“Novel Treatment Strategies for Glioblastoma Using AAV-mediated CNS Gene Transfer of Monoclonal Antibodies”

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Abstract: Abstract: Glioblastoma multiforme (GBM), the most common CNS malignancy, has a median survival of ~14 months. Although a great deal is known about the aberrant biology exhibited by GBM, applying therapies against these biologic processes is limited by the blood-brain barrier which restricts systemically administered therapies from reaching the brain. We propose a novel strategy to bypass these barriers using CNS administration of adenoassociated virus (AAV) gene transfer vectors to deliver the genetic sequences for monoclonal antibodies, modifying normal CNS cells to chronically deliver therapeutic monoclonal antibodies in the local milieu. This proposal represents the unique collaboration of the Tabar and Crystal laboratories, bringing together expertise in human GBM biology and neurosurgery (Tabar) with expertise *in* gene therapy, including ongoing human studies with AAV-mediated CNS gene transfer (Crystal). Using *in vitro* and *in vivo* assessments of primary human GBM, we will test the hypothesis that AAV-mediated CNS genetic delivery of therapeutic monoclonals will suppress the CNS growth of human GBM in NOD/SCID mice. Aim 1. Assess genetic delivery of bevacizumab, a monoclonal directed against VEGF, thus inhibiting tumor-mediated angiogenesis. Aim 2. Test genetic delivery of an anti-EGFRvIII monoclonal that suppresses EGFRvIII function, a mutated constitutively activated receptor contributing to GBM growth. Aim 3. Evaluate genetic delivery of an anti-CXCL12 monoclonal that sequester CXCL12, the ligand for CXCR4, a GBM proliferation/invasion-promoting pathway function. Finally, combinations of the 3 approaches will be compared against each alone, as will safety of genetic modification of CNS cells to produce monoclonals.