Background Intratumoral immunotherapy is a clinically investigated approach based on the premise that local priming of the antitumor immune response can yield durable systemic immunity and avoid toxicities associated with systemic administration. However, direct intratumoral injection rapidly disseminates from the tumor, resulting in diminished efficacy and undesirable systemic exposure. Variations in intratumoral injection methods as well as lesion type and location could further affect local bioavailability and consequently, clinical outcome. Moreover, clinical protocols typically require repeated administration, which could be challenging for hard to reach tumors. To address these challenges, we present an immunotherapy eluting intratumoral ‘nanoseed’ for in situ treatment. Sustained intratumoral immunotherapy release occurs autonomously through diffusion across a nanofluidic membrane mounted on the nanoseed without requiring pumps, ports or manipulation after implantation. We posit that nanoseed-mediated sustained intratumoral release of agonist CD40 antibody could promote local and systemic antitumor responses for effective tumor control.

Methods We investigated our approach using the syngeneic KPC pancreatic cancer murine model. When tumor volumes approximated ~140 mm³, nanoseed containing agonist CD40 antibody was intratumorally implanted in a one-time minimally invasive trocar procedure for sustained in situ delivery (8 µg/day), in comparison to systemic administration (100 µg every other day for a total of 4 doses) and vehicle controls. Treatment response and adverse effects were evaluated using tumor volume, flow cytometry and imaging mass cytometry assessment of immune activity, serum ELISA, liver histology and Kaplan Meier survival analysis.

Results Sustained release of agonist CD40 antibody directly into the tumor microenvironment through the nanoseed resulted in significant tumor burden reduction and prolonged survival of KPC mice without toxicities. With nanoseed-CD40 treatment, local tumor immune microenvironment modulation was observed with increased intratumoral CD8+ effector T cells and M1 macrophages, as well as decreased M2 macrophages and Foxp3+ Treg. Moreover, local treatment with nanoseed-CD40 yielded systemic reduction of M2 macrophages. As opposed to systemically treated mice, which showed inflammatory liver histology and elevated serum IL-6, IFN-γ, TNFa, and M-CSF levels indicative of cytokine storm, nanoseed-CD40 cohort were comparable to vehicle controls. Further, in a bilateral KPC model, nanoseed-CD40 treatment significantly inhibited growth of the contralateral untreated tumor, suggestive of a systemic antitumor response.

Conclusions Overall, our results support further development of the nanoseed as a clinically viable approach for intratumoral immunotherapy delivery in a safe and effective manner to locally modulate tumor immune microenvironment for systemic antitumor effects.

REFERENCES