Potential new therapy for childhood brain cancer could heal treatment-resistant tumors

by Emory University

Brain cancer is the second-leading cause of death in children in the developed world. For the children who survive, standard treatments have long-term impacts on their development and quality of life, particularly in small children and infants.

Research out of Emory University and QIMR Berghofer Medical Research Institute in Queensland, Australia, has shown that a potential new targeted therapy for childhood brain cancer is effective in infiltrating and killing tumor cells in preclinical models tested in mice.

In a paper published in ***Nature Communications,*** the novel drug CT-179 was shown to target a specific subset of tumor cells responsible for recurrence and therapy resistance in pediatric brain cancer. The findings could lead to more effective, less toxic treatments, improving survival and quality of life for young patients.

The lead researchers have acknowledged the findings as potentially transformative for the treatment of the most common childhood brain cancer, medulloblastoma, and could apply to other brain cancers such as glioblastoma (GBM) and diffuse intrinsic pontine glioma (DIPG).

Emory University Professor Timothy Gershon, who is also a pediatric neurologist at Children's Healthcare of Atlanta and director of the Children's Center for Neurosciences Research in the U.S., says the study findings are a significant advance in our understanding of the biological processes that lead to tumor growth and recurrence.

"Current treatments, including radiation and chemotherapy, often eliminate most of the tumor, but sometimes fail to eliminate cancer stem cells," says Gershon.

"These cancer stem cells can regrow the tumor after treatment, causing fatal recurrence. We show that CT-179 treatment specifically disrupts cancer stem cells. Combining CT-179 with treatments such as radiation therapy treats the whole tumor more effectively, including both

stem cells and tumor cells that are not stem cells. Adding CT-179 to combinations of treatments may bring new efficacy to brain tumor therapy."

The research teams collaborated with U.S. drug company, Curtana Pharmaceuticals, that developed the experimental small molecule drug, termed CT-179. They found that the drug effectively targets the protein OLIG2, which is a known stem cell marker crucial in the initiation and recurrence of brain cancers.

The findings are a breakthrough

Professor Bryan Day, who leads QIMR Berghofer's Sid Faithfull Brain Cancer Laboratory and is co-director of the Children's Brain Cancer Center in Australia, described the findings as a breakthrough, made more significant because they result from independent studies.

"Children with brain cancer urgently need more effective and less toxic treatments," says Day.

"Our study demonstrated that the drug CT-179, used in combination with standard radiation therapy can cross the blood brain barrier and penetrate the tumor. It prolonged survival in a range of preclinical medulloblastoma models, delayed recurrence of the disease, and increased the effectiveness of radiotherapy.

"Brain cancer is an incredibly tough puzzle to solve. As researchers, what gets us out of bed every day is trying to solve that puzzle. This global research could potentially lead to new combination therapies that improve outcomes for these young patients," says Day.

An international collaboration

The QIMR Berghofer and Emory University findings complement the results of another study published in *Nature Communications* led by Professor Peter Dirks from the University of Toronto and neurosurgeon-in-chief and a senior scientist at the Hospital for Sick Children (SickKids) in Canada.

In the study, the researchers focused on medulloblastomas, a common childhood brain tumor. Through advanced tools like CRISPR gene editing, single-cell RNA sequencing, and collaborative drug testing, the study identified the OLIG2 protein as a key regulator of the tumor's growth transitions.

The findings present a novel therapeutic angle, highlighting a shift from general tumor treatment to precise interventions targeting tumor-initiating cells.

"Our study demonstrated that the OLIG2 protein is a critical driver of the complex early stages of medulloblastoma tumor formation, making it a highly promising treatment target," Dirks says.

"We showed that inhibiting the OLIG2 protein with the CT-179 drug prevented cancer stem cells from changing to a proliferative state, effectively blocking the growth and recurrence of tumors. This could have potentially profound implications for treatment in the future."

QIMR Berghofer post-doctoral researcher Dr. Yuchen Li, who was joint first author on the QIMR Berghofer and Emory University study, is hopeful this translational research can improve the quality of life of children with brain cancer in the future.

"This has been a long-running study and it is very rewarding to see it published," Li says.

Day said the next step is to undertake clinical trials.

"We've been working with our collaborators, particularly in the U.S. and in Australia, and we're very hopeful that the culmination of all this work has paved the way for the first in-human clinical testing of CT-179 in patients with brain cancer," Day says.

The international collaboration included institutions in Canada, Australia, the U.S., Korea, and Sweden.

More information: Yuchen Li et al, Suppressing recurrence in Sonic Hedgehog subgroup medulloblastoma using the OLIG2 inhibitor CT-179, *Nature Communications* (2025). DOI: 10.1038/s41467-024-54861-3

Kinjal Desai et al, OLIG2 mediates a rare targetable stem cell fate transition in sonic hedgehog medulloblastoma, *Nature Communications* (2025). DOI: 10.1038/s41467-024-54858-y
Journal information: Nature Communications
Provided by Emory University

- **www.medicalxpress.com, February 4, 2025**