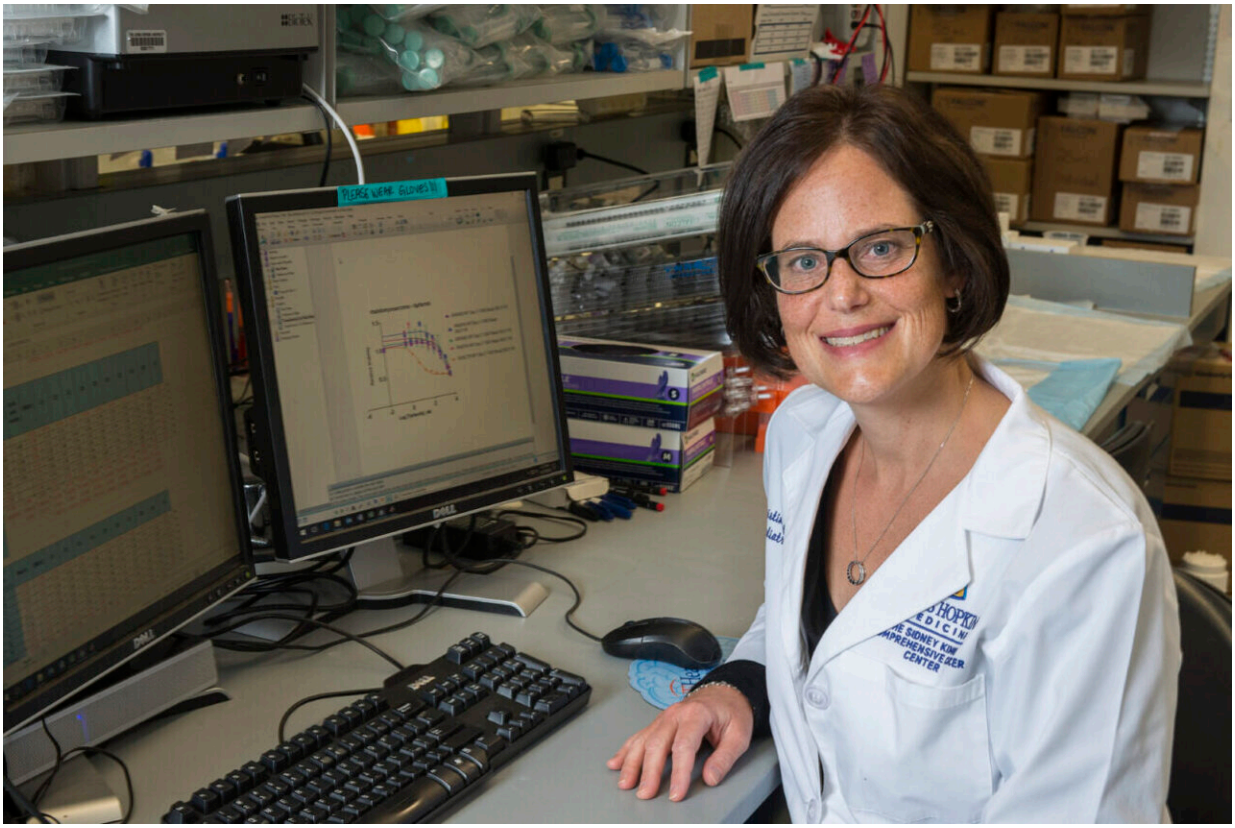
# Combination drug therapy shows promise for a treatment-resistant cancer

January 31 2024



Christine Pratilas, M.D., in the lab. Credit: Frederick W. Dubs, Johns Hopkins Pathology Photography & Graphics

A combination of two cancer drugs could be effective against malignant peripheral nerve sheath tumors (MPNSTs)—soft tissue tumors that are

stubbornly resistant to chemotherapy and radiation—according to a laboratory study led by researchers at the Johns Hopkins Kimmel Cancer Center.

Both drugs interfere with cell growth and replication but have different mechanisms of action. Used together, they suppressed the growth of MPNSTs in mouse models of human disease, the researchers found. The findings were published Nov. 24, 2023, in the journal *Science Advances*.

MPNSTs grow in the soft tissue surrounding nerve cells. They are often associated with neurofibromatosis type 1, a genetic condition caused by a mutation in the tumor-suppressing gene NF1. While rare, these tumors are aggressive and notoriously hard to treat.

"Every single clinical trial done to date has been a negative trial—there have been a lot of trials, and very limited responses," says Christine Pratilas, M.D., an associate professor of oncology at Johns Hopkins and the study's senior author. "So we're always working for better treatments."

Pratilas and her collaborators turned to SHP2 inhibitors, an emerging class of cancer drugs. They interfere with cell growth and division in many ways, and have shown early promise in clinical trials for other types of cancers such as colorectal and gastrointestinal stromal tumors.

Initial experiments in MPNST cell lines showed that knocking out the gene that makes SHP2 suppressed tumor cell growth. This suggested that SHP2 could be a promising drug target for this patient population.

Then, the researchers tested an SHP2 inhibitor drug, TNO155, in combination with ribociclib. Ribociclib belongs to a category of drugs called CDK4/6 inhibitors, which also help prevent cancer cells from dividing.

Pratilas and her colleagues tested the drugs in six different patient-derived xenografts—models in which human tumors are transplanted into mice. This approach allowed the researchers to see how the same treatment might play out for a variety of patients with different tumor genetics.

The SHP2 inhibitor worked well alone in half of the mouse models tested. Adding in ribociclib enhanced the tumor-suppressing effects in the other models.

Combining the drugs produced a response that held up better over time. Four weeks into the trial, TNO155 alone seemed about as effective as the two drugs combined in some of the mice. But by 10 weeks, the tumors in mice treated with just TNO155 had started to grow, while the combination strategy was still effectively holding tumors at bay.

Used together, the drugs disrupted tumor cell replication and triggered cell death, the study showed.

These two drugs are currently being tested together in an unrelated clinical trial for different kinds of cancer, so "we knew if we found this drug combination was active in pre-clinical tests, there would be a pathway to translation," Pratilas says.

Other cancers, such as melanomas and lung cancers, also can arise from mutations in NF1, so the drug combination could be similarly effective in other types of tumors.

"SHP2 inhibitor clinical trials in humans are relatively new, so where they'll achieve successful clinical applications is relatively unknown," says Pratilas. "Our data support SHP2 as a target for tumors driven by the loss of NF1."

Study co-authors included Jiawan Wang, Ana Calizo, Lindy Zhang, Kai Pollard and Nicolas Llosa of Johns Hopkins. Other authors were from the Pacific Northwest National Laboratory in Seattle, the Siteman Cancer Center at Washington University in St. Louis, the Masonic Cancer Center and Department of Biomedical Engineering at the University of Minnesota and Novartis Institutes for BioMedical Research in Cambridge, Massachusetts.

**More information:** Jiawan Wang et al, CDK4/6 inhibition enhances SHP2 inhibitor efficacy and is dependent upon RB function in malignant peripheral nerve sheath tumors, *Science Advances* (2023). DOI: 10.1126/sciadv.adg8876

Provided by Johns Hopkins University School of Medicine

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