Double-therapy Approach Effectively Inhibited Brain Cancer Recurrence

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Glioblastoma multiforme is the most common and aggressive brain tumor. Combining temozolomide with a Notch inhibitor decreased tumor recurrence.

PHILADELPHIA - Researchers from the University of Massachusetts Medical School have identified a novel approach of combining chemotherapy with a targeted therapy to decrease the recurrence of glioblastoma multiforme, the most common and aggressive brain tumor.

"Glioblastomas are horrendous tumors, and new therapies are desperately needed," said lead researcher Alonzo H. Ross, Ph.D. [1], professor of biochemistry and molecular pharmacology at the University of Massachusetts Medical School.

"We found that this double therapy of combining temozolomide with a Notch inhibitor was highly effective at treating tumor cells in culture and in mice," he added.

Results of this study are published in the September issue of *Cancer Research* [2], a journal of the American Association for Cancer Research.

Despite treatment with surgery, radiotherapy and chemotherapy, glioblastoma prognosis and survival rates are poor. This may in part be due to the fact that some cells within the tumor - cancer stem cells - are more resistant to these therapies, eventually allowing the tumor to recur, according to Ross.

"Were both very successful and unsuccessful with cancer therapy; in most cases we can substantially diminish the tumor mass. The problem is that it comes back with vengeance, and is even more resistant and difficult to treat," he said.

Temozolomide is one chemotherapeutic agent that helps patients with glioblastomas live longer; two-year survival rates increase from approximately 10 percent with radiation alone to 25 percent when temozolomide is combined with radiation, according to Ross. Likewise, data have indicated that the Notch signaling pathway is often over-expressed in glioma tissue and tumor cells.

Ross and colleagues evaluated this double-therapy approach of combining temozolomide with a Notch inhibitor in cell culture and in immunodeficient mice to determine if this combination therapy enhances therapy to reduce tumor recurrence.

In both models, the researchers saw that the combination of temozolomide with the Notch inhibitor much more effectively reduced tumor growth and recurrence

compared to either agent alone. Either drug used individually only transiently slowed tumor growth.

"Temozolomide is a chemotherapy drug of choice for glioblastomas, and the results of our preclinical study represent a potential promising new approach to combat an extremely difficult tumor," Ross said. "The effect of the two together is very dramatic."

Patrick M. OConnor, Ph.D. [3], chief scientific officer of Selexagen Therapeutics and editorial board member for *Cancer Research*, believes this study provides preclinical proof-of-concept evidence that the Notch pathway confers a survival advantage to glioma cells treated with temozolamide.

"These results help lay the groundwork for future clinical research and are yet another stepping stone towards a future era dominated by â€˜precision therapeutics designed to specifically target the underlying molecular drivers of cancer growth and spread," said OConnor.

The researchers are currently investigating the mechanism of action for cell death and hope to move these findings into the clinic.

The mission of the American Association for Cancer Research is to prevent and cure cancer. Founded in 1907, the AACR is the worlds oldest and largest professional organization dedicated to advancing cancer research. The membership includes 32,000 basic, translational and clinical researchers; health care professionals; and cancer survivors and advocates in the United States and more than 90 other countries. The AACR marshals the full spectrum of expertise from the cancer community to accelerate progress in the prevention, diagnosis and treatment of cancer through high-quality scientific and educational programs. It funds innovative, meritorious research grants, research fellowship and career development awards. The AACR Annual Meeting attracts more than 17,000 participants who share the latest discoveries and developments in the field. Special conferences throughout the year present novel data across a wide variety of topics in cancer research, treatment and patient care. The AACR publishes six major peer-reviewed journals: *Cancer Research; Clinical Cancer Research; Molecular Cancer Therapeutics; Molecular Cancer Research; Cancer Epidemiology, Biomarkers & Prevention*; and *Cancer Prevention Research*. The AACR also publishes *CR*, a magazine for cancer survivors and their families, patient advocates, physicians and scientists. *CR* provides a forum for sharing essential, evidence-based information and perspectives on progress in cancer research, survivorship and advocacy.

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