Reviewer’s report

**Title:** The Critical Role of ERK in Death Resistance and Invasiveness of Hypoxia-selected Glioblastoma Cells

**Version:** 1  **Date:** 3 August 2008

**Reviewer:** Zheng Dong

**Reviewer’s report:**

The study by Kim et al. examined the mechanism of death resistance of cells that were selected by repeated episodes of hypoxia. It was shown that the selected cells expressed higher levels of the antiapoptotic proteins Bcl-2 and Bcl-XL. Also the cells showed higher activation status of ERK as indicated by ERK phosphorylation. Using pharmacological ERK inhibitors and activators, they further suggested that ERK activation was important to the death resistance of the selected cells. In addition, they showed higher ERK activation in malignant glioblastomas exposed to hypoxia. These results provide some mechanistic information pertaining to the cell death or therapy resistance of solid tumors. However, the study needs to address the following issues.

1. A previous study selected death resistant cells by repeated episodes of hypoxia and also reported the importance of Bcl-2 protein regulation (Dong and Wang J Biol Chem 2004). The current study should carefully discuss the similarities or consistency between these two studies and also point out the new findings of the current study.

2. It would be interesting to determine if the selected T98G cells have undergone epithelial-mesenchymal transition, although Brooks et al. (Am J Physiol 2008) suggested that in their selected cells EMT did not occur. This is important consider the current results of high invasive potential of selected cells.

3. Fig 2 should provide representative immunoblots for the analysis of the various proteins.

4. It is important to examine if ERK inhibition affects Bcl-2 and Bcl-XL expression in the selected cells, therefore sensitize the cells to death.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests