Researchers refine experimental prodrug treatment of high-risk neuroblastoma

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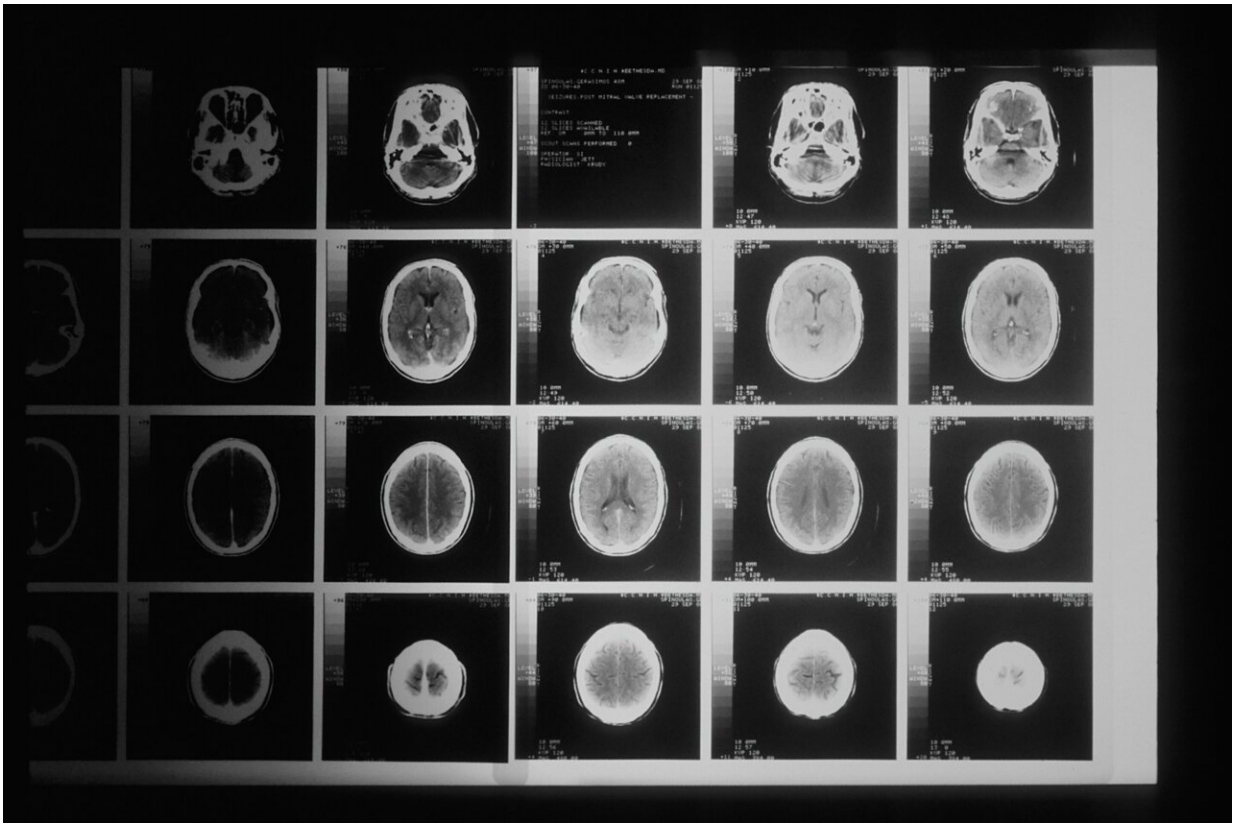

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A new study by researchers at Children's Hospital of Philadelphia (CHOP) shows that linking a tumor-killing prodrug to a macromolecular carrier of the Poloxamer family improves retention of the drug in

treatment-resistant neuroblastoma tumors, leading to rapid tumor regression and lasting therapeutic responses in several preclinical models. The findings were recently published in *The Federation of American Societies for Experimental Biology Journal*.

Despite aggressive therapy, less than half of patients with high-risk neuroblastoma survive. Some tumors are inherently treatment resistant, due to the overexpression of cell transporters that pump drugs out of tumor cells as a defense mechanism, preventing drugs from killing the tumor. Alternatively, tumor cells may acquire drug resistance following intensive treatment as a result of mutations that cause dysfunction of tumor suppression genes, like TP53.

To circumvent these challenges, CHOP researchers developed a polymer-linked prodrug, a medication that is inert until it is converted by the body into a pharmacologically active drug. The active drug, SN22, belongs to a family of camptothecins, compounds known to promote death of rapidly dividing cells and thus destroy tumors. Other camptothecins, such as irinotecan and topotecan, have been used to treat different types of cancer, but they have serious side effects on healthy tissues, and they are often ineffective against high-risk disease because the tumors are either intrinsically resistant to the drug or develop resistance over time. SN22, however, was structurally optimized so it has advantages over these other camptothecins. It is not recognized by the transporters that pump other drugs out of cells, allowing it to enter, remain in, and kill tumor cells much more effectively. It is also designed to avoid the dose-limiting side effects often encountered with irinotecan.

In earlier studies, the research team led by Michael Chorny, Garrett Brodeur, and Ivan Alferiev created a prodrug that is heading into a phase 1 clinical trial run by Peel Therapeutics, where four residues of SN22 were linked through a breakable bond to a polyethylene glycol carrier. In the latest study, the researchers investigated linking SN22 to a

biocompatible polyalkylene glycol block co-polymer of the Poloxamer (Pluronic) family, which they predicted would allow the treatment to circulate in the blood longer, enhance the uptake by cancer cells, and extend the therapeutic exposure time of the bioactive drug in the tumor. In essence, the Poloxamer carrier would disguise the active drug like a Trojan horse, allowing SN22 to be taken up by the tumor, and this in turn would lead to rapid and robust tumor cell death. Remarkably, by integrating several design enhancements, the researchers demonstrated that this prodrug not only promotes cell killing with high efficiency, but it also protects healthy tissues from severe side effects, like intractable diarrhea and low blood counts.

The researchers tested this prodrug in three preclinical models of neuroblastoma driven by MYCN, a protooncogene associated with high-risk disease: 1) a tumor model established using a neuroblastoma cell line derived form a tumor before any treatment and retaining most of its drug sensitivity; 2) another reproducing multidrug resistance acquired after several rounds of treatment; and 3) a genetically engineered mouse model where both MYCN and the drug efflux pump are both overexpressed by the tumor, mimicking an intrinsically drug resistant human neuroblastoma.

The Poloxamer-linked prodrug achieved protracted tumor exposure to the bioactive SN22 at levels at least 40 times higher than the levels required to kill tumor cells, whereas conventional treatment with irinotecan showed only trace amounts of the drug in the tumor after 24 hours. The increased and lasting exposure to SN22 after four weekly doses of the prodrug led to the rapid disappearance of neuroblastoma tumors in all tested models, including those with intrinsic and acquired multidrug resistance. In many cases, there was complete tumor regression with no regrowth even several months after the last administered dose of the prodrug.

"Our results demonstrate that by adjusting the polymeric carrier in our prodrug, we can take full advantage of the unique pharmacology of SN22 and make possible rapid tumor regression and lasting therapeutic responses in models of newly diagnosed and relapsed, MYCN-amplified neuroblastoma," said Michael Chorny, Ph.D., an investigator at Children's Hospital of Philadelphia and senior author of the study. "The ability of Poloxamer-linked SN22 to markedly extend survival and to overcome mechanisms governing drug resistance at different phases of refractory disease is an important step toward addressing the urgent need for more robust therapeutic strategies effective against high-risk tumors."

More information: Ivan S. Alferiev et al, Poloxamer-linked prodrug of a topoisomerase I inhibitor SN22 shows efficacy in models of high-risk neuroblastoma with primary and acquired chemoresistance, *The FASEB Journal* (2022). DOI: 10.1096/fj.202101830RR

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