572 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 (exoSTING^{TM}) or engineered to express the cytokine interleukin-12 (exoIL-12^{TM}) 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

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Ethics Approval All animals were maintained and treated at the animal care facility of Codiak Biosciences in accordance with the regulations and guidelines of the Institutional Animal Care and Use Committee (CB2020-001).

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