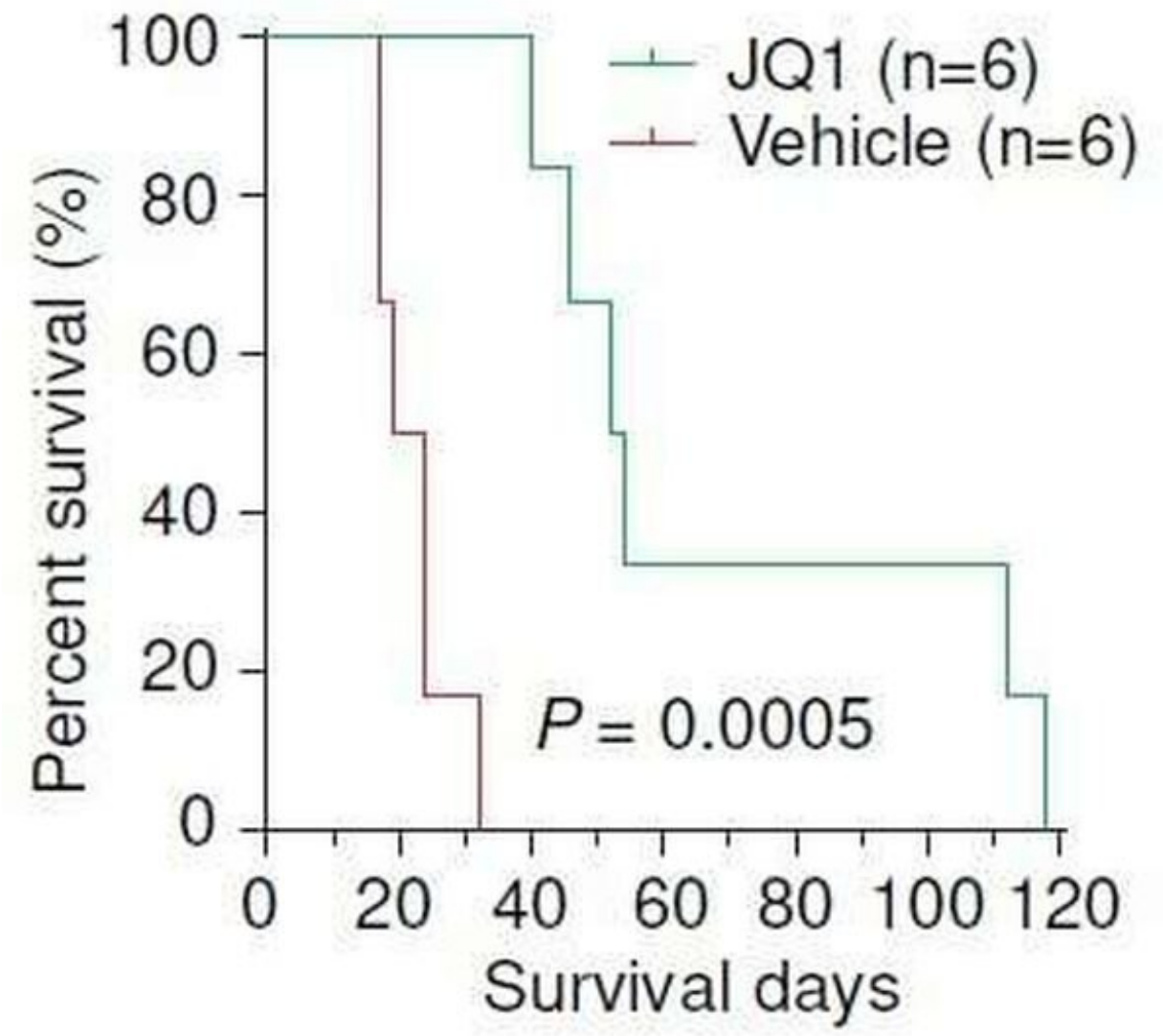
Small molecule inhibitors show early-stage promise against YAP fusion-driven cancers

February 2 2023



In an early proof-of-concept success, a team led by experts at Cincinnati

Children's reports that mice induced to develop brain tumors featuring fused proteins survived longer when treated with BRD4 inhibitors. Credit: Cincinnati Children's Hospital Medical Center

An unexpected discovery made by experts at the Brain Tumor Center at Cincinnati Children's while studying a rare-but-deadly type of brain tumor may also lead to improved treatments for several other forms of cancer that share a common influencing factor called a YAP fusion protein.

The findings, published Feb. 2, 2023, in *Nature Cell Biology*, come from a team led by co-first authors Xiaohua Hu, Ph.D., and Xiaoping Wu, Ph.D., and corresponding author Qing Richard Lu, Ph.D., scientific director of the Brain Tumor Center. The work also includes contributions from 15 co-authors based in Cincinnati, Cleveland, Seattle, Shanghai, China, and Warsaw, Poland.

The research team was studying why fatal outcomes occur among a subset of children diagnosed with ependymoma (EPN), a rare cancer that occurs in the brain and along the spinal column. About 1,100 people a year in the US are diagnosed with EPN, including about 250 children.

Adults usually experience these tumors developing along the spinal cord, and in many cases, they can be removed with surgery. Overall, the five-year survival rate for this type of cancer is nearly 84%, according to the National Cancer Institute and the American Society of Clinical Oncology.

However, children with EPN are more likely to develop tumors in the brain. While survival rates are high for tumors that can be removed surgically, about one-third of children with EPN experience relapses

despite surgery, radiation, and chemotherapy. For these children, relapse is nearly always fatal.

The exact causes of EPN tumors are not fully understood. However, children with inherited genetic conditions including Turcot syndrome and neurofibromatosis type 2 (NF2) have an increased risk of developing this form of cancer.

New data about YAP fusion proteins opens doors

Previous studies had already shown that the growth of a set of EPN tumors is driven in large part by the formation of YAP fusion proteins. By itself the gene YAP1 produces a protein that blocks the tumor suppressing power of another gene called HIPPO.

But in recent years, scientists have discovered an entire family of YAP proteins that arise from YAP1 fusions with other genes in ways that promote even more aggressive cancer tumor growth. YAP fusion proteins have been detected in subtypes of skin cancer, breast cancer and a variety of soft-tissue tumors called sarcomas.

The new study reveals that YAP fusion proteins disrupt the body's cancer defenses in a different way than many scientists had thought. Instead of simply enhancing YAP1 activity, these fused YAP proteins trigger the formation of "condensates" in the nucleus of cells that provide platforms to drive brain cell transformation and tumor formation.

By studying the components of these platforms, the team learned that they can be prevented from forming tumors by blocking the function of a gene expression regulator called BRD4. Known as a transcription factor, this protein sends critical signals to activate other oncogenic genes within nuclear condensates.

The team achieved an early proof-of-concept success when testing their idea in mice that were induced to develop tumors similar to human EPN. The mice treated with two different BRD4 inhibitors survived much longer than mice that did not receive the inhibitors.

What does this mean for people with EPN?

It likely will require several years of safety testing and related work to launch a clinical trial to measure the benefits and risks of treating people with EPN with a BRD4 inhibitor. Until now, however, the primary way to survive this type of cancer depended upon successful surgery. Traditional forms of chemotherapy have shown little to no benefit in relapsed cases.

"Our findings suggest that targeting biomolecular condensates may eventually prove beneficial for treating relapsed EPN," Lu says. "But first, more research is needed to build upon these findings."

What does this mean for other types of cancer?

By establishing a successful method for slowing the growth of one form of YAP fusion-mediated cancer, the study implies that similar approaches may work in other types.

"Rather than attempting to prevent the gene fusions from occurring, our study shows that targeting allied molecular processes can reduce the ability of YAP fusion proteins to spur tumor growth," Lu says.

More information: Richard Lu, Nuclear condensates of YAP fusion proteins alter transcription to drive ependymoma tumourigenesis, *Nature Cell Biology* (2023). DOI: 10.1038/s41556-022-01069-6. www.nature.com/articles/s41556-022-01069-6

Provided by Cincinnati Children's Hospital Medical Center