NT-04. THE Jak2 SMALL MOLECULE INHIBITOR, G6, REDUCES THE TUMORIGENIC POTENTIAL OF T98G Glioblastoma Cells in Vitro and In Vivo
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Glioblastoma multiforme (GBM) is the most common and the most aggressive form of primary brain tumor. Jak2 is a non-receptor tyrosine kinase that is involved in proliferative signaling through its association with various cell surface receptors. Hyperactive Jak2 signaling has been implicated in numerous hematological disorders as well as in various solid tumors including GBM. Our lab has developed a Jak2 small molecule inhibitor known as G6. It exhibits potent efficacy in vitro and in several in vivo models of Jak2-mediated hematological disease. Here, we hypothesized that G6 would inhibit the pathogenic growth of GBM cells expressing hyperactive Jak2. To test this, we screened several GBM cell lines and found that T98G cells express readily detectable levels of active Jak2. We found that G6 treatment of these cells reduced the phosphorylation of Jak2 and STAT3, in a dose-dependent manner. In addition, G6 treatment reduced the migratory potential, invasive potential, clonogenic growth potential, and overall viability of these cells. The effect of G6 was due to its direct suppression of Jak2 function and not via suppression of off-target kinases, as these effects were recapitulated in cells that received Jak2 specific shRNA. G6 also significantly increased the levels of caspase-dependent apoptosis in T98G cells, when compared to cells that were treated with vehicle control. Lastly, when T98G cells were injected into nude mice, G6 treatment significantly reduced tumor volume and this was concomitant with significantly decreased levels of phospho-Jak2 and phospho-STAT3 within the tumors themselves. Lastly, tumors harvested from mice that received G6 had significantly less vimentin protein levels and significantly increased fibrosis when compared to tumors from mice that received vehicle control solution. Overall, these combined in vitro and in vivo results indicate that G6 may be a viable therapeutic option against GBM exhibiting hyperactivation of Jak2.