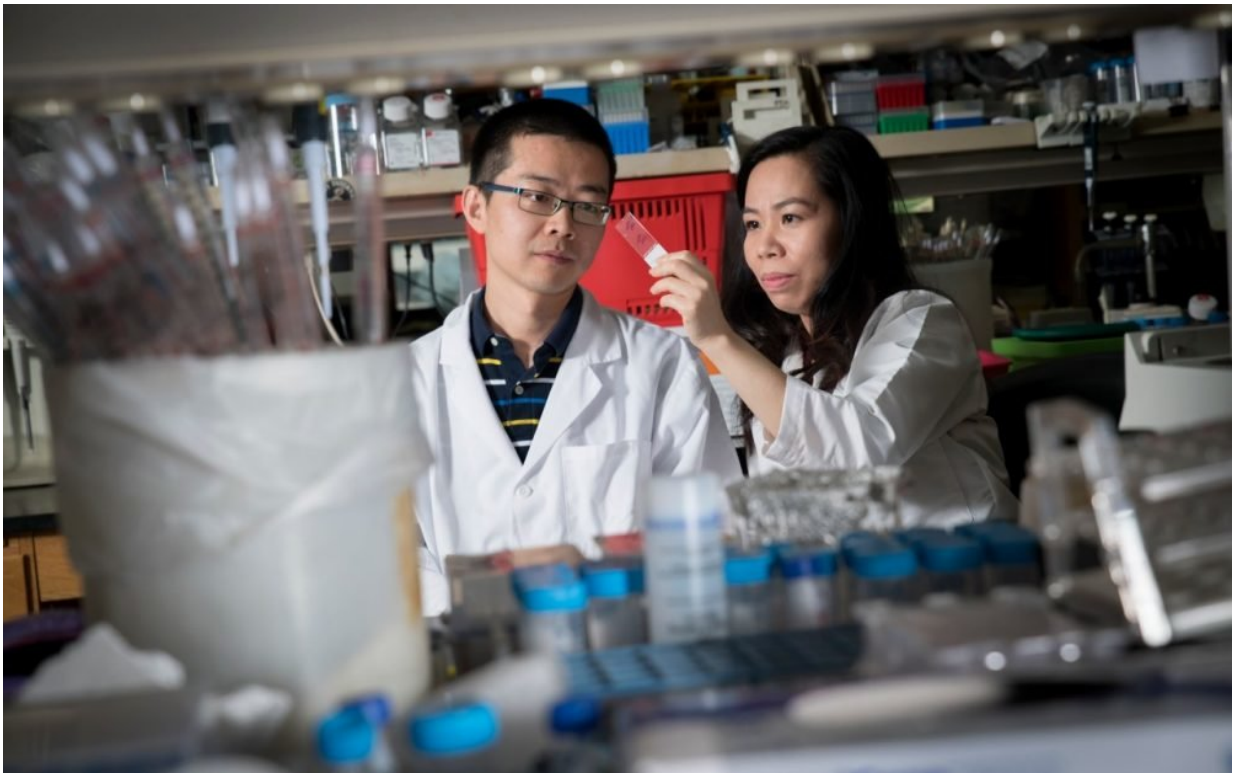
MedicalXpress

Engineered 'starter key' for brain tumor offers new model for drug testing

June 26 2018



Co-first authors Chunliang Li, Ph.D. (left) and BaoHan Vo, Ph.D, (right) applied CRISPR technology to activate MYC in neural cells by homing in on the promoter, which helped create medulloblastoma tumors for research study. Credit: St. Jude Children's Research Hospital

Researchers at St. Jude Children's Research Hospital have applied a new way to trigger the brain tumor medulloblastoma in neural cells that will

lead to the ability to test a promising class of anti-tumor drugs. The technology they used, called CRISPR/dCas9 activation, is the equivalent of using a key to start a car, while previous approaches to producing tumors were more like bypassing the key to hot-wire the vehicle.

The interdisciplinary research team included Martine F. Roussel, Ph.D., a member in the Department of Tumor Cell Biology and co-leader of the Cancer Biology Program. The findings appeared online June 7 in the journal *Scientific Reports*.

Researchers studied Group 3 medulloblastoma, which is the most common aggressive subtype of medulloblastoma in children. Group 3 medulloblastoma is triggered by over-activation of a gene called MYC.

Previously scientists had generated medulloblastoma tumors in mice for drug testing by introducing a virus carrying activated MYC into neural cells. However, these mouse models bypassed critical MYC genetic controls—the biological equivalent of a car key. The problem with such "hot-wired" models was that they did not allow researchers to test a promising class of drugs called BET inhibitors that could suppress MYC by interfering with the gene's promoter.

In their research, co-first author Chunliang Li, Ph.D. in collaboration with Jin-Ha Kwon Ph.D. and BaoHan Vo, Ph.D, applied CRISPR technology to activate MYC in neural cells by homing in on the promoter. Many applications of the technology use CRISPR/Cas9, which is a molecular assemblage that can target a specific genetic sequence and snip it apart. However, Li used a "deficient" version, called CRISPRa/dCas9, in which the cutting ability was crippled. Instead, he engineered the assemblage to home in on the MYC promoter and switch it on. Engineered neural cells were implanted into mice. The cells grew into tumors that were medulloblastoma. Li and Kwon work in the laboratory of co-author Charles J. Sherr, M.D., Ph.D., member and chair

of the Department of Tumor Biology and a Howard Hughes Medical Institute Investigator.

A central question was whether CRISPRa/dCas9 produced tumors that exactly mimicked clinical medulloblastomas. Indeed, pathology examination of the tumors by co-author Brent Orr, M.D., Ph.D.,—using a technique called immunostaining—established that the tumors had all the characteristics of clinically occurring tumors. Also, genetic analysis by co-author David Finkelstein, Ph.D., established that the tumors were genetically identical to clinical medulloblastomas. And critically, Vo found that a BET inhibiting drug suppressed the activity of MYC in tumors.

"Our use of this technology represents the first time it has been used to induce tumor development," Roussel said. "Now, we are using the mouse model to test BET inhibitors in various combinations with other drugs in clinical use, to determine whether we can achieve a synergy that will be effective against medulloblastoma." Roussel said that the effective drug combinations they discover might go into clinical trials at St. Jude.

Roussel also pointed out that the CRISPRa/dCas9 technique could be readily adapted to produce mouse models of other cancers driven by over-activated MYC. These include breast, colorectal, pancreatic, gastric and uterine cancers. And in principle, the technology could be applied to any cancers to produce more accurate mouse models that utilize the natural control mechanisms for the genes driving the cancers, she said.

More information: BaoHan T. Vo et al. Mouse medulloblastoma driven by CRISPR activation of cellular Myc, *Scientific Reports* (2018). DOI: 10.1038/s41598-018-24956-1

Provided by St. Jude Children's Research Hospital