SENTI-101, an allogeneic cell product, induces potent and durable anti-tumor immunity in preclinical models of peritoneal carcinomatosis


BACKGROUND
More effective therapies for disseminated peritoneal carcinomatosis, including high-grade serous ovarian cancer, remain a major medical need [1]. Although several treatments offer initial responses to localized disease, patients with disseminated peritoneal tumors face poor overall survival [2].

SENTI-101 is a novel therapeutic agent comprising allogeneic mesenchymal stromal cells (MSCs) genetically modified to express a potent combination of immunomodulatory cytokines: IL12 and IL21. Upon administration, SENTI-101 innately homes to peritoneal tumors, secretes IL12 and IL21 in a localized and sustained fashion, and induces a robust anti-tumor immune response.

METHODS
Two syngeneic pre-clinical models of disseminated peritoneal carcinomatosis with distinct immune phenotypes were established by implanting cells in the peritoneal cavities of mice (CT26-flUC = immune-inflamed; B16-F10-flUC = immune-excluded) [3]. A library of over 50 murine MSC lines engineered to express immune effectors (cytokines, chemokines, growth factors), either individually or in combination, was administered intraperitoneally and evaluated for anti-tumor activity via bioluminescence and tumor weight measurements. Immune phenotype was characterized by flow-cytometry and multiplexed immunohistochemistry.

RESULTS
MSCs expressing the combination of IL12 and IL21 (SENTI-101) were selected based on significant tumor-burden reduction and immune profile changes in both syngeneic models. Notably, the combination outperformed each individual cytokine in extending survival (p=0.02).
Intraperitoneal administration of SENTI-101 in tumor-bearing mice led to preferential co-localization with tumors (>10-fold higher vs. normal tissues, \( p=0.001 \)). Local concentrations of IL12 and IL21 were \( \sim 100 \)-fold greater in the peritoneal space vs. serum \( (p=0.002) \). SENTI-101 treatment reduced tumor-burden more than 200-fold \( (p<0.0001) \) and 10-fold \( (p<0.0001) \) in the CT26-flUC and B16-F10-flUC models, respectively. SENTI-101 administration significantly prolonged survival compared to control and anti-PD1 antibody treatment in the B16-F10 model. >50% of the mice were tumor-free after 90 days, while control groups and groups treated with anti-PD1 antibody had a median survival of 21 to 30 days. Surviving mice were able to reject newly implanted tumor cells, demonstrating anti-tumor immune memory.

Anti-tumor effects of SENTI-101 are mediated by a multi-modal immune response. The frequency of antigen-presenting cells in peritoneal tumor-draining lymph nodes was more than doubled vs. controls \( (p=0.01) \). This correlated with increased T-cell and B-cell tumor infiltrates forming tertiary-lymphoid structures, which are associated with improved prognosis in cancer \([4]\). T-cell activation markers (CD38, IFNg, GranzymeB) were significantly increased locally.

**CONCLUSIONS**

SENTI-101 induces localized immune-modulation, regulates multiple steps of the cancer immunity cycle, and results in durable anti-tumor responses. These data warrant further development of SENTI-101 for the loco-regional treatment of advanced solid tumors.

**References**