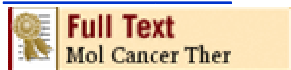




A service of the [U.S. National Library of Medicine](#)
and the [National Institutes of Health](#)

Select **19208828**

1: [Mol Cancer Ther.](#) 2009 Feb;8(2):386-93. Epub 2009 Feb 10.



Inhibition of Akt inhibits growth of glioblastoma and glioblastoma stem-like cells.

[Gallia GL](#), [Tyler BM](#), [Hann CL](#), [Siu IM](#), [Giranda VL](#), [Vescovi AL](#), [Brem H](#), [Riggins GJ](#).

Department of Neurosurgery, Johns Hopkins University School of Medicine, Johns Hopkins Hospital, Baltimore, MD 21231, USA. ggallia1@jhmi.edu

A commonly activated signaling cascade in many human malignancies, including glioblastoma multiforme, is the Akt pathway. This pathway can be activated via numerous upstream alterations including genomic amplification of epidermal growth factor receptor, PTEN deletion, or PIK3CA mutations. In this study, we screened phosphatidylinositol 3-kinase/Akt small-molecule inhibitors in an isogenic cell culture system with an activated Akt pathway secondary to a PIK3CA mutation. One small molecule, A-443654, showed the greatest selective inhibition of cells with the mutant phenotype. Based on these findings, this inhibitor was screened in vitro against a panel of glioblastoma multiforme cell lines. All cell lines tested were sensitive to A-443654 with a mean IC(50) of approximately 150 nmol/L. An analogue of A-443654, methylated at a region that blocks Akt binding, was on average 36-fold less active. Caspase assays and dual flow cytometric analysis showed an apoptotic mechanism of cell death. A-443654 was further tested in a rat intracranial model of glioblastoma multiforme. Animals treated intracranially with polymers containing A-443654 had significantly extended survival compared with control animals; animals survived 79% and 43% longer than controls when A-443654-containing polymers were implanted simultaneously or in a delayed fashion, respectively. This small molecule also inhibited glioblastoma multiforme stem-like cells with similar efficacy compared with traditionally cultured glioblastoma multiforme cell lines. These results suggest that local delivery of an Akt small-molecule inhibitor is effective against experimental intracranial glioma, with no observed resistance to glioblastoma multiforme cells grown in stem cell conditions.

Publication Types:

- [Research Support, N.I.H., Extramural](#)
- [Research Support, Non-U.S. Gov't](#)

PMID: 19208828 [PubMed - in process]
