Researchers demonstrate in mice a new way to deliver medication to malignant brain tumors

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Researchers have demonstrated in mice a new approach for delivering medication across the blood-brain barrier to treat tumors that cause aggressive, lethal brain cancer.

In a new study, the researchers show in mice how a modified peptide helps a cancer drug pass through the blood-brain barrier, which is known to be extremely difficult to penetrate and thus serves as a massive hindrance to treating brain tumors. The study was published online in advance of the December issue of the Journal of Controlled Release.

"We were not only able to get a drug into the brain, but to deliver it at a concentration that should be able to kill tumor cells," said Sean Lawler, a study author and Brown University associate professor of pathology and laboratory medicine, whose lab investigates therapeutic approaches for the treatment of brain cancer.

Brain malignancies are some of the most lethal forms of cancer, as well as the hardest to treat. Glioblastoma is the most common malignant brain cancer—it's highly aggressive, and most patients live for only around 15 months after diagnosis. Despite the poor prognosis, Lawler said, there has been frustratingly little progress in treating glioblastoma and improving the chances of survival over the past 20 years.

"We think this is a significant finding that could ultimately inform new approaches to treating people who face some of the most severe brain cancer diagnoses," Lawler said.

One of the challenges in treating brain cancer, Lawler said, is getting therapeutic substances through the blood-brain barrier, a network of blood vessels and tissue made up of closely spaced cells that protects the brain from harmful substances. When it comes to anti-cancer drugs, the blood-brain barrier does its job almost too well: the cancer-fighting drugs can't penetrate the barrier in sufficient amounts to have a therapeutic effect on tumors. Even drugs that have been shown to be effective against other types of cancers haven't shown much of an effect on brain cancer—likely because the blood-brain barrier gets in the way.

"The question became, 'How do we get more of the drug into the brain tumor so that we can improve treatment outcomes?"' said Lawler, who co-leads the Central Nervous System Cancer Translational Disease Research Group at the Warren Alpert Medical School's Legorreta Cancer Center. The Brown researchers collaborated on the study with a team at the Massachusetts Institute of Technology led by study author and Professor of Chemistry Bradley Pentelute.

The researchers focused on a type of peptide, or
chain of amino acids linked by chemical bonds, that has an intrinsic ability to cross membranes and penetrate tissues. They modified the peptide by creating a staple between amino acids in the sequence, which helped to fortify and stabilize the peptide, and incorporated fluorine molecules. The collaborative research team had previously shown that this design could improve the peptide's penetration across the blood-brain barrier.

"We had this enhanced peptide that was not only better at getting through the blood-brain barrier, but could also last longer in the body," Lawler said. "And then we were able to hook it up to a cancer drug and test it in mouse models of glioblastoma. That was our major step forward."

The researchers saw an opportunity, said Jorge L. Jimenez Macias, a study author and postdoctoral fellow in Lawler's lab.

"This new technology allowed us to test drugs against brain cancer that previously hadn't been used against glioblastoma because they hadn't been able to cross the blood-brain barrier," Jimenez Macias said.

The researchers put together a pre-clinical trial—essentially a clinical trial in mice subjects instead of humans. They used a control of the drug with the peptide and tested it against the drug with the enhanced, macrocyclic barrier-penetrating peptide (referred to as M13) in mice with brain tumors. Subsequent experiments were conducted to assess the concentration of drugs needed to kill the tumor cells, as well as to understand how to deliver the drug at a safe level, in a way that would not harm the mouse patients. When those variables were tested, the researchers conducted a treatment study.

The study results showed that cell death due to the enhanced, macrocyclic cell-penetrating peptide M13 was observed mainly in tumor cells, and not in healthy regions of the brain. This is the first time that researchers have demonstrated how to use this modified peptide delivery system to get cancer drugs into the brain in the context of disease, Jimenez Macias said.

"We have shown for the first time that the linking of an anti-cancer drug to a macrocyclic cell-penetrating peptide leads to effective dosing in mice at many times higher than the drug alone, which can significantly extend survival," Jimenez Macias said.

According to the study, the survival rate of the mice treated with the enhanced peptide increased by 50%.

Lawler expressed optimism for future studies.

"This is only the first attempt," Lawler said. "We think that with some further optimization and tweaking of the drug and the delivery system, we should be able to improve the treatment, and the survival rate, quite significantly."

In addition to Brown University and the Massachusetts Institute of Technology, study collaborators included researchers at the Harvey Cushing Neuro-Oncology Laboratories in the Department of Neurosurgery at Brigham and Women's Hospital and Harvard Medical School; the Université Libre de Bruxelles in Brussels, Belgium; and the National Cheng Kung University in Taiwan.


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