Pre-clinical Pharmacological Evaluation of Letrozole, a Third Generation Aromatase Inhibitor, as Novel Treatment for Primary Tumors

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Purpose
Treatment of primary brain tumors remains one of the most formidable challenges in oncology. We investigated the potential role of aromatase (CYP19) as a target for the treatment of CNS malignancies and also assessed in vitro and in vivo efficacy of letrozole against gliomas.

Methods
Cytotoxicity and aromatase activity of letrozole against human glioma cell lines were measured using MTT assay and Enzyme Immunoassay, respectively. C6 glioma were orthotopically implanted in the striatum region of the right hemisphere of the brains in Sprague-Dawley rats and the tumor was allowed to grow for 10 days. μPET/CT imaging was then performed using 18F FDG to evaluate changes in active tumor volumes pre- and post-treatment of letrozole. 4mg/kg letrozole was administered daily for up to 15 days in initial efficacy studies and later for up to 60 days for long-term efficacy studies. Brain tissues were collected at the end of the experiment for histological evaluations.

Results
All glioma cell lines included in this study expressed CYP19 and letrozole exerted marked cytotoxicity against these cells (IC50 values; 0.1 – 3.5 μM). μPET/CT imaging showed a marked reduction of active tumor volume (~75-90%) after 8-10 days of letrozole treatment (N=7). Oral and Intraperitoneal (I.P.) administration of letrozole also showed similar brain disposition and efficacy. Long term survival studies showed that the rats in the treatment group showed continuous decrease in the active tumor volumes for up to 60 days. During the 60 day treatment period, no serious toxicity of letrozole was observed. Immunohistochemical analysis of aromatase demonstrated markedly higher aromatase expression in tumoral regions of the brain and a considerable reduction in aromatase expression in letrozole-treated rats relative to the control group.

Conclusion
Thus, employing multifaceted and cutting edge in vitro and in vivo methods, we conclude: a) aromatase is abundantly expressed in glioma cell lines examined, b) letrozole exerts marked cytotoxicity in these cells presumably due to aromatase inhibition, and c) in vivo μPET/CT studies show marked efficacy of letrozole on C6 glioma in a preclinical rat model.