

## The Glioblastoma Multiforme Brain Tumor Research Grant

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*Regional variation in Inhibitors of Apoptosis (IAPs) in GBMs and their role in apoptosis and therapeutic resistance*

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#### Abstract:

Goal: GBMs usually recur around the *central* necrotic contrast enhancing hypoxic zones surrounded by pseudopalisading tumor cells after local therapy such as surgery or radiation. Why these pseudopalisading GBM cells are resistant to apoptosis induced by the hostile hypoxic microenvironment or interventions is of biological and therapeutic interests. Using Laser Capture Microdissection (LCM), we have selectively isolated these pseudopalisading and peripheral invading GBM cells from 10 human GBM operative specimens, with aid of MRI stereotaxy. Using quantitative Real-Time PCR (qRT-PCR) we have found increased levels of XIAP and Survivin, members of a family of proteins which are termed Inhibitors of Apoptosis (IAPs) in the pseudopalisading cells, compared to the peripheral invading tumor cells or normal brain controls.

These results have been verified at the protein level using immunohistochemistry. *Based on these results we hypothesize and test in this proposal that regional variations in IAPs plays a role in GBM resistance to hypoxia or therapeutic (radiation, chemotherapy) induced apoptosis.* Our proposal will test the functional relevance of our observations using in vitro, intracranial xenograft and transgenic glioma models that we have developed.

Timeline: Since most of the reagents and model systems are available in our lab, the in vitro and xenograft aims of this proposal should be achievable in 12-16 mths. The transgenic glioma model experiments will take a longer period of time (~2-3 yrs) due to the nature of these experiments, even though we already have developed or obtained in collaboration all of the proposed transgenics. Deliverables: Tumor formation and recurrence requires not only oncogenic drive, but also aberrations in cell survival regulation. These molecular regulators we believe vary within regions of GBMs due to tumor microenvironmental influences, giving rise to the well-recognized pathological heterogeneity or "Multiforme" nature of these tumors. If IAPs are demonstrated to be important in GBM biology, inhibitors of IAPs which are under current development<sup>1</sup> may provide a biological therapeutic strategy to favorable alter therapeutic response of GBMs.