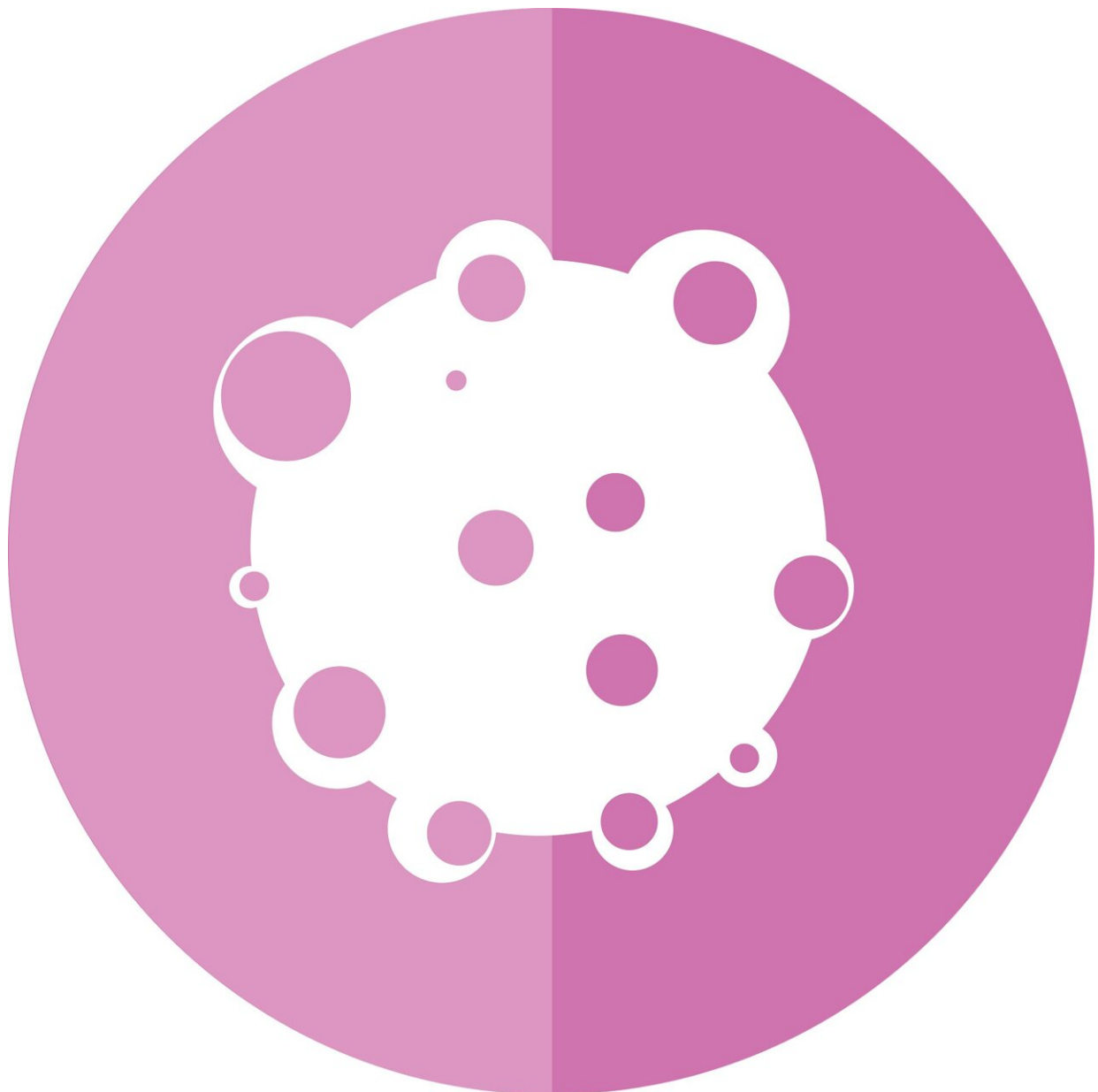


Nanoparticle-formulated drug combination is effective in medulloblastoma, a pediatric brain tumor

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UNC Lineberger Comprehensive Cancer Center researchers have demonstrated that a novel combination of two drugs that act as targeted inhibitors, delivered in a nanoparticle formulation, extend the survival of mice with medulloblastoma. The research team believes this laboratory success could be translated into a less toxic treatment for medulloblastoma, the most common malignant pediatric brain tumor. Advances such as this are crucial because current treatments, while effective for many patients, often result in potentially disabling brain injury.

"We showed that palbociclib, an FDA-approved drug for [breast cancer](#), may be effective for [medulloblastoma](#), but as a single agent it is not curative because it does not stay in the brain for long enough, and because tumors can become resistant to it," said Timothy R. Gershon, MD, Ph.D., professor and vice-chair for research, UNC School of Medicine department of neurology, and co-corresponding author of the article. "In our mouse studies, we addressed the limited brain penetration by developing a nanoparticle formulation that delivers the therapeutics into the brain more effectively. We then we studied why resistance developed over the long-term and ultimately, we found a mechanism of resistance that we could target by adding another drug, sapanisertib."

The researchers' finding appeared January 26, 2022, in *Science Advances*.

Medulloblastoma is an aggressive brain tumor that can spread to other parts of the brain as well as the spinal cord. According to the Central

Brain Tumor Registry of the U.S. Statistical Report, between 250 and 500 children are diagnosed with medulloblastoma each year in the U.S., often before the age of 10. Overall, the survival rate for children with medulloblastoma that has not spread is close to 80%, and the survival rate drops to about 60% if the cancer has spread. For patients whose tumor recurs—or returns—after treatment, there is no effective established therapy.

The current standard of care for medulloblastoma includes surgery, radiation and chemotherapy. This therapeutic approach, though often effective, can produce disabling side effects. Therefore, the investigators wanted to develop a drug to complement radiation so that clinicians could lower the dose of radiation and cause less [brain injury](#). Of special interest to the researchers were the 20% of patients whose experience cancer recurrence; this is the group of patients where the new dual nanoparticle drug could provide the greatest benefit.

The researchers focused on the drug palbociclib, which disrupts the proliferation cycle of cancer cells and has been effective in breast cancer. Because palbociclib's ability to get into the [brain](#) is limited, the researchers turned to nanoparticle carriers to help increase medulloblastoma drug exposure and reduce off-target toxicity. The method they used to formulate the nanoparticle has proven effective and works for other drugs.

By analyzing gene expression patterns of medulloblastoma cells that were able to grow in mice treated with palbociclib, the authors identified a resistance mechanism that could be targeted by the mTOR inhibitor sapanisertib. The authors then showed that the combination of palbociclib and sapanisertib, delivered in nanoparticles, was more effective than either drug alone, as well as being more effective than combinations of other drugs with palbociclib. These data show that targeting the mTOR pathway, which affects cell growth and blood flow

to tumors, makes palbociclib markedly more effective. This finding may be relevant to palbociclib in other cancers.

"The nanoparticle formulation incorporating palbociclib plus sapanisertib may also combine well with standard radiation, potentially enabling lower, less toxic doses of radiation without increasing recurrence risk," said Marina Sokolsky-Papkov, Ph.D., co-corresponding author and associate professor and director of the Translational Nanoformulation Research Core Facility at the UNC Eshelman School of Pharmacy. "Our next steps are getting the nanoparticle approved for use in people and also finding ways to ramp up production for potential use in humans."

Gershon noted that if [drug](#) approval and production plans proceed quickly, the investigators look forward to opening a clinical trial for patients with recurrent medulloblastoma in collaboration with multiple institutions, optimizing the chance of gathering enough patients and allowing patients to be treated near their homes.

In addition to Gershon and Sokolsky-Papkov, the paper's other authors at UNC include Chaemin Lim, Ph.D., Taylor Dismuke, MS, Daniel Malawsky, Jacob D. Ramsey, Ph.D., Duhyeong Hwang, Ph.D., Virginia L. Godfrey, DVM, Ph.D., and Alexander V. Kabanov, Ph.D., DrSci.

More information: Chaemin Lim et al, Enhancing CDK4/6 inhibitor therapy for medulloblastoma using nanoparticle delivery and scRNA-seq-guided combination with sapanisertib, *Science Advances* (2022).

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