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**EXOSTING DEMONSTRATES POTENT ANTI-TUMOR ACTIVITY IN A MOUSE MODEL OF LEPTOMENINGEAL DISEASE**

Xudong Feng\*, John Lin\*, Su Chul Jang, Seveda Lule, Paloma Sanchez-Jauregui, Katherine Kirwin, Tong Zi, Samuel Kaser, Silvia Siso, Kelvin Zhang, Shil Patel, Sriram Sathyanarayanan, Kyriakos Economides, Wendy Broom. *Codiak BioSciences, Cambridge, MA, United States*

**Background** Leptomeningeal disease (LMD) occurs when cells from primary tumors metastasize to the cerebrospinal fluid (CSF) space leading to multifocal neurological deficits. LMD has an overall prevalence of ~5% in cancer patients, but is most commonly observed in breast, lung and melanoma patients. With improved therapies emerging for several primary tumor types, the incidence of LMD is rising, and with treatment options limited to radiotherapy and chemotherapy, the median survival of LMD patients remains poor at 3–6 months. Thus, there is high unmet medical need for development of effective therapeutic strategies for LMD. The STING (Stimulator of Interferon Genes) pathway has been shown to play a critical role in activating anti-tumor immunity through initiation of a tumor antigen-specific T cell response. exoSTING is an engineered extracellular vesicle exogenously loaded with a CDN (cyclic dinucleotide) STING agonist. We have previously demonstrated that it enhances the potency of the CDN, preferentially activates antigen presenting cells in the tumor microenvironment and increases CNS retention of the drug without systemic inflammatory cytokine stimulation. Histological data in LMD is scarce, however high levels of inhibitory macrophages and low T cell infiltration have recently been described, providing support for the therapeutic potential of exoSTING in LMD.

**Methods** A mouse model of LMD was generated by intracerebral inoculation of B16F10-Luc melanoma cells and was used to assess the efficacy of intracranial administration of exoSTING.

**Results** Tumor growth was monitored by bioluminescence imaging during course of each study, with rapid loss of signal post treatment observed in exoSTING treated groups compared to steady tumor growth in vehicle treated groups. Animals within vehicle treated groups demonstrated survival less than 30 days, whereas exoSTING treated mice survived 50+ days with a high complete response rate (over 85%), confirmed by ex vivo histopathological analysis. Peripheral immunological responses were demonstrated by lack of tumor growth following flank rechallenge in exoSTING treated mice. Strong anti-tumor response and tumor-specific immune activation in the absence of systemic inflammation was demonstrated. The presentation will summarize the immunological changes in the tumor microenvironment following exoSTING administration.

**Conclusions** exoSTING, which previously showed strong efficacy against primary melanoma in mouse models, has been demonstrated in this study to also suppress tumor growth and improve survival in the LMD context. Our study supports the therapeutic rationale for using exoSTING for the treatment of LMD.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.761>