IL-12-BASED CYTOKINE FACTORIES MODULATE TUMOR MICROENVIRONMENT TO ERADICATE PANCREATIC TUMORS IN MICE AND ARE WELL TOLERATED IN NON-HUMAN PRIMATES

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Background Pancreatic cancer is often diagnosed at advanced stages and responds poorly to chemotherapy. Because high tumor T cell infiltration corresponds with better clinical outcomes in pancreatic cancer patients, immunotherapy has gained significant interest for treatment. IL-12 is a proinflammatory cytokine that activates CD8+ T cells and NK cells. Unfortunately, systemic high dose IL-12 administration led to severe toxicities in clinical trials which limited further development of this cytokine as a cancer therapeutic. To address this limitation, we developed an implantable cytokine delivery platform for local administration of IL-12. These cytokine factories, composed of genetically engineered cells encapsulated in biocompatible polymers, allow for safe and controlled dosing in vivo.

Methods
Cytokine PK Studies Supernatant from individual capsules were assayed at 1-, 2-, 4-, or 24-hours using ELISA (n=6).
Mouse Studies For IP tumors, 1e6 pan02 cells were injected in the IP space of mice. Cytokine factories were implanted 7 days post tumor injection.
Primate Studies Cytokine factories were administered to cynomolgus macaques (n=1). Complete blood count and blood chemistry analysis were performed for 28 days after administration.
IVIS Imaging Mice were injected in the IP space with D-luciferin (300 µg/mL, PerkinElmer). Photographs and luminescent images were acquired 10 minutes after injection.

Results Local administration of IL-12-based cytokine factories caused reduction of pan02 tumor burden by 80% after 1 week of treatment in mice (figure 1). Single cell RNAseq of the tumor adjacent immune cells showed 2x more T cells in IL-12 treated mice than untreated mice suggesting immune cell infiltration. Importantly, the IL-12 dose was well tolerated in all mice for 180 days. In efforts to evaluate the translatability of this platform, we further tested IL-12-based cytokine factories in a non-human primate. The cytokine factories produced a high local IL-12 concentration without substantial leakage into the systemic circulation and were well tolerated by the primates as shown by the lack of fever or weight loss, as well as the lack of renal or liver toxicity.

Conclusions Our findings highlight the therapeutic potential of IL-12 treatments when administered locally via cytokine factories in preclinical animal models. Further, these findings provide rationale for future clinical testing of cytokine factories in a wide range of metastatic cancers in humans.

REFERENCES