and the protocols approved by the Institutional Animal Care and Use Committee (IACUC) of West China hospital, Sichuan University.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0897-E