

New approach to treating human brain cancer could lead to improved outcomes

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A new experimental approach to treating a type of brain cancer called medulloblastoma has been developed by researchers at Sanford-Burnham Medical Research Institute (Sanford-Burnham). The method targets cancer stem cells—the cells that are critical for maintaining tumor growth—and halts their ability to proliferate by inhibiting enzymes that are essential for tumor progression. The process destroys the ability of the cancer cells to grow and divide, paving the way for a new type of treatment for patients with this disease.

The research team, led by Robert Wechsler-Reya, Ph.D., professor in Sanford-Burnham's NCI-Designated Cancer Center and director of the Tumor Initiation and Maintenance Program, discovered that the medulloblastoma [cancer cells](#) responsible for tumor growth and progression (called cancer [stem cells](#) or tumor-propagating cells—TPCs) divide more quickly than normal cells. Correspondingly, they have higher levels of certain enzymes that regulate the cell cycle (Aurora and Polo-like kinases). By using small-[molecule inhibitors](#) to stop the action of these enzymes, the researchers were able to block the growth of tumor cells from mice as well as humans. The research findings are described in an online paper published September 25 by *Cancer Research*.

"One tumor can have many different types of cells in it, and they can grow at different rates. By targeting fast-growing TPCs with cell-cycle inhibitors, we have developed a new route to assault medulloblastoma. In this study, we have shown that cell-cycle inhibitors essentially block medulloblastoma tumor progression by halting TPC expansion, and have opened the window to preventing [cancer recurrence](#)," said Wechsler-Reya.

For their research, the scientists tested the effectiveness of cell-cycle inhibitors in a specific type of [brain cancer](#) called Sonic Hedgehog (SHH)-associated medulloblastoma. These

cancers have mutations in components of the SHH pathway that regulate cell growth during normal development. The mutations cause cell signaling to go awry, triggering the creation of cancer cells that grow uncontrollably and establish tumors. SHH-associated tumors account for 25 percent of all human cases of medulloblastoma, and the SHH pathway has been implicated in other tumor types such as lung, breast, prostate, and skin cancer.

"Our increased understanding of SHH-associated tumors has recently led to the development of drugs that specifically inhibit the SHH pathway. Early studies in humans with these new drugs have offered some hope for patients, but many do not respond and most patients who do respond develop resistance to the drug. For this reason, it is essential to develop alternative, or additional, therapies that are more effective than current treatment options," Wechsler-Reya said.

The team's first set of experiments used a mouse model for SHH-dependent medulloblastoma. In-vitro studies of mouse tumor cells showed that cell-cycle inhibitors caused tumor cell death. In vivo, mice that were treated with the inhibitor had smaller tumors that weighed less compared to mice that were not treated, essentially halting the progression of the tumor.

The second set of experiments used human SHH-dependent medulloblastoma cells. When the researchers treated these human [tumor cells](#) with cell-cycle inhibitors, they also observed a significant reduction in [tumor growth](#) and progression.

Finally, when the scientists combined SHH inhibitors with cell-cycle inhibitors, they found that the combination worked together to produce results that were greater than either inhibitor alone.

"These results strongly support an approach to treatment that combines SHH inhibitors with cell-cycle inhibitors to treat medulloblastoma. Our hope

is that the combination of these inhibitors will prevent [tumor progression](#) and drug resistance, and improve the overall effectiveness of current treatment options. We look forward to clinical studies in human medulloblastoma patients as well as other cancers that are suitable for this approach," Wechsler-Reya said.

Provided by Sanford-Burnham Medical Research Institute

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