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'Metabolic inhibitor' compound extends survival in mice with MYC-expressing pediatric brain tumors

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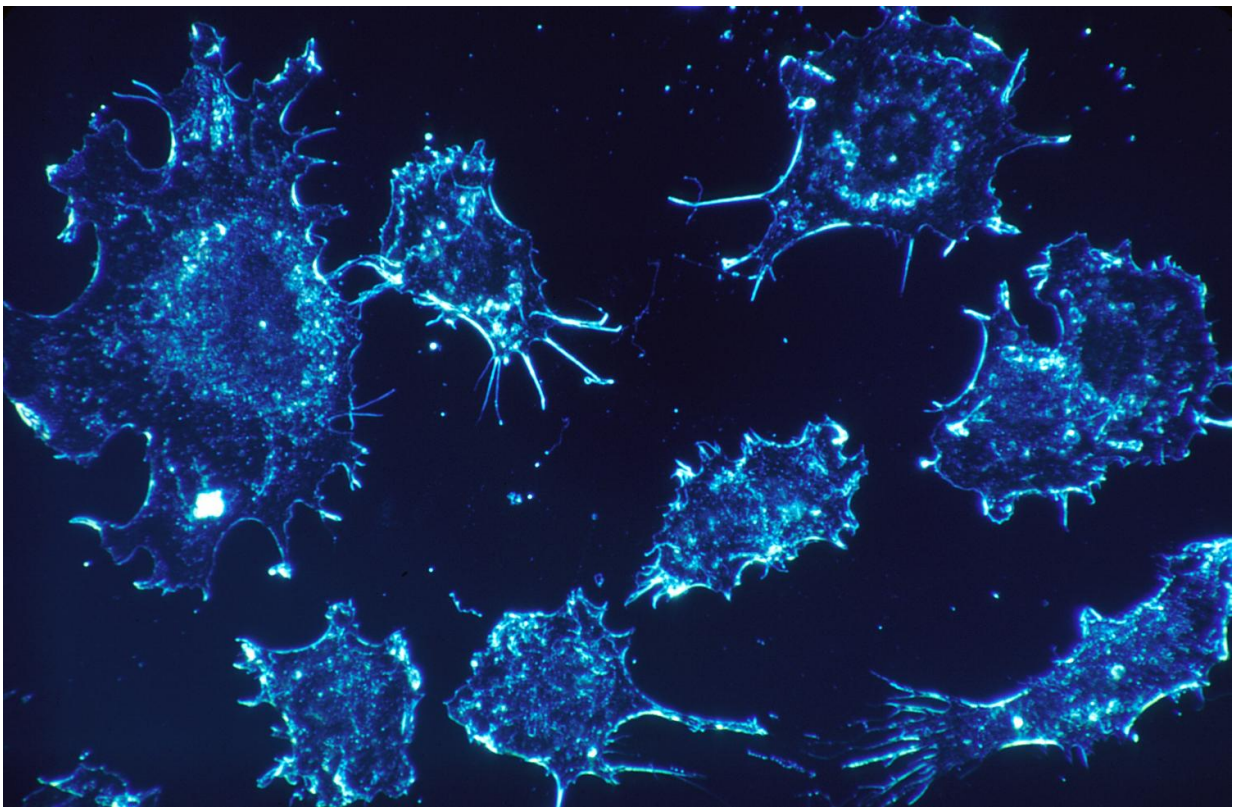

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Versions of an antibiotic drug called DON first isolated from soil bacteria more than 60 years ago have shown promising signs of

extending survival in mice models of especially lethal pediatric brain tumors marked by the high expression of a cancer-causing gene known as the MYC oncogene, according to results of two studies from researchers at the Johns Hopkins Kimmel Cancer Center.

The MYC-expressing subgroups of atypical teratoid/rhabdoid tumors and medulloblastoma, while rare, are especially aggressive, with a minority of patients surviving their disease, even with the use of intensive chemotherapy and radiation. The poor outcomes for patients have brought urgency, scientists say, to the search for new ways to treat the cancers in conjunction with current therapies such as surgery, chemotherapy and radiation therapy. The new findings, they say, suggest that the altered metabolism of an amino acid in these tumors needed to make proteins and energy for the cancer cell could be a productive target for clinicians.

Tumors with high MYC expression have increased metabolism of the key amino acid glutamine, the scientists say. By inhibiting glutamine metabolism with DON or a so-called "prodrug" version of it that converts to DON in the brain, the researchers were able to extend survival times by more than 30% in mice transplanted with these human cancer cells. DON was first isolated in 1956 from bacteria in soil found in Peru, and its ability to block glutamine has long made it a candidate for cancer therapy, but it was never systematically tested against high-MYC-expressing cancers.

For the current experiments, the Johns Hopkins scientists gave a weekly DON injection to mice bearing high-MYC-expressing AT/RT cell lines and extended the animals' median survival times from 21 to 36 days, and to 45 days when DON was combined with the chemotherapy drug carboplatin. The scientists performed metabolic experiments that showed that DON blocked glutamine from being made into glutathione, one of major detoxifying substances that cancer cells use to thwart

carboplatin chemotherapy. DON depleted the cancer cells of glutathione, making carboplatin chemotherapy more effective.

In mice with MYC-expressing medulloblastoma who were treated twice weekly with JHU-083 by mouth, an experimental DON version designed to be better metabolized and less toxic in the brain and in development at Johns Hopkins Drug Discovery, median survival rose from 21 to 28 days in immune-deficient mice and 16 to 25 days in immune-competent mice.

Disrupting abnormal metabolism is targeting "an Achilles' heel that would hurt the cancer cells but not hurt the normal cells in the brain or body," said Eric Raabe, M.D., Ph.D., an associate professor of oncology at the Johns Hopkins University School of Medicine, who was a co-author on both papers and lead author of the paper on medulloblastoma published July 21 in *Translational Oncology*.

AT/RT, the most common malignant brain tumors in infancy, are usually treated with intensive chemotherapy and radiation. The median survival time is less than one year after diagnosis. Medulloblastoma is the most common malignant brain tumor of childhood, and is treated with surgical removal of the tumor, radiation and chemotherapy. The MYC subgroup of medulloblastoma (also known as "Group 3") has a particularly poor outcome, with fewer than 50% of the patients surviving more than five years after diagnosis. Similarly, the MYC subgroup of AT/RT is also associated with worse outcome. "They are the baddest of the bad players," says Jeffrey Rubens, M.D., an assistant professor of oncology and pediatrics at the Johns Hopkins University School of Medicine who led the study on AT/RT and DON published July 12 in *Clinical Cancer Research*. "They seem to be more aggressive, more resistant to chemotherapy, and lead to worse survival rates than other subgroups."

MYC is difficult to target directly with a drug, however. Its protein-binding site is "flat and featureless," says Rubens, "and it's hard to design

a small molecule that will fit into it. We're trying to identify a drug that we can use to treat kids relatively soon."

To look for other vulnerabilities of MYC-driven tumors, Rubens and his colleagues analyzed the metabolic profiles of MYC-expressing AT/RT cell lines derived from patients, discovering that the cells were dependent on increased levels of glutamine metabolism for their survival.

To inhibit this metabolic pathway in the cancer, they turned to DON, not only because of its well-known characteristics, but also because it has already been tested for safety in a phase 1 pediatric cancer clinical trial in the 1980s.

"Our hope would be to someday add this drug to the standard therapy for AT/RT to decrease some of the chemotherapy resistance that we see and to help improve survival," says Rubens.

Rubens says this metabolic approach might also be used to identify tumors that are sensitive to DON therapy even before the tumor is biopsied. A technique called MRI spectroscopy can pinpoint peaks of glutamine production and its metabolic byproduct glutamate in brain tissue. When the MRI scans show a high ratio of glutamine to glutamate in tumors, they indicate that the cancer might be sensitive to DON, he says. "This could be important to know in patients who have relapsed," says Rubens, "where you might not want to perform another surgery."

In the *Translational Oncology* study, Raabe and colleagues used a twice-weekly oral dose of JHU-083, developed by Barbara Slusher, Ph.D., director of Johns Hopkins Drug Discovery, and colleagues at Johns Hopkins, in mice with MYC-driven medulloblastoma.

"The rationale for the development of so-called 'prodrugs' is to

maximize the brain penetration of DON to the brain tumor and to minimize the side effects that would come from delivering DON peripherally," such as nausea and a lower white blood cell count, says Raabe.

Raabe says testing JHU-083 in mice with intact immune systems in the study was significant because these mice more closely resemble the immune environment in human patients. "If we can combine JHU-083 or other DON prodrugs with other drugs that we think work with medulloblastoma, or other drugs that we identify through metabolic analysis, we hope to be able to further extend the survival of these mice," Raabe says.

Looking ahead, the researchers plan to learn more about the best time to add DON to a therapeutic regimen and how well JHU-083 and other DON prodrugs might pair with other drugs used to treat pediatric brain cancers.

"The initial efficacy that we show of DON prodrugs in these tumors is encouraging," says Raabe, "and leads us to believe that we will be able to further improve the survival of laboratory mice bearing aggressive MYC medulloblastoma."

More information: Allison R. Hanaford et al, Orally bioavailable glutamine antagonist prodrug JHU-083 penetrates mouse brain and suppresses the growth of MYC-driven medulloblastoma, *Translational Oncology* (2019). DOI: 10.1016/j.tranon.2019.05.013

Sabrina Z. Wang et al. Unbiased Metabolic Profiling Predicts Sensitivity of High MYC-Expressing Atypical Teratoid/Rhabdoid Tumors to Glutamine Inhibition with 6-Diazo-5-Oxo-L-Norleucine, *Clinical Cancer Research* (2019). DOI: 10.1158/1078-0432.CCR-19-0189

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