

Applicant's Name: Xing Fan, M.D., Ph.D.

Applicant's Division: Neuropathology

“Notch Pathway Blockade Targets Medulloblastoma-Initiating Cancer Stem Cells”

Xing Fan, William Matsui, Leila Khaki, Jiong Chun, Yue-Ming Li, CharlesG. Eberhart.

Background: Many tumors, like normal organs, contain stem-like cells capable of long-term self renewal. These “cancer stem cells” appear to be critical for neoplastic initiation and growth. Therefore, only by targeting malignant stem cells can durable cures be achieved in cancer patients.

Design and Results: We investigated whether Notch activity, which is required in non-neoplastic neural stem cells, might also regulate cancer stem cells in malignant brain tumors such as medulloblastoma. Constitutive Notch2 activation in medulloblastoma cultures increased side population, a marker of cancer stem cells, several-fold, while Notch pathway blockade using a gamma-secretase inhibitor eliminated the side population in several cell lines. The cell fraction expressing other stem cell markers such as CD133 and nestin was also significantly reduced by pharmacological Notch inhibition. Both forced differentiation and Akt-dependant apoptosis caused depletion of stem-like tumor cells. A large viable cell population remained after gamma-secretase inhibitor therapy, but did not efficiently initiate tumor xenografts, while equal numbers of vehicle-treated cells always did.

Conclusion: Our data suggest that Notch signaling is critical in brain tumor stem cells, and that gamma-secretase inhibitors preferentially target this tumor-initiating cell fraction, leaving behind a population of viable cells with significantly reduced malignant potential.