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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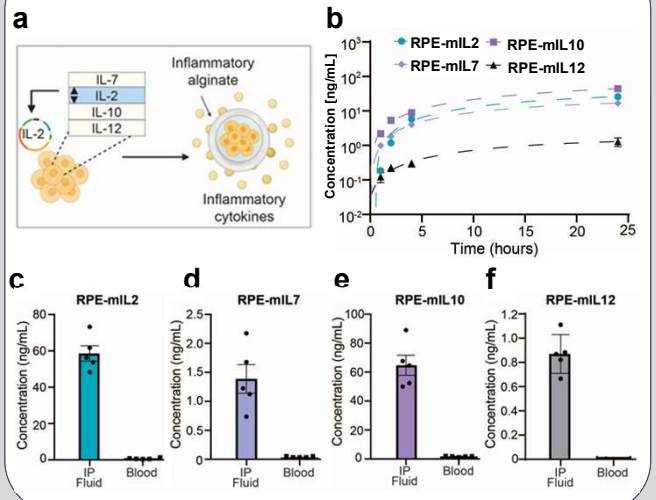
Background

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 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.

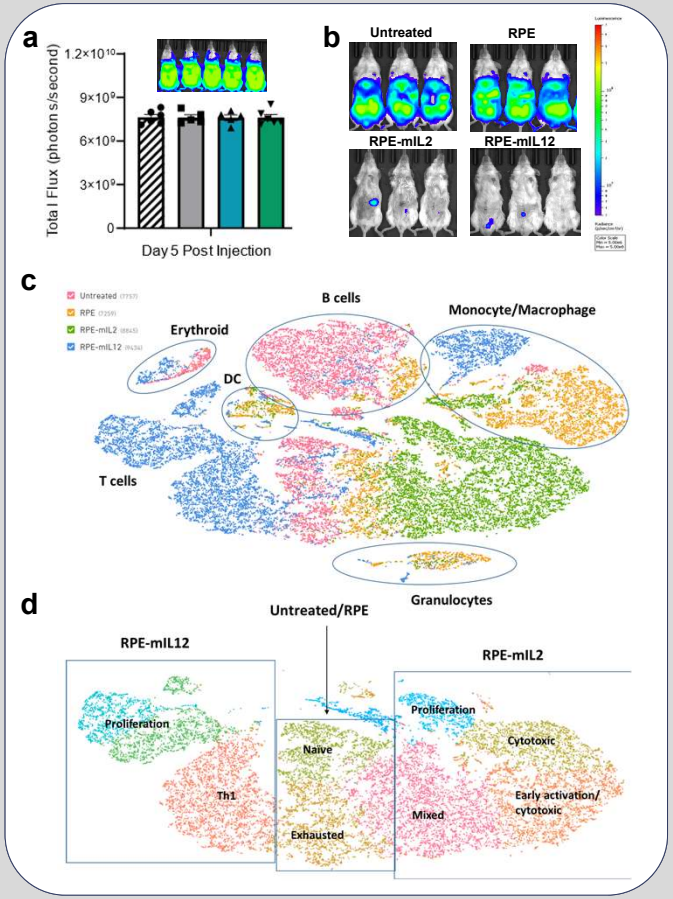
Tunable dose for personalized treatment

Cytokine Production *In Vitro* and *In Vivo*



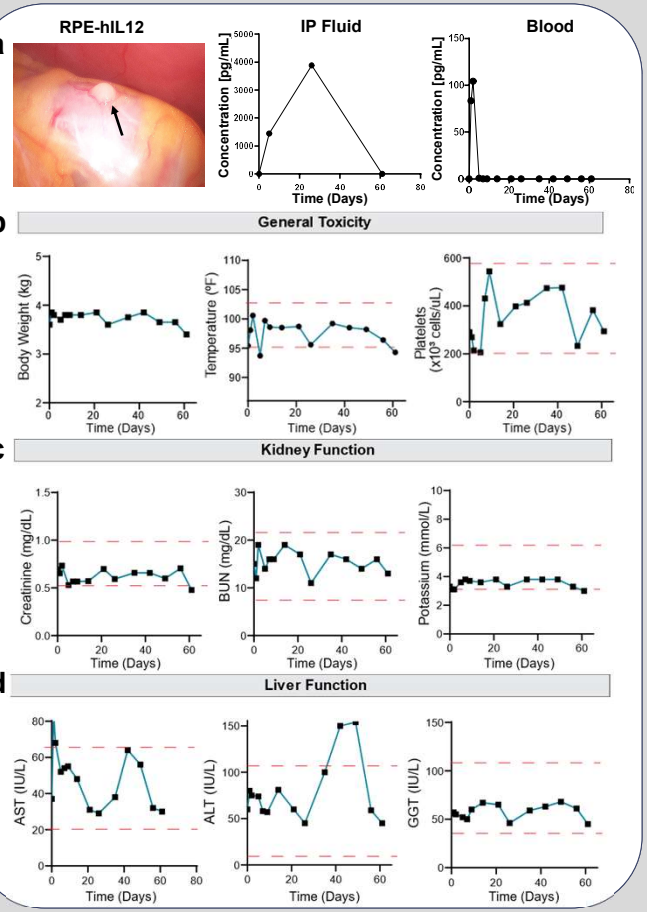
Above: a) Schematic of cell engineering and encapsulation approach. b) *In vitro* cytokine concentration at 1, 2, 4 and 24 hours (n=5). c-f) Cytokine concentration in IP fluid of mice 24 hours after implantation of RPE-mIL12, RPE-mIL7, RPE-mIL10, or RPE-mIL2 (n=5). Concentrations were measured using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

RPE-mIL12 monotherapy eradicates PAN02 pancreatic cancer



Above: a) Total flux calculated from IVIS imaging prior to treatment with RPE-mIL2, RPE-mIL12, RPE only, or untreated (n=5). b) Representative IVIS images of each treatment group 5 days post treatment. c) tSNE plot of pooled immune cells from each treatment group with major immune cell populations identified. d) tSNE plot of T cells from each treatment group with major subpopulations identified.

RPE-hIL12 is Well Tolerated in Non-human Primates



Above: a) Laparoscopic images of RPE-hIL12 in the IP space of a cynomolgus macaque 61 days after administration. Black arrow points to the cytokine factory (left). Concentration of hIL-12 in the IP fluid (middle) and blood (right) over time. b) Body weight, temp, and platelet count over time (n=1). c) Creatinine, BUN, and potassium levels over time (n=1). d) AST, ALT, and GGT levels over time (n=1).

ACKNOWLEDGEMENTS

- Rice University Shared Equipment Authority
- Baylor University Cell Sorting Core
- MD Anderson Cancer Center
- Veiseh Lab - Rice University
- Peng Lab – University of Houston
- Funding support from Avenge Bio, Inc