Drug modifies epigenome in aggressive brain tumors

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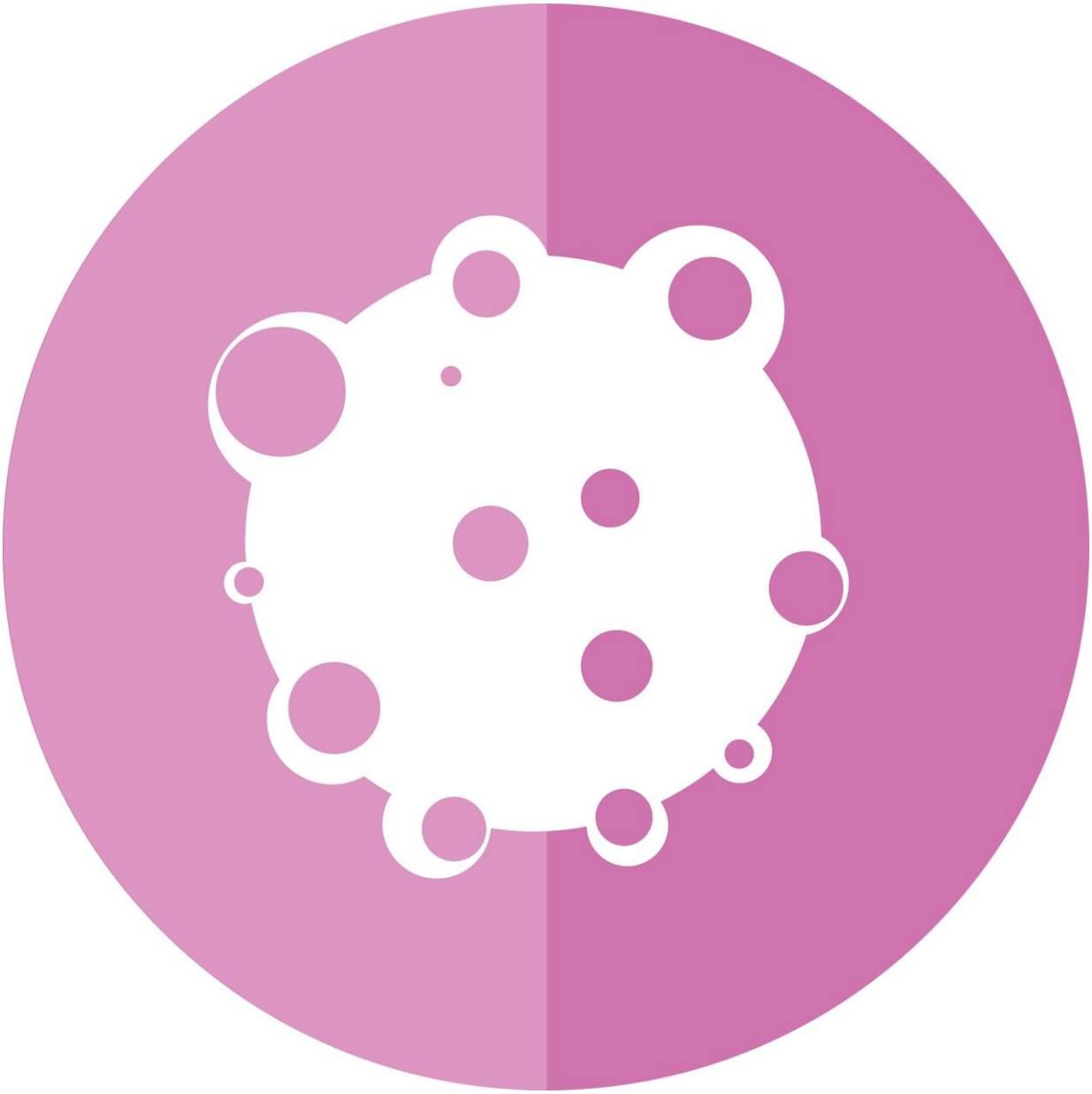

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A folic acid-like drug, L-methylfolate, when administered alongside the standard therapy for patients with recurrent glioblastoma, changed a DNA process within their brain tumors, according to results from a phase 1 clinical trial.

The researchers showed for the first time that the DNA methylome of these brain tumors can be reprogrammed. The study was published on Jan. 5 in *Cancer Research Communications*. Stephen Clark, MD, Ph.D., a neuro-oncologist at Vanderbilt-Ingram Cancer Center, who is the study's corresponding and lead author, said that this is the first time DNA methylome reprogramming has occurred with any solid human tumor.

The DNA methylome is one aspect of the epigenome; the epigenome is a modification of DNA and proteins in a cell that is influenced by the environment. DNA methylation is one such modification, where methyl groups are added to DNA and is a mechanism that controls gene expression, including the silencing or activation of genes related to cancer.

The researchers sought to determine if re-methylation of IDH wild-type tumors, which have a worse prognosis and lower DNA methylation than IDH mutant tumors, could improve survival. They succeeded in showing that the DNA methylome of IDH wild-type, high-grade gliomas could be reprogrammed, but the study group was too small to ascertain the impact on survival.

"This is an important first step in understanding how we can manipulate the epigenome, and hopefully, this study will help design future epigenetic studies in glioblastoma treatment," said Clark, assistant

professor of Neurology in the Division of Neuro-Oncology at Vanderbilt University Medical Center.

Although the study group of 14 patients was not large enough to detect a statistically significant survival advantage, the patients treated with the folic acid supplement L-methylfolate had a median overall survival of 9.5 months, compared to the typical median overall survival of 8.6 months. One of the patients is still alive.

The study provides greater insight into the dynamics of epigenetic reprogramming, which is an emerging treatment for enhancing immunotherapies. In this phase 1 clinical trial, the researchers assessed the response of patients receiving bevacizumab, a monoclonal antibody that prevents the growth and maintenance of tumor blood vessels, when the treatment is augmented with L-methylfolate. The patients also received temozolomide, a chemotherapeutic agent. L-methylfolate was well tolerated, with no toxicities reported.

"Epigenetic reprogramming is not a new concept; for instance, a DNA methyltransferase inhibitor treatment (5-Azacytidine) has been studied and is approved for the treatment of some leukemias. What is exciting about this work is that L-methylfolate, acts oppositely to 5-Azacytidine; it increases the availability of the active folate for the DNA methyltransferases. Consequently, it could remethylate and repress genes activated during tumorigenesis," said the study's first author, Lucas Salas, MD, Ph.D., MPH, assistant professor of Epidemiology at the Geisel School of Medicine at Dartmouth and investigator in the Cancer Population Sciences Research Program at Dartmouth's Norris Cotton Cancer Center.

"Further, we observed changes in the level of DNA methylation in the tumors of those receiving L-methylfolate, suggesting that L-methylfolate not only crosses the blood-brain barrier, but it seems to modify the

tumor epigenetic landscape actively."

Six of the trial participants donated their brains at death for additional studies. Autopsies indicated a significant methylation dysregulation difference between these six autopsy samples and the patient's initial tumor sample at diagnosis.

The researchers plan to expand the study to include a larger group with a phase 2 clinical trial of patients with recurrent glioblastoma. Future studies could also include combinations of epigenetic drugs with immunotherapy.

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