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MV-626, a potent and selective inhibitor of ENPP1 enhances STING activation and augments T-cell mediated anti-tumor activity in vivo

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**MV-626, A Potent and Selective Inhibitor of ENPP1, Enhances STING Activation and Augments T-cell Mediated Anti-tumor Activity in Vivo**

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**Background**

STING is an endogenous sensor of cGAMP, which is synthesized by cGAS following detection of cytoplasmic DNA. STING activation leads to interferon production and activation of inflammatory pathways that facilitate cytotoxic T cell priming. STING agonists administered intratumorally show potent anti-tumor efficacy in a range of preclinical models; several agonists are in clinical development. Radiation therapy also increases cytoplasmic DNA levels in cancer cells, resulting in STING activation and secretion of inflammatory cytokines. Ectonucleotidase pyrophosphatase/ phosphodiesterase 1 (ENPP1) is the phosphodiesterase that negatively regulates STING by hydrolyzing cGAMP. MV-626, a highly potent and selective ENPP1 inhibitor with 100% oral bioavailability in rats and mice, blocks cGAMP hydrolysis and increases STING activation in cells where cGAS is active. We hypothesize that by conditionally enhancing STING activation, ENPP1 inhibitors will facilitate development of anti-tumor cellular immune responses, particularly following radiation therapy.

**Methods**

The effects of ENPP1 inhibition on STING activation using cGAMP or DNA treatment were assessed in vitro. Pano2-STY tumors were implanted in C57BL/6 mice and randomized to receive 200 Gy CT-guided radiation therapy, 5 daily ip doses of MV-626, or both MV-626 and radiation. Mice were followed for outcome, tumor antigen specific T cell responses and changes in the tumor immune environment. Additional studies were conducted in C57BL/6 mice bearing MC38 tumors treated with anti-PDL1, MV-626 or MV-626 + anti-PDL1.

**Results**

In vitro, MV-626 blocks ENPP1-mediated hydrolysis of cGAMP and enhances STING activation by DNA-mediated cGAS activation or exogenous cGAMP. Therapeutic doses of MV-626 were well tolerated in mice, with no evidence of toxicity or clinically-significant increases in systemic cytokine levels. Systemic administration of MV-626 monotherapy caused tumor growth delay. MV-626 combined with radiation therapy significantly increased overall survival, and most animals achieved durable tumor cures. Additional studies in the MC38 model confirmed MV-626 activity. Studies characterizing effects of MV-626 in the tumor microenvironment are underway.

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**MV-626 Shows Monotherapy Activity and Enhances anti-PD-L1 Efficacy in MC38 Tumor Model**

**Immune Environment Changes**

- **ATG**
  - Tumor cells
  - Antigen specific

**Conclusions**

These data demonstrate the potent and selective ENPP1 inhibitor MV-626, when delivered orally or IP augments STING activation in vitro and enhances immune responses to tumors in vivo. We demonstrate for the first time that, in combination with radiation therapy or anti-PD-L1 mAb treatment, ENPP1 inhibition improves outcomes and cures tumors in preclinical models through changes in the tumor immune environment. The loss of this efficacy in IFN receptor knockout mice confirms STING-pathway mechanism of action, and the ability of the majority of MV-626 treated mice to reject tumor rechallenge indicates that MV-626 drives disseminated, durable, adaptive immune responses. These translational studies demonstrate a novel approach to STING pathway modulation and form the foundation for clinical development of an ENPP1 inhibitor as a cancer immunotherapy.

**Future Directions**

- Anti-CTLA-4 cytokine blockade
- Further profiling of immune changes in the tumor and IL6
- Additional profiling of tumor antigen specific responses
- Additional profiling of ENPP1 inhibition with other anti-cancer agents that produce immunomodulatory effects

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