COMBINATION THERAPY OF EXOSTING, EXOIL-12 ACTIVATES SYSTEMIC ANTI-TUMOR IMMUNITY

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Background Engineered exosomes are emerging as a novel therapeutic modality for cancer immunotherapy. Leveraging cell type specific delivery, tumor restricted pharmacology and compartmental dosing, exosome-based immunotherapy can elicit a tumor specific immune response that may not be achievable with other traditional drugging modalities. Pre-clinical studies have shown that exosomes loaded with a STING agonist (exoSTINGTM) or engineered to express the cytokine interleukin-12 (exoIL-12TM) can substantially improve potency and selectivity resulting in improved therapeutic window [1,2]. Both exoSTING and exoIL-12 are currently in clinical trials in cancer patients. Utilizing a combination strategy involving exoSTING and exoIL-12, we demonstrate the development of potent systemic anti-tumor responses in both injected and non-injected tumors.

Methods exoSTING exosomes are engineered to overexpress PTGFRN, an abundant exosome surface protein, and loaded ex vivo with a proprietary STING agonist. exoIL-12 exosomes are engineered to overexpress functional IL-12 attached via fusion to PTGFRN. In these studies, exoSTING and exoIL-12 were dosed intratumorally into one flank tumor into mice bearing dual flank subcutaneous MC38 or B16F10 tumors, or B16F10 single flank subcutaneous tumors with B16F10 lung metastases. T-cell infiltration in the non-injected tumor was monitored by histopathology.

Results In the checkpoint therapy refractory B16F10 melanoma dual flank tumor model, exoSTING/exoIL-12 combination provided 93% and 78% tumor growth inhibition (TGI) in both the injected and non-injected tumors, respectively, whereas monotherapy of exoSTING or exoIL-12 provided modest anti-tumor activity (44% and 48% TGI) in the non-injected tumors, respectively. In a MC38 subcutaneous CRC model, the addition of anti-PD-1 checkpoint inhibitor further enhanced anti-tumor activity with 100% TGI (7/7 CR) in injected and non-injected tumors. The tumor free animals were refractory to tumor re-challenge demonstrating immunological memory. A dosing schedule optimization experiment showed that same day dosing of exoSTING and exoIL-12 significantly inhibited the tumor growth in the non-injected tumors. In a lung metastasis model, the triple combination also showed potent anti-tumor effect in decreasing distal lung metastases when dosed intratumorally into the subcutaneous tumors. Subsequent imaging and histology studies demonstrated enhanced T cell infiltration in the non-injected subcutaneous tumor with the combination therapy.

Conclusions By combining both exosome immunotherapies with a checkpoint blockade, we are able to elicit systemic anti-tumor immune immunity in both injected and non-injected tumors.

REFERENCES