

The Glioblastoma Multiforme Brain Tumor Research Grant

E. Antonio Chiocca, M.D. Ph.D.

Validation of GSK-3 as an Anti-Invasive Target in Glioma

The Ohio State University, James Cancer Hospital and Solove Research Institute, Columbus, Ohio

Abstract:

Invasiveness is one of the main hallmarks of primary glial brain tumors¹. Malignant cells diffusely infiltrate normal brain tissue and migrate along defined structures of the brain preventing complete surgical tumor removal and contributing to the continued poor prognosis seen in glioblastoma multiforme, the most common primary brain tumor. Currently there are no available therapies to deal with this problem in the clinic, therefore, approaches that target invading cells are highly sought after. Extensive preliminary data has been gathered in my laboratory demonstrating that pharmacologic inhibitors of the intracellular signaling molecule GSK-3 (glycogen synthase kinase 3) specifically block glioma cell motility and therefore may be useful in anti-invasive therapy. The goal of this proposal is therefore to determine whether GSK-3 inhibition can be exploited therapeutically to arrest glioma cell invasion *in vivo*, using an invasive human glioma xenograft model in nude mice. For "proof of principle", cells transduced with dominant negative GSK-3 constructs and shRNA expressing vectors will be examined, and for therapeutic efficacy a panel of commercially available pharmacologic GSK-3 inhibitors will be screened. The early part of the project will be spent analyzing cell lines *in vivo* and optimizing drug regimens, by assessing GSK-3 activity in the brains of inhibitor treated mice. Optimal conditions as judged by GSK-3 inactivation *in vivo*, with minimal apparent toxicity will be pursued in the second half of the study and their effects on tumor volume invasiveness, cell proliferation and survival monitored, in order to assess the potential clinical value of this approach. Ideally, an FDA approved GSK-3 inhibitor such as lithium chloride could be moved quickly into the clinic. However, if other inhibitors may exhibit greater therapeutic efficacy and these will be followed with more intensity. The information obtained during the course of this work will justify further grants, to allow us to realize our goal to develop clinically useful anti-invasive strategies for brain tumor treatment.