

**96th Annual Meeting**  
**April 16-20, 2005**  
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**Abstract Number:** 2075  
**Presentation Title:** The Role of PTEN Tumor Suppressor in Brain Growth and Tumor Development  
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Glioblastoma Multiforme (GBM) is one of the most common and aggressive forms of human brain tumors. Genetic aberrations of the PTEN tumor suppressor gene (phosphatase and tensin homologue deleted on chromosome 10) are found in more than 30% of primary GBM. PTEN is a lipid/protein phosphatase that antagonizes the PI3K/AKT signaling pathway. Loss of PTEN leads to enhanced cell proliferation, survival, and invasiveness. In order to study PTEN's role in brain growth and tumorigenesis, we generated *Pten*<sup>loxP/loxP</sup> mice and crossed them to different brain-specific Cre strains. Mice lacking PTEN in embryonic day 14 (E14) neural stem/progenitor cells (NSPC) develop enlarged brains due to increased cell proliferation, decreased cell death, and enlarged cell size. *In vitro* cell cycle studies on NSPCs from E14 *Pten*<sup>-/-</sup> and wild-type brains show that loss of PTEN facilitates the G0-G1 cell cycle transition. Due to the perinatal lethality of the mutant animals, PTEN's role in regulating adult neural stem cells (NSC) and tumorigenesis could not be evaluated. Therefore we generated mouse models with *Pten* deletion in the brain during late development and in the adult. Our preliminary results demonstrate an enhanced proliferation index in cortical and hippocampal regions and an increased cell number in the dentate gyrus upon *Pten* deletion. These mice suffered from progressively increased brain size, leading to brain pressure complications and subsequent death without obvious GBM formation. Thus, longer survival time may be necessary for tumor development. Therefore, we have stereotactically injected helper-dependent adenovirus expressing Cre (HDA-CRE-YFP) into adult *Pten*<sup>loxP/loxP</sup> mice. Since human GBM tumors initiate focally and may arise from mutated precursor/stem cells, we have chosen to focally delete *Pten* in the proliferation permissive areas of the subventricular zone (SVZ) and dentate gyrus (DG). Our preliminary *in vivo* data demonstrates our accuracy in the stereotactic delivery of HDA-CRE-YFP into the DG and SVZ. In addition, PTEN's deletion in these areas results in increased cell proliferation in postnatal animals. Hence PTEN might be important for the regulation of adult NSC proliferation. Furthermore, loss of PTEN in NSCs may be an important genetic event contributing to GBM pathogenesis.

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