Targeted agent blocked growth of deadly brain cancer in preclinical studies

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A drug already in clinical trials to treat a variety of tumors shows a remarkable ability to shut down growth of glioblastoma in both laboratory cells and in animals, say researchers from Georgetown Lombardi Comprehensive Cancer Center and the University of California, San Francisco (UCSF). In their experiments, the agent put a brake on growth of laboratory cancer cell lines, and no mice with glioblastoma in their brain died as a result of their tumor while on therapy.

They say their findings, reported in the April 15 issue of *Cancer Research*, provides hope that the drug, PD-0332991, could offer a new treatment option for glioblastoma, which is the most common as well as the deadliest form of brain cancer. A clinical trial testing the therapy in patients with recurrent brain cancer is under development.

"We have had just amazing results in these preclinical studies," says Todd Waldman, MD, PhD, an associate professor of oncology at Lombardi. "We are hopeful it will prove to be effective in brain cancer patients for which there is little effective therapy."

Waldman is the study's co-lead investigator, along with C. David James, PhD, professor of neurological surgery at UCSF. "What is especially encouraging about this agent is that we found it can easily pass through the blood-brain barrier and access glioblastoma, and that there is already a simple test available for screening glioblastoma patients in advance to see whether or not they should be responsive to this therapy," James

says.

Given the molecular data from a recently published study by The Cancer Genome Atlas Research Network, about 90 percent of glioblastoma patients have a molecular profile that would make them candidates for the drug, the researchers say.

The drug is currently being tested in clinical trials for otherwise untreatable teratomas, as well as multiple myeloma and breast cancer. It is designed to shut down the activity of molecules, cyclin-dependent kinases 4 and 6 (cdk4/6), that drive cell division. "In normal cells, these kinases are kept under exquisite control by a gene known as p16," says Waldman. "But in glioblastoma, and other cancers, p16 is frequently deleted, and these two kinases are uncontrollably activated, which drives the cell to divide and form cancer."

The agent, however, does not work if the cancer is missing expression of a tumor suppressor protein known as retinoblastoma (Rb) because Rb is needed to control growth in these cells even if cdk4/6 are inhibited. A test to determine if RB is present is already being used to screen patients for use of PD-0332991 in the ongoing clinical trials.

A research team at Georgetown led by Waldman, conducted laboratory studies on 21 different cell lines derived from the tumors of patients with glioblastoma. They tested PD-0332991 at various concentrations to see if it could stop growth of the cancer cells, and found it to be effective in all 16 cell lines with a functioning Rb gene, but it did not work in 5 cell lines missing Rb. "The agent was very potent in stopping cancer growth, but it was also quite clean in that it only seemed to inhibit the two molecules it targeted, and no other," says Waldman. "Most drugs are dirtier than that - they hit multiple unintended targets."

What intrigues Waldman, he says, is that no one has discovered what the

"normal" function for cdk4/6 is. "Mice lacking either cdk4 or cdk6 grow up to be relatively healthy, so it may be that these kinases are really only important for cancer growth," Waldman says. "That would be an exciting development, if true, but no one knows yet."

James led a team of scientists at UCSF that implanted three different kinds of human glioblastoma directly into the brains of mice, and then they treated them with PD-0332991. They discovered first that the agent effectively reached intracranial tumors - "and it wasn't known beforehand that it would, so this was very good news," says James - and that the cancer did not grow as long as the mice continued on the drug, but that they quickly died from the cancer when the agent was withdrawn.

Because PD-0332991 itself does not kill cancer cells - just arrests their growth - the researchers then combined the agent with radiation and found that outcomes were superior to use of PD-0332991 alone. They further successfully tested the agent in mice in which glioblastoma had come back after treatment with temozolomide, a chemotherapy that is the standard-of-care for many patients.

"We don't know how well this agent will perform in patients with glioblastoma, but in the mice we studied, we saw very impressive, durable effect that was sustained as long as therapy was administered," says James.

Provided by Georgetown University Medical Center