Adolescent glioma subtype responds to CDK4/6 inhibitor

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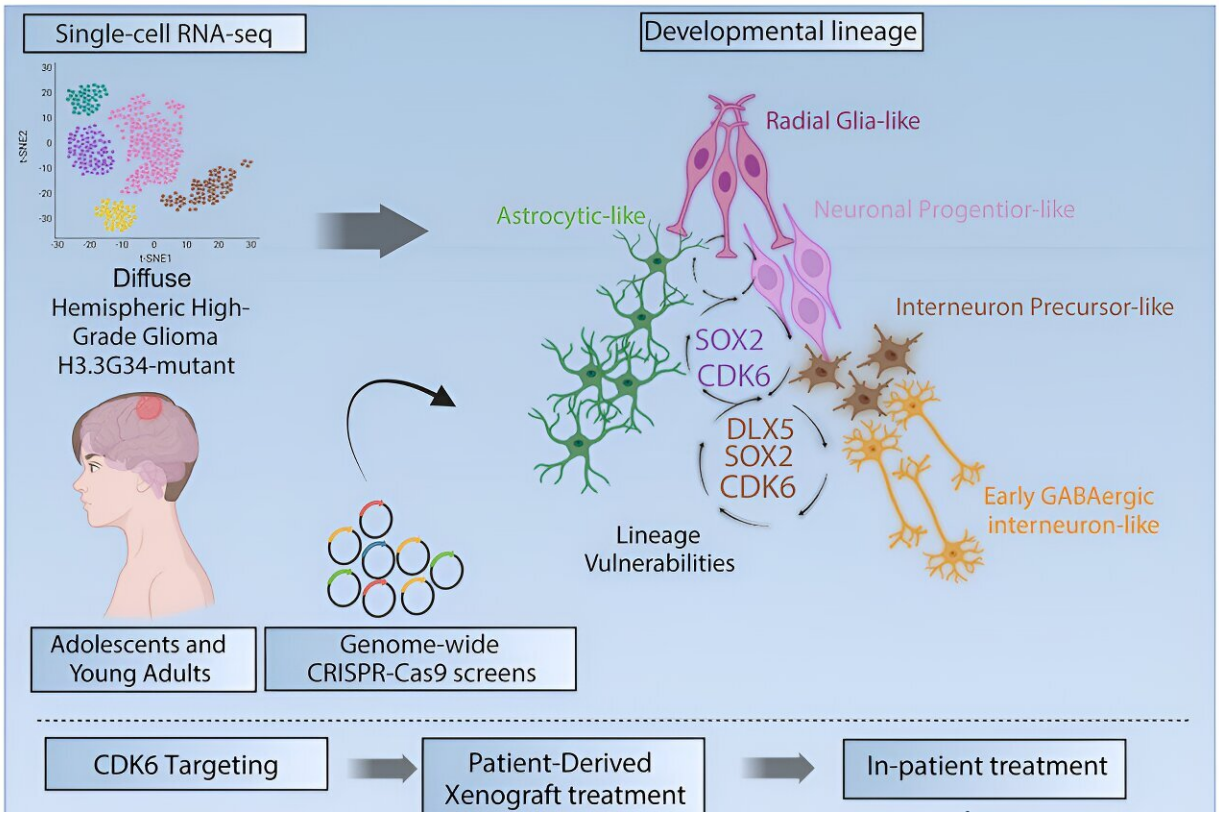

Graphical abstract. Credit: *Cancer Cell* (2024). DOI: 10.1016/j.ccell.2024.08.006

CDK4/6 inhibitors, which are already FDA approved for the treatment of other forms of cancer, show early signs of promise in the treatment of a subtype of pediatric high-grade glioma, according to new research

from Dana-Farber Cancer Institute and the Institute of Cancer Research in London. Treatment of a patient with a second relapse of this glioma subtype and no other treatment options resulted in 18 months of progression-free survival.

"We are finally starting to see more targeted therapies come out for different forms of brain cancer," says senior author Mariella Filbin, MD, Ph.D., co-director of the Brain Tumor Center of Excellence at Dana-Farber/Boston Children's Cancer and Blood Disorders Center and research director of the Pediatric Neuro-oncology Program at Dana-Farber. "Our patients really need these new treatment options."

The study is published in Cancer Cell.

High-grade gliomas are the leading cause of cancer-related deaths in children and adolescents. There are few effective targeted therapies for these cancers and only about a fifth of children diagnosed with high-grade gliomas live more than five years.

A subtype of high-grade glioma, called H3G34R/V-mutant diffuse hemispheric glioma (DHG-H3G34), typically occurs during adolescence and accounts for approximately 30% of childhood high-grade gliomas. Prior to this research, these cancers were thought to arise from glial cells , which provide a scaffold for signal transmitting neurons in the brain.

Filbin and her team discovered, surprisingly, that the tumor cells more closely resemble neurons. The team made this discovery using single cell multi-omic sequencing—the analysis of the active genes and proteins in individual cells in the tumor samples.

"Once we knew what kinds of cells we are working with, we can start to look at therapeutic vulnerabilities," says Filbin.

To discover those vulnerabilities, Filbin's lab initiated a CRISPR screen on these neuron-like tumor cells. The screen disables genes one-by-one across the human genome to determine if any of its 20,000 genes are essential for the cells to survive. They found several vulnerabilities, many of which are specific to neuron-like cancer cells. However, most of those genes are not yet targetable by any known drugs.

The screen's results also pointed to CDK6 as a key vulnerability. CDK6 is a gene that regulates the cell division cycle and is important in cell fate decisions as cells differentiate. Several CDK4/6 inhibitors are already approved for the treatment of other cancers such as breast cancer.

Shortly after completing the screen, Filbin learned that the lab of co-senior author Chris Jones, Ph.D., at the Institute of Cancer Research in London, had done a similar CRISPR screen with similar results. "We joined forces and combined our data," says Filbin.

The next step was to test CDK4/6 inhibitors on patient-derived tumor models. There are no public repositories of this rare form of brain cancer, so all the samples tested came from patients who had been treated at Boston Children's Hospital and in hospitals in Vienna, London, Rome, Hamburg, and Munich.

The team first confirmed that three CDK4/6 inhibitors, ribociclib, palbociclib, and abemaciclib, could penetrate the blood brain barrier. Ribociclib, however, had several advantages, including being better tolerated at higher concentrations and more specificity to CDK6. In mouse models with patient-derived xenografts, treatment with ribociclib slowed tumor growth and extended survival.

When co-author Fernando Carseller, MD, of the Royal Marsden Hospital, learned about this work, he contacted Filbin. He had a patient, a 13-year-old whose cancer had relapsed twice. There were no more

treatment options available. Ribociclib had been tested in clinical trials in children in the past, so the team had the dosing and safety data needed to administer the medicine safely.

When treated with ribociclib, the patient's cancer stopped progressing for 18 months. Filbin and Karen Wright, MD, MS, a clinician-scientist in the Brain Tumor Center at Dana-Farber/Boston Children's Cancer and Blood Disorders Center, are now working with the Connect Consortium, the Collaborative Network for Neuro-oncology Clinical Trials, to initiate a global clinical trial of ribociclib in patients with this subtype of high-grade glioma up front before any other treatments are provided.

"We want to see how the monotherapy works before relapse happens," says Filbin.

The treatment, however, is not likely to be enough for a cure. Filbin and Jones learned through their study that inhibiting CDK6 does not always kill the cancerous cells. Rather, it sometimes results in a pause in the cell cycle that enables the cells to continue to differentiate into neurons—but not good ones.

"They are wonky neurons, and they are still cancer cells," says Filbin, who is focused now on finding additional medicines that could be combined with ribociclib to treat the cancer more effectively.

"We are at a time when we are starting to see positive effects with one drug," says Filbin. "Like with leukemia decades ago, where there was only little effect with one drug, we started layering on multiple drugs, and now we have a very high cure rate in kids with leukemia. That's our hope."

More information: Ilon Liu et al, GABAergic neuronal lineage development determines clinically actionable targets in diffuse

hemispheric glioma, H3G34-mutant, *Cancer Cell* (2024). DOI: 10.1016/j.ccell.2024.08.006