New 'nano-drug' hits brain-tumor target found in 2001

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Nine years ago, scientists at Cedars-Sinai's Maxine Dunitz Neurosurgical Institute detected a subtle shift occurring in the molecular makeup of the most aggressive type of brain tumors, glioblastoma multiforme. With further study, they found that a specific protein called laminin-411 plays a major role in a tumor's ability to build new blood vessels to support its growth and spread. But technology did not exist then to block this protein.

Now, employing new drug-engineering technology that is part of an advanced science called nanomedicine, the research team has created a "nanobioconjugate" drug that may be given by intravenous injection and carried in the blood to target the brain tumor. It is engineered to specifically permeate the tumor cell wall, entering endosomes, mobile compartments within cells.

As endosomes mature, they grow acidic (low pH), and a chemical component of the drug triggers at this point, breaking the endosomes' membranes. Freed drugs block the tumor cell's production of laminin-411, the "malignant" protein of new tumor vessels. By its nature, the drug is nontoxic to non-tumor cells; side effects associated with conventional chemotherapy are not an issue with this class of drugs.

This approach is believed to be the first of its kind – the first application of a pH-dependent endosome escape unit in drugs administered intravenously for brain cancer treatment – as reported in *Proceedings of the National Academy of Sciences*. Studies in lab mice show this system

allows large amounts of antitumor drug to accumulate in tumors, significantly slowing the growth of new vessels and the tumors themselves. Tumors in animals treated with the drug were 90 percent smaller than those in a control group.

Gliomas, a type of malignant brain tumors, are extremely difficult to treat. Their tendency to spread into healthy brain tissue and their ability to reappear in distant locations make them virtually impossible to surgically remove completely. They resist chemotherapy and radiation therapy, and the brain itself is "protected" by the blood-brain barrier and immune system mechanisms that thwart most therapies.

The system developed at Cedars-Sinai – a nanobioconjugate – appears to clear major hurdles to brain tumor drug treatment. Nanoconjugates are the latest evolution of molecular drugs designed to enter cells and specifically alter defined targets within them. As suggested by the term "bioconjugate," these systems contain chemical "modules" attached (conjugated) to a delivery vehicle by strong chemical bonds. Such bonds prevent the components from being damaged or separated in tissues or blood plasma during transit. But with inventive drug engineering, the antitumor component activates directly inside tumor cells.

A nanoconjugate exists as a single chemical unit, with its components performing critical tasks in a predetermined sequence and attacking several targets simultaneously. The ultimate assault on a tumor cell depends on a complex, well-choreographed chain of biochemical events, such as: penetrating the blood-brain barrier and the blood-brain tumor barrier; specifically homing to tumor cells; permeating the walls of blood vessels and tumor cells; releasing antitumor drugs at the right place and time; and dismantling mechanisms that help tumor-feeding blood vessels grow.

"This nanobioconjugate is different from earlier nanomedicine drugs

because it delivers and releases antitumor drugs within tumor cells, not just at the site of a tumor," said research scientist Julia Y. Ljubimova, M.D., Ph.D., senior author of the article. She directs the Drug Delivery and Nanomedicine Laboratory in the Department of Neurosurgery at Cedars-Sinai. Other major contributors to this study and the article include: Hui Ding, Ph.D., and Eggehard Holler, Ph.D., chemists, biochemists and immunologists. Holler is affiliated with both Cedars-Sinai and the University of Regensburg in Germany.

Cedars-Sinai's drug, a macromolecule of 20 to 30 nanometers in size, is based on a highly purified form of polymalic acid derived from the single cell organism Physarum polycephalum. When the nanoconjugate has accomplished its tasks, the body digests it completely, leaving no harmful residue.

"Based on our studies, this nanoconjugate appears to be a safe and efficient delivery platform that also may be appropriate in the treatment of degenerative brain conditions and a wide array of other disorders. It is harmlessly degraded to carbon dioxide and water, nontoxic to normal tissue, and, unlike some drugs, it is non-immunogenic, meaning that it does not stimulate the immune system to the point of causing allergic reactions that can range from mild coughs or rashes to sudden, life-threatening symptoms," Ljubimova said. Researchers anticipate that human clinical trials of the drug will begin in the near future.

More information: Citation: *Proceedings of the National Academy of Sciences*: "Inhibition of brain tumor growth by intravenous polymalic acid nanobioconjugate with pH-dependent drug release."

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