TUMOR ADJACENT CYTOKINE FACTORIES FOR ERADICATION OF OVARIAN CANCER TUMOR BURDEN IN MICE THROUGH CYTOTOXIC T-CELL ACTIVATION WITH SAFE AND PREDICTABLE DOSING IN NON-HUMAN PRIMATES

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Background Pro-inflammatory cytokines have been approved by the FDA for the treatment of metastatic melanoma and renal carcinoma.^{1 2} However, effective cytokine therapy is limited by its short half-life in circulation and the severe adverse effects associated with high systemic exposure.³ To overcome these limitations, we developed a clinically translatable localized cytokine delivery platform composed of polymer encapsulated epithelial cells that produce localized natural cytokines (IL2, IL7, IL10, or IL12) with temporal regulation.

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 tumor models of ID8-Fluc; 10x10⁶ cells suspended in HBSS were injected in the IP space of female albino C57BL/6 or NU/NU Nude mice (n=4–6). Cytokine factories were implanted 7 days post tumor injection. **Primate Studies:** Increasing doses of cytokine factories were administered to cynomolgus macaques (n=3). Complete blood count and blood chemistry analysis were performed 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. **Flow Cytometry:** All antibodies were commercially obtained and prepared the day of staining. Intracellular staining was performed using the FOXP3/Transcription Factor Staining Buffer Set (Cat. 00-5523-00, eBioscience) and the BD Cytofix/cytoperm fixation/permeabilization solution kit (Cat. 554714, BD Bioscience).

Results Tumor-adjacent local administration of these cytokine factories demonstrated predictable dose modulation with spatial and temporal control and provided ovarian cancer immunotherapy without systemic toxicities. Interestingly, the murine IL2 local concentration (IP space) was greater than 100x higher than the systemic concentration (blood) demonstrating the ability of the platform to deliver native cytokines in vivo and create a high local concentration of cytokines with limited peripheral exposure. A similar concentration differential was seen with IL7, IL10 and IL12. Treatment of peritoneal tumors using IL2 producing cytokine factories provided sustained eradication of peritoneal tumors in an ovarian cancer mouse model. Our data confirmed local increases in the activation (CD25+CD8+) and proliferation (Ki67+CD8+) of cytotoxic T cells within the IP space of cytokine factory treated mice. Significantly, this platform produced local and systemic T cell biomarker profiles that predict efficacy without toxicity in non-human primates.

Conclusions Our findings demonstrate the safety and efficacy of IL2 cytokine factories in preclinical animal models and provide rationale for future clinical testing for the treatment of metastatic peritoneal cancers in humans.

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Ethics Approval All mouse experiments were approved by Rice University's Institution Animal Care and Use Committee (IACUC). All cynomolgus macaque procedures and post-operative care were performed in accordance with the Guidelines for Care and Use of Laboratory Animals of the University of Illinois-Chicago (UIC) and approved by the Institutional Use and Animal Care Committee (IACUC) of UIC.

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