**T cell priming by Toca 511 and 5-FC coupled with T regulatory cell depletion by αCTLA-4 synergistically enhances anti-tumor immune memory in a mouse model of glioma**

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**Abstract**

Toca 511 (ucilogene ammoresel) is a gamma retroviral replicating vector that selectively infects cancer cells in vivo and encodes cytosine deaminase. In combination with the prodrug, 5-fluorocytosine (5-FU), Toca 511 drives 5-fluorouracil (5-FU) locally in the tumor microenvironment. Prior work has demonstrated a reduction in immunosuppressive myeloid cells and an increase in CD8 and CD4 T cells in tumors while T regulatory cells remain unchanged with treatment with Toca 511 and 5-FU. This work, in a mouse model of gliomas, aimed to determine if the addition of a checkpoint inhibitor, αCTLA-4, would provide therapeutic benefit to Toca 511 and 5-FC. Initially, we noted that Toca 511 and 5-FC was highly efficacious and that it provided little room for further improvement and therefore combination with αCTLA-4 did not show additive benefit against the primary cancer. However, tumor-associated regulatory T cells were significantly reduced with αCTLA-4 treatment and long-term memory was significantly improved with the combination as shown in adoptive transfer studies. Adoptive transfer of immune cells from animals that cleared their primary tumor through Toca 511 and 5-FC, and αCTLA-4 showed 100% survival benefit to animals bearing orthotopic gliomas, significantly greater than the ~50% survival seen with transfer from animals that cleared primary tumors through Toca 511 alone.

**Introduction**

Toca 511 shows selectivity for tumor leading to conversion of the pro-drug, 5-FC, into 5-FU in the tumor microenvironment.

**Approach and Results**

Toca 511 spreads within tumors. Initial infection of just 2% of tumor cells will result in high numbers of tumor cells becoming infected with time.

**Conclusion**

Combining Toca 511 & 5-FC with αCTLA-4 further enhances anti-tumor immune memory through depletion of Regulatory T cells.