Cell-generated IL12 combined with PD-1 inhibition produces local and abscopal immune activation to eradicate metastatic melanoma and pancreatic cancer

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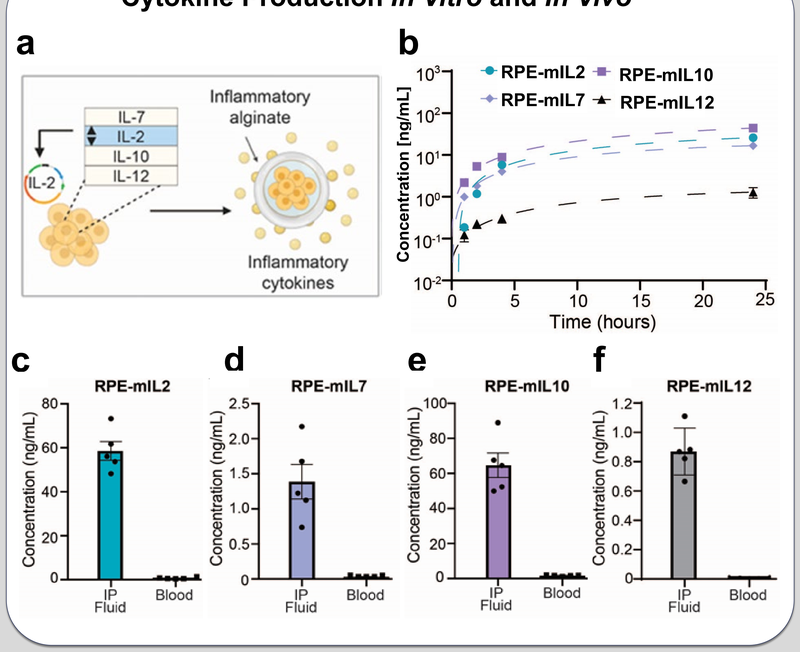
Background

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 over the last decade for the treatment of recurrent pancreatic cancer. IL-12 is a proinflammatory cytokine with pleiotropic effects including activation of CD8+ T cells and NK cell. Unfortunately, systemic high dose IL-12 administration led to severe toxicities in clinical trials which has limited further development of this cytokine as a cancer therapeutic. To address this limitation, we developed an implantable cytokine delivery platform to allow for local administration of IL-12. These cytokine factories, composed of genetically engineered epithelial cells encapsulated in biocompatible polymers, allow for safe and controlled dosing in vivo. **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 development and clinical testing of cytokine factories for treatment of a wide range of metastatic peritoneal cancers in humans.

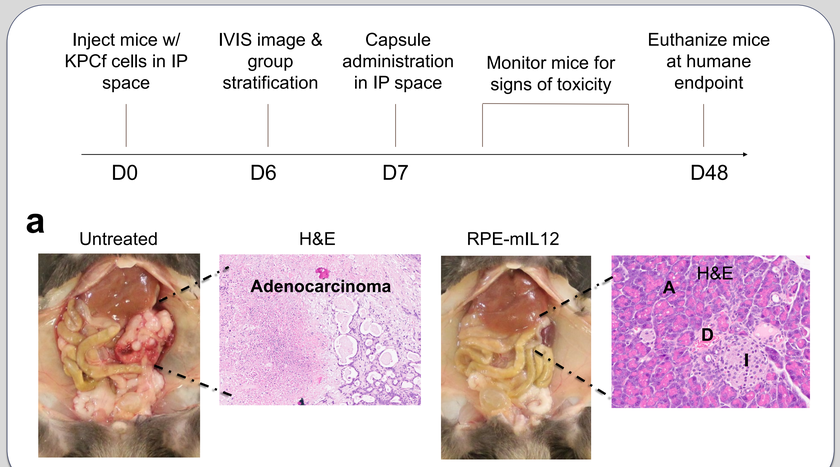
Tunable dose for personalized treatment

Cytokine Production *In Vitro* and *In Vivo*

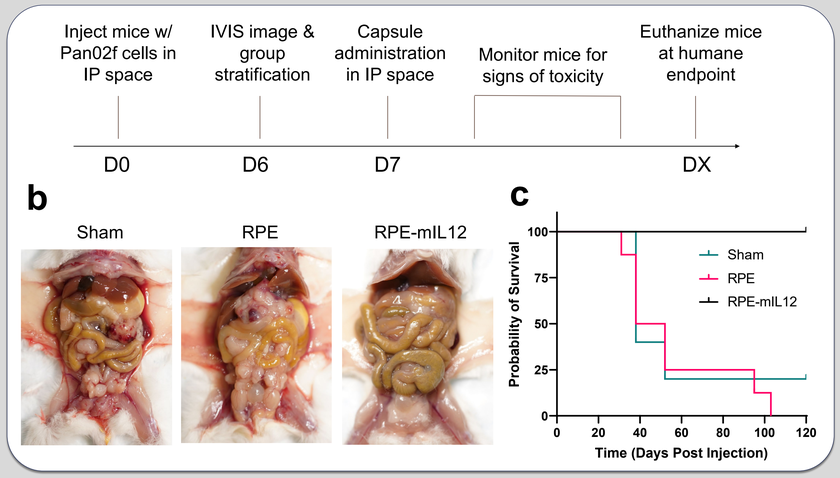


Above: a) Schematic of cell engineering and encapsulation approach. b) *In vitro* cytokine concentration at 1, 2, 4 and 24 hours (n=5). c-f) Cytokine concentration in IP fluid of mice 24 hours after implantation of RPE-mIL12, RPE-mIL7, RPE-mIL10, or RPE-mIL2 (n=5). Concentrations were measured using ELISA.

RPE-mIL12 treatment eradicates pancreatic cancer in mice

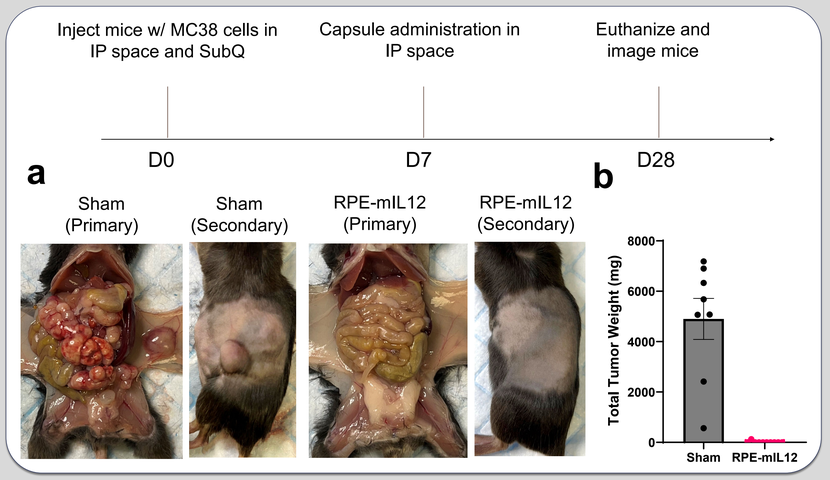


RPE-mIL12 treatment significantly extends survival in mice with pancreatic cancer

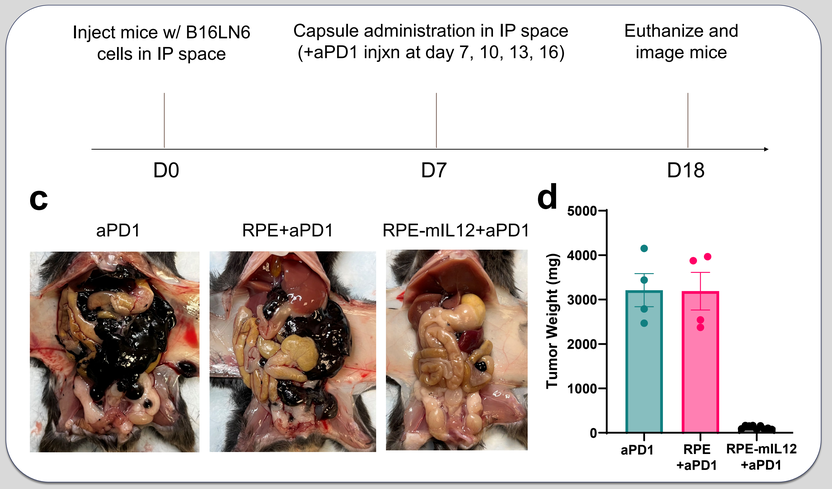


Above: a) Macroscopic and H&E images of the IP space and the pancreas 8 weeks post-treatment. H&E images are 20x magnification. A denotes acinar cells, D denotes ducts, and I denotes Islet of Langerhans (n=8 per group). b) Representative macroscopic images of each treatment at endpoints (day 38 for sham and RPE, day 121 for RPE-mIL12). c) Survival curve generated through survival study (n=8 per group).

RPE-mIL12 treatment eradicates local and distant colorectal tumors in mice



RPE-mIL12 plus aPD1 checkpoint inhibitor reduces metastatic melanoma



Above: a) Representative macroscopic images of primary and secondary tumors in mice 28 days post MC38 tumor cell injection (n=8). b) Total tumor weight collected from each animal at day 28. c) Representative macroscopic images of IP melanoma tumors in mice 18 days post B16LN6 tumor cell injection (n=4-8). d) Total tumor weight collected from each animal at day 18.

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