LOCALIZED INTERLEUKIN-2 CYTOKINE FACTORIES ERADICATE MESOTHELIOMA TUMORS VIA ACTIVATION OF ADAPTIVE AND INNATE IMMUNE CELLS

Background High-dose interleukin-2 (IL-2) immunotherapy has previously demonstrated effective tumor lysis via activation of effector immune cells, but clinical utility is limited due to pharmacokinetic challenges and life-threatening toxicities experienced by patients. To overcome these challenges, we developed a safe and clinically translatable localized IL-2 delivery system to boost the potency of therapy while minimizing systemic cytokine exposure.

Methods We evaluated the therapeutic efficacy of hydrogel-encapsulated, cell-based IL-2 cytokine factories in a mouse model of malignant mesothelioma. An effective and well-tolerated dose was determined by tracking tumor burden in response to increasing doses of our cytokine factories. Therapeutic efficacy of the optimal dose was subsequently evaluated in combination with anti-PD1 checkpoint inhibitor. Changes in immune populations across groups were analyzed using time-of-flight mass cytometry (CyTOF). Finally, safety and translatable ability of the platform were evaluated following pleural implant in rats, using complete blood counts and serum chemistry analysis.

Results IL-2 cytokine factories enabled 150x higher IL-2 concentrations in the local compartment with limited leakage into systemic circulation. Additionally, AB1 tumor burden was reduced by 80% after one week of monotherapy treatment, and 7/7 animals exhibited tumor eradication when IL-2 cytokine factories were combined with aPD1 therapy (figure 1A). Resultantly, IL-2+aPD1 combination therapy led to significant improvements in tumor-free survival compared to controls (figure 1B). Further, CyTOF analysis showed an increase in CD69+CD44+ and CD69-CD44+CD62L- T cells (figure 1C-F), reduction of CD86-PD-L1- M2-like macrophages, and a corresponding increase in CD86+PD-L1+ M1-like macrophages (figure 1G and H) and MHC II+ dendritic cells after treatment. Finally, healthy blood chemistry ranges in rodents demonstrated the safety of cytokine factory treatment and reinforced its potential for clinical use.

Conclusions IL-2 cytokine factories led to eradication of aggressive mouse malignant mesothelioma tumors, protection from tumor recurrence, and increased the therapeutic efficacy of anti-PD1 checkpoint therapy. The results of this study provide support for clinical evaluation of our IL-2-based delivery system.

REFERENCES