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*“Characterizing cell resistance to small molecular inhibitors of EGFR in malignant gliomas” (first year funded)*



Dr. Hui-Kuo Shu, Emory University, Atlanta, GA, **“Role of efbB2 in the sensitivity of EGFR signaling to guinzoline based EGFR inhibitors in glioma,”** (second year)

2007

My main lab interest has been in the study of EGFR signaling in malignant gliomas. Over the past two years, support from the Childhood Brain Tumor Foundation has helped us carry out research primarily in this area. We have continued to make progress in understanding the underlying mechanisms for why many malignant glioma cells display resistance to the monospecific quinazoline-based EGFR inhibitors and how these drugs may actually enhance growth of these brain tumors cells when given at relatively low drug concentrations. Finally, we have begun to extend our work beyond what we initially proposed into understanding downstream events that occur as a consequence of EGFR activation. We have specifically characterized a new pathway leading through p38-MAP kinase and Sp1 transcription factor that leads to transcriptional activation of cyclooxygenase-2 (COX-2), an enzyme that is likely playing important roles in promoting tumor angiogenesis and resistance to apoptosis which likely leads to resistance to cytotoxic therapies used to treat these tumors (including chemotherapy and radiation therapy).

This work has progressed very rapidly over the past several months. We have actually already completed this manuscript and will be submitting it to a scientific journal in the first week of September. We also intend to submit this work for presentation at the next meeting of the American Association for Cancer Research (AACR) in 2007. I have included a PDF file of our most recently updated manuscript that will be submitted for review.

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[http://www.ncbi.nlm.nih.gov/pubmed/14612544?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/14612544?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

2006

Malignant gliomas are aggressive brain tumors in children that have an extremely poor outcome. Epidermal growth factor receptor (EGFR) is thought to be important in the pathogenesis of these tumors and likely represents a good therapeutic target, especially since inhibitors of this receptor are now available for clinical use. However, my lab has previously shown that EGFR signaling within malignant glioma cell lines are not efficiently inhibited by these new drugs. One goal of our study is to elucidate the underlying molecular mechanism for this resistant response in malignant glioma. Interestingly, we also found that in some of our cell lines, EGFR signaling was not just resistant to these EGFR inhibitors but that low levels of these drugs actually enhanced cellular proliferation. This is particularly concerning for a drug that will be used clinically because of the suggestion that sub-therapeutic drug levels may actually promote tumor growth in certain instances. Therefore, we are also interested in determining the cause for this growth enhancing response and why it is seen in some but not all glioma cell lines. By defining the underlying mechanisms for these problematic responses, we hope to find new ways to improve the efficacy of these EGFR inhibitors.

This study aims to explore the mechanism by which resistance to these small molecule inhibitors of EGFR develops; to assess whether mutant EGFR (EGFRvIII) also displays a similar resistance to these inhibitors; and to determine the basis for enhanced proliferation seen with some glioma cells in the presence of low EGFR inhibitor levels. This study could potentially help researchers gain a better understanding of how these EGFR inhibitors act on malignant gliomas and lead to the development of strategies that can help improve the efficacy of these new treatment agents. This two-year study was also funded by support from all our donors. A special thank you to the Lilly Family for added support from Becca's Run.