

New treatment developed shows success in high-risk solid tumors

August 24 2020





Credit: CC0 Public Domain

Despite intensive treatment, high-risk solid tumors like neuroblastoma, Ewing sarcoma, and rhabdomyosarcoma are challenging to cure because the disease in those high-risk patients does not respond to therapy. Conventional chemotherapy given by vein or by mouth delivers only a small amount of the drugs to the tumor, which not only renders the treatment ineffective but also leads to drug resistance and severe side effects, including diarrhea, bone marrow suppression and secondary malignancies.

Now, in a breakthrough study, researchers at Children's Hospital of Philadelphia (CHOP) have shown that an enhanced treatment developed in their lab leads to long-term remissions in 80% to 100% of mice with <u>drug-resistant</u> or high-risk solid tumors. The research, which could soon lead to clinical trials, was described today in *Cancer Research*, a journal of the American Association for Cancer Research.

"The results of our studies show that the cancer therapeutic we developed is highly effective in treating at least three different types of high-risk pediatric solid tumors with intrinsic or acquired drug resistance," said Garrett M. Brodeur, MD, Director of the Cancer Predisposition Program at CHOP and co-senior author of the study, along with Michael Chorny, Ph.D., and Ivan Alferiev, Ph.D. "Given that this treatment is also likely to be much less toxic than most cancer therapies for these types of tumors, in addition to showing remarkable therapeutic effects against aggressive disease, we think these results warrant further exploration of the agent in clinical trials."

Building a Better (Pro)Drug



The agent developed by the researchers is a prodrug, a medication that is inert until it is converted by the body into a pharmacologically active drug. The active drug in this study belongs to a family of camptothecins, compounds known to promote cell death and destroy tumors. Other camptothecins, in particular irinotecan and topotecan, have been used to treat solid tumors, but they are often ineffective against high-risk disease because the tumors are either initially resistant to the drug or develop resistance over time. Irinotecan itself is also a prodrug whose active agent, SN38, shows limited efficacy because it rapidly gets inactivated and removed from the body, so only a small fraction of it reaches the tumor. At the same time, irinotecan still manages to cause serious side effects, including bone marrow suppression and intractable diarrhea.

To overcome the issues of poor efficacy and high toxicity, the researchers engineered a prodrug that links four residues of a pharmacologically enhanced drug, SN22, through a breakable bond to a four-arm polyethylene glycol scaffold. By attaching the SN22 components in this way, the research team was able to extend the drug's circulation time, which in turn allowed 50 to 100 times as much drug to be taken up by the tumor.

Due to its modified structure, SN22 is also protected from enzymes that could inactivate it, as they do other camptothecins, and from cell transporters that could pump the drug out of tumor cells. Together, all of these modifications helped more drug accumulate in the tumor, where it stayed in the cells without being exported, so the high drug levels in the tumor tissue were sustained for hours and days.

The researchers tested their prodrug in several mouse models of disease, including neuroblastoma with both intrinsic and acquired <u>drug resistance</u>, a chemo-resistant Ewing sarcoma, and a fusion-positive rhabdomyosarcoma. Prodrug delivery of SN22 resulted in complete tumor disappearance in all models, and these complete remissions lasted



for more than 6 months in 80 to 100% of cases, whereas treatment with irinotecan had little or no effect.

Better Safety Profile

In addition to being highly effective against drug-resistant tumors, the engineered prodrug also had less toxicity than irinotecan. Whereas irinotecan led to elevated <u>liver enzymes</u> and altered blood counts, the SN22 prodrug did not, nor did it lead to any other adverse effects. SN22 delivery in the prodrug form also reduced the exposure of healthy organs to the active drug, and the increased potency of SN22 in comparison to irinotecan meant that the researchers could use less total drug to shrink the tumors—a low and slow approach that exposes tissues to a low level of <u>drug</u> over long period of time.

"Taken together, the superior efficacy and improved biocompatibility of our prodrug, which we demonstrated in several clinically relevant models of high-risk cancer, make it a highly promising new therapeutic capable of addressing the considerable limitations of current treatments," said Chorny. "Our strategy is readily scalable, and we look forward to assessing its effectiveness and safety in patients."

More information: Ivette Valencia-Sama et al. NRAS Status Determines Sensitivity to SHP2 Inhibitor Combination Therapies Targeting the RAS–MAPK Pathway in Neuroblastoma, *Cancer Research* (2020). DOI: 10.1158/0008-5472.CAN-19-3822

Provided by Children's Hospital of Philadelphia

Citation: New treatment developed shows success in high-risk solid tumors (2020, August 24) retrieved 1 May 2024 from



https://medicalxpress.com/news/2020-08-treatment-success-high-risk-solid-tumors.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.