When combined, a novel LSD1 inhibitor and an existing therapy enhance each other's anti-cancer effects

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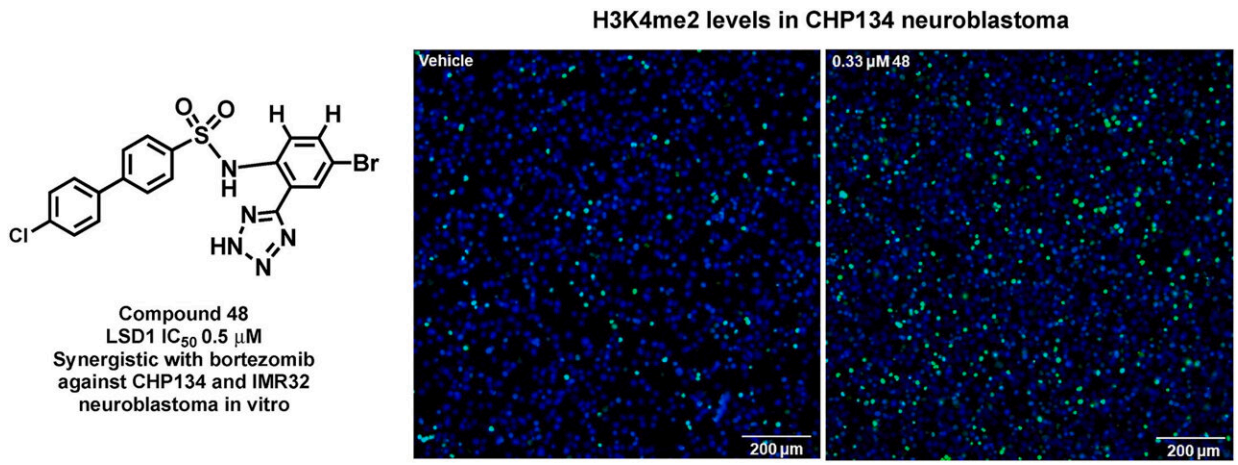

Graphical abstract. Credit: *European Journal of Medicinal Chemistry* (2022). DOI: 10.1016/j.ejmech.2022.114818

A Medical University of South Carolina (MUSC) research team has developed novel compounds that show early promise at fighting the rare pediatric cancer neuroblastoma when paired with the existing anti-cancer drug bortezomib (Velcade, Takeda Oncology). The novel compounds block or inhibit an enzyme known as lysine-specific demethylase 1 (LSD1). The MUSC team, led by Patrick M. Woster, Ph.D., reports its findings in the *European Journal of Medicinal Chemistry.*

"Our compounds are a new chemical class of LSD1 inhibitors and are the first small molecules to produce a synergistic anti-tumor response in combination with bortezomib," said Woster. Woster is the SmartState Endowed Chair in Drug Discovery and head of the Department of Drug Discovery and Biomedical Sciences at MUSC.

Such combination therapies are the way of the future, said co-author Yuri Peterson, Ph.D. Peterson is assistant director of the Drug Discovery Core and director of Bioenergetics Profiling at MUSC.

"Drug development in cancer therapeutics is moving away from single toxic agents to specific combinations that are personalized according to the patient's genetics," said Peterson. "By using these combined therapies, we can increase the positive effect while limiting the negative effects of cancer-killing agents like bortezomib."

Such new treatment options are urgently needed for children with high-risk disease. Current therapies are often ineffective and incredibly painful. Nearly half of these children die within five years of diagnosis.

The Woster team is keenly aware of the challenges faced by these children and motivated to provide them new options.

"We need treatments that are not only more effective against high-risk disease but that are better tolerated by patients," said postdoctoral scholar Catherine Mills, Ph.D., first author of the article.

Woster and scientists in his laboratory are investigating compounds that block the activity of LSD1. Previous work has shown that LSD1 acts as scaffolding to support and stabilize the protein factor MYCN. This scaffolding helps tumors to form and spread, and so patients with increased MYCN tumors are considered to have high-risk disease. The Woster lab wants to disrupt that scaffolding with their novel LSD1

inhibitors.

Using resources provided by the MUSC Drug Discovery Core, the team tested the novel inhibitors alone and together with bortezomib in neuroblastoma cells with abnormally high levels of MYCN. When used together, the novel inhibitor and bortezomib were much more potent killers of these cancer cells than when either was used alone.

"Our studies are the first to show that inhibition of LSD1 is a viable strategy for targeting high-risk MYCN-amplified neuroblastoma," said Woster.

Several LSD1 inhibitors are in clinical trials for solid tumors. However, few of them interact with LSD1 in a reversible manner. Irreversible drugs bind to their targets and never unbind, producing toxicity-related side effects.

"You can think about reversible and irreversible drugs and how they interact with a target protein in terms of a handshake," said Mills.

"At the end of the handshake, reversible drugs allow both parties to remove their hands and go on about their business. However, with irreversible drugs, their hands remain superglued together," she explained. "Can you imagine carrying out your day with your hand stuck to another person's? You would lose the function of that hand. Similarly, you lose the function of the protein that is stuck to the irreversible drug, causing toxic side effects."

The study's findings suggest that combining a reversible and less toxic LSD1 inhibitor and bortezomib could pack a particularly powerful anti-cancer punch.

Next steps are to adjust the inhibitor to make it even more effective

against high-risk neuroblastoma when combined with bortezomib.

"We plan to optimize the structure of our LSD1 inhibitor to increase its potency against LSD1 and hope that it can produce an even greater synergistic effect," said Woster. "We also hope to test this combined approach in several other cancer types with increased MYCN."

More information: Catherine M. Mills et al, Synthesis and evaluation of small molecule inhibitors of LSD1 for use against MYCN-expressing neuroblastoma, *European Journal of Medicinal Chemistry* (2022). DOI: 10.1016/j.ejmech.2022.114818

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