Scientists identify a new drug that halts recurring brain tumor growth

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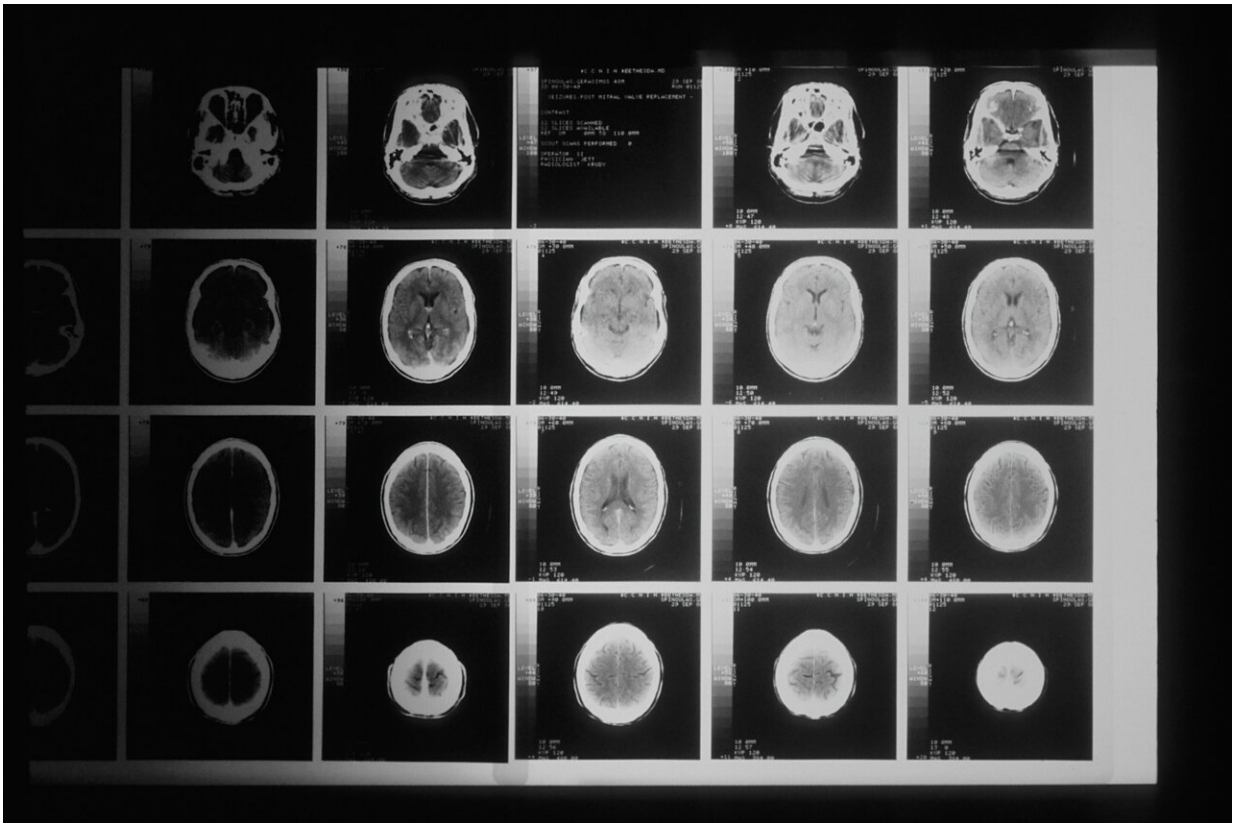

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When a non-metastatic brain tumor—a meningioma—recurs after surgery and radiation treatment, a patient is out of options. No drugs are approved for these aggressive tumors, which occur in up to 20% of cases

and can lead to patient disability or even death.

But now, Northwestern Medicine scientists, in an international collaboration with scientists at the University of California, San Francisco and the University of Hong Kong, have identified a drug that inhibits growth of the most aggressive meningiomas and how to most accurately identify which meningiomas will respond to the drug.

The drug is a newer cancer treatment called abemaciclib.

The scientists demonstrated the effectiveness of the drug in select patients, mouse models, a 3D living tissue brain tumor (organoids) and cell cultures.

Investigators discovered that meningiomas can be divided into molecular subgroups with different clinical outcomes and recurrence rates. This new method of classifying tumors allows scientists to predict recurrence more accurately than the current method of classifying the tumor.

Currently, after surgery, doctors examine a specimen of a tumor under a microscope and grade it one, two or three in its aggressiveness. But the grade is only about 70% accurate, meaning some tumors will behave in a way that doesn't fit with how it appears under the microscope.

"Our study identifies which patients we should treat with this drug, because their tumor will likely respond to it," said study leader and corresponding author, Dr. Stephen Magill, an assistant professor of neurological surgery at Northwestern University Feinberg School of Medicine and a Northwestern Medicine physician. "We now have the potential to give them options and hope for a longer, symptom-free life."

Magill also is a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

The paper was published today in *Nature Genetics*.

Meningiomas are the most common primary (non-metastatic) tumor in the central nervous system, with about 31,000 people diagnosed with a meningioma every year in the U.S. The symptoms are headaches, seizures or neurological deficits (weakness, vision loss, double vision or sensory changes).

The drug is a cell cycle inhibitor, meaning it blocks the cell division cycle and inhibits tumor growth.

"Eventually we hope to tailor medical therapy to the genetic changes within each individual person's meningioma," Magill said.

Investigators studied molecular changes in the tumor to understand what drives its growth and design therapies that target the Achilles heel of the tumor.

"We can find a weakness in that tumor, put a stick in the spokes and stop it from growing," Magill said.

The new study was conducted by doing DNA methylation profiling and RNA sequencing on 565 meningiomas. This enabled investigators to see what genes are expressed by the tumor and the level of expression, revealing a signature of the DNA.

"By doing that we found three separate groups of meningiomas based off their biology," Magill said. "For each group, we found a different biological mechanism promoting the tumors' growth, with each group having a different clinical outcome."

These groups are different than the previous grading system and "are more accurate at predicting the clinical behavior of the tumor," Magill

said.

Scientists discovered that aggressive tumors have multiple molecular changes in a common pathway of cell division that enables the cells to divide more and come back after surgery.

"We wondered if by inhibiting that pathway we could stop the tumors from growing," Magill said. "We tested that in multiple ways and found it was true in patients, mouse models and cell cultures."

Mice with meningiomas treated with the medication lived longer and their tumors didn't grow as rapidly. The drug was also used off label as compassionate use in several patients whose tumors decreased in size and whose symptoms improved, suggesting the drug should be considered for clinical trials, Magill said.

The next steps in the research are to validate these findings in additional populations and build on them to determine whether we can use molecular features to predict which meningioma patients should be treated with radiation in addition to surgery.

Scientists plan to translate these findings and methods to make this molecular profiling generalizable and available to all patients with meningioma.

Scientists validated their findings in an independent cohort by collaborating with investigators at the University of Hong Kong.

More information: Meningioma DNA methylation groups identify biological drivers and therapeutic vulnerabilities, *Nature Genetics* (2022). DOI: 10.1038/s41588-022-01061-8

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