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# Combination therapy improved chemoresistance in ovarian cancer

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Treating ovarian cancer with platinum-based chemotherapy drugs such as cisplatin is initially very effective, with about four out of five patients responding favorably. However, most of these patients quickly become resistant to chemotherapy and may not respond as well to this standard treatment for the disease.

Researchers at The Wistar Institute have shown that a class of drugs called bromodomain and extraterminal domain (BET) inhibitors can be used in combination with cisplatin to reduce a tumor's resistance to chemotherapy, and therefore increase the effectiveness of the drug and improve long-term survival rates. The results were published in the journal *Cancer Research*.

"There is a tremendous need for novel therapeutic strategies for patients with chemotherapy resistant ovarian cancer, given the prevalence of the clinical challenge and the limited number of other options available," said Rugang Zhang, Ph.D., professor and co-program leader in the Gene Expression and Regulation program at Wistar and lead author of the study. "This study demonstrates how an existing class of targeted therapies could be used to potentiate the tumor suppression induced by cisplatin."

Several studies have shown how cancer stem-like cells (CSCs) contribute to chemotherapy resistance. Specifically, an increase in the activity of aldehyde dehyrogenase (ALDH) due to higher levels of ALDH1A1 protein expression appears to increase resistance, while reducing its

activity sensitizes epithelial ovarian cancer cells to chemotherapy, making the treatment more effective.

Zhang and colleagues were able to show that BET inhibitors are able to suppress the activity of ALDH in epithelial ovarian cancer cells. Prior studies have shown that cisplatin increases ALDH activity, which then leads to cisplatin resistance. They also demonstrated that bromodomain-containing protein 4 (BRD4), one of the members of the BET family that is inhibited by BET inhibiting drugs, is a regulator of ALDH1A1 expression, and the protein is found in higher levels in epithelial ovarian cancer cell lines and high-grade serous epithelial ovarian cancer samples.

To test the combination, mice with epithelial ovarian cancer-derived tumor cells were given either the combination of cisplatin and the experimental BET inhibitor JQ1 or cisplatin alone. The group that received the combination therapy experienced significantly extended survival compared with the group of mice that only received cisplatin. Additionally, the outgrowth of tumors in the group of mice that received the combination was significantly delayed.

"The use of BET inhibitors for the treatment of cancer appears to be both safe and effective in clinical trials," said Yuhki Yokoyama, Ph.D., a postdoctoral fellow in the Zhang lab and first author of the study. "This combination appears to significantly extend the effectiveness of cisplatin, one of the most important drugs for treating ovarian cancer, and we hope our newly discovered approach will be validated in future clinical trials."

Provided by The Wistar Institute

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