762 STING AGONISM COMBINED WITH ARGINASE, NOS2, AND PTGES/COX2 INHIBITORS FOR IMPROVED ANTI-TUMOR IMMUNOTHERAPEUTIC BENEFIT

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Background Tertiary lymphoid structures (TLS) are non-encapsulated immune cell aggregates that form at sites of chronic inflammation. Recent studies have shown that the presence of TLS in human tumors predicts extended survival and superior response to interventional immunotherapy. Our lab has recently demonstrated that treating mice bearing established tumors with agonists of STING, a cytosolic dsDNA sensor, leads to an inhibition in tumor growth in association with tumor vascular normalization, immune cell recruitment, and local formation of non-classical TLS within the tumor microenvironment. However, STING agonism also results in the upregulated expression of compensatory immune regulatory molecules, including ARG2 and enzymes involved in the production of immunosuppressive prostaglandins (i.e. PTGES and PTGS2/COX2), yielding an overall sub-optimal therapeutic paradigm. We are currently determining if combined treatment with STING agonists along with pharmacologic inhibitors of ARG2, NOS2 and/or PTGES/COX2 results in improved control of tumor growth, increased formation of TLS, and more robust anti-tumor immune responses in vivo in murine melanoma models.

Methods Melanoma tumor-bearing C57Bl/6 were treated with pharmacologic inhibitors of ARG2 or PTGES/COX2 i.p. in combination with STING agonist treatment i.t. Mice were monitored for tumor survival and growth. Tumors were also collected from mice at various timepoints post-treatment to evaluate the immune cell infiltration by flow cytometry and immunofluorescence microscopy (IFM). Tumor sections were also evaluated for TLS formation by IFM.

Results Treatment of mice systemically with inhibitors of ARG2, NOS2, and COX2/PTGES leads to changes in the immune composition of the tumor, including increases in effector immune cells and decreases in suppressive/regulatory immune cells. Combined treatment of melanoma-bearing mice with STING agonist ADU-S100 along with immune regulatory inhibitors (ARGi, NOSi, Celecoxib) slows tumor growth vs. individual monotherapies and is expected to extend overall survival.

Conclusions Combination of STING agonism with inhibitors of various immune regulatory molecules (ARG2, COX2) has the potential to improve the anti-tumor benefits of STING agonism alone.

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