

1158

## HIGH POTENCY STING AGONISTS INDUCE ADAPTIVE-IMMUNITY DEPENDENT CURATIVE RESPONSES IN CHECKPOINT-REFRACTORY GLIOBLASTOMA MODELS

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**Background** Glioblastoma (GBM) is the most common and aggressive adult primary brain malignancy, with a median overall survival of 15 months post-diagnosis. Clinically, GBM is refractory to T cell immune checkpoint blockade (ICB), which may be attributable to its immunosuppressive tumor microenvironment enriched in glioma-associated myeloid cells (GAM) and lacking in effector T cells.<sup>1,2</sup> This phenotype is reflected in the Qki<sup>-/-</sup> Pten<sup>-/-</sup> P53<sup>-/-</sup> (QPP8) tumor model,<sup>3</sup> which we show is ICB-refractory but sensitive to agonists of the Stimulator of Interferon Genes (STING) innate immune sensing pathway. While we have shown that STING agonists potently repolarize *in vitro* generated suppressive myeloid cells towards more T cell supportive phenotypes,<sup>4,5</sup> their function in the context of the GBM myeloid compartment remains poorly understood.

**Methods** Using the synthetic cyclic di-nucleotide STING agonist IACS-8803 we treated orthotopic QPP8 tumors intratumorally. We then analyzed survival and performed high parameter flow cytometry profiling of the tumor immune microenvironment following STING agonist treatment. To assess the contribution of adaptive immunity to STING agonist therapeutic efficacy, we treated orthotopic QPP8 tumors implanted in RAG1 KO mice and monitored survival.

**Results** We found that STING agonist therapy cured murine orthotopic QPP8 tumors, in contrast to ICB that showed no survival benefit. In RAG1<sup>-/-</sup> mice bearing QPP8 tumors STING agonist therapy extended survival, however, the curative effect observed in wild-type mice was lost in the absence of adaptive immunity. STING agonist-treated QPP8 tumors displayed increased counts of CD8 T cells and NK cells, and decreased CD8 T cell PD1 expression. Infiltration of STING-treated gliomas by Ly6C+ F4/80+ Mono-MDSC substantially increased; however, these cells expressed reduced CD206 and CD163 and increased CD86, suggestive of a more proinflammatory state. Finally, in the cervical lymph node of QPP8-treated mice the frequency and CD86 expression of cDC1 cells increased.

**Conclusions** We found that STING agonists induce adaptive immunity-dependent curative responses in ICB-refractory murine QPP8 GBM tumors. Increased frequencies of cDC1 dendritic cells in the draining lymph node, as well as augmented CD8 T cell densities within treated tumors likely help drive regression of these established gliomas. While STING agonist therapy also increased the frequency of cells classically defined as monocytic MDSC, their suppressive capacity may have been reduced, similar to previous publications on expanded Ly6C+ F4/80+ populations in other STING-treated tumors.<sup>6</sup> Together these results indicate that STING activation induces proinflammatory repolarization of the murine GBM myeloid stroma that drives rejection of established, ICB-refractory tumors.

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