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Scientists find protein inhibitor revives chemotherapy for ovarian patients

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Investigators at the Translational Genomics Research Institute (TGen) have discovered a way that may help ovarian cancer patients who no longer respond to conventional chemotherapy.

A scientific paper that will be published in the September issue of the journal *Gynecologic Oncology* describes how the inhibition of a protein, CHEK1, may be an effective element to incorporate into therapies for women with ovarian cancer.

The research led by TGen's Dr. David Azorsa, a Senior Investigator, and Dr. Shilpi Arora, a Staff Scientist, found that inhibiting CHEK1 by a small molecule known as PD 407824, enabled ovarian cancer cells to be attacked again by cisplatin, a widely used platinum-based chemotherapy drug for women with ovarian cancer.

"PD 407824 is only available for laboratory research, but other drugs inhibiting CHEK1 are already used to treat patients in the clinic," said Dr. Raoul Tibes, one of the paper's senior a co-authors and an Associate Investigator in TGen's Clinical Translational Research Division.

The prognosis remains poor for patients with ovarian cancer, which kills nearly 14,600 women in the U.S. annually. The standard treatment for cancer of the ovaries, which produce human egg cells, is surgical removal of the cancer, followed by chemotherapy.

The TGen team proved their method in the research laboratory, which is

very encouraging, considering that the use of protein inhibitors in combination with cisplatin, is also proving to be effective in clinical trials with cancer patients.

"The clinical relevance is high, as such novel molecular concepts — inhibiting the repair of cancer cells after treatment with chemotherapies — are in development for many different cancers," said Dr. Tibes, a medical oncologist who treats patients with advanced cancers at TGen Clinical Research Services (TCRS) at Scottsdale Healthcare.

"We actually have similar drug combinations that go after preventing cancer cells to repair themselves, in the clinic already, and we have seen early exciting results. Patients whose tumors had stopped responding to conventional chemotherapy have been made sensitive again, meaning some of these patients responded again to the chemotherapy. The importance of the paper is that it provides evidence that combinations of cisplatin and CHEK1 inhibitors may be worthwhile pursuing in patients with ovarian cancer," said Dr. Tibes.

TCRS is a partnership between TGen and Scottsdale Healthcare that enables laboratory discoveries to be quickly translated into effective therapies for patients at the Virginia G. Piper Cancer Center at Scottsdale Healthcare.

For this research, TGen investigators used cutting-edge technology to screen 572 kinases, the body's protein enzymes that affect how cells function. They discovered 55 siRNAs — strands of RNA molecules that affect the expression of genes — that to some degree enabled cisplatin to slow the growth of cancer cells.

According to the paper, one of those small molecule inhibitors, PD 407824, was especially effective in sensitizing ovarian cancer cells, SKOV3 and OVCAR3, to the growth inhibiting effects of cisplatin. PD

407824 and SB 218078 were the two small molecule inhibitors to CHEK1, that were found to sensitize pancreatic cancer cells to the chemotherapy drug gemcitabine, according to a paper published by the same group last year in the Journal of Translational Medicine.

"Our new data provide kinase targets that could be exploited to design better therapeutics for ovarian cancer patients," said Dr. David Azorsa, Head of TGen's Biological Therapeutics Lab and the senior author of the paper published in Gynecologic Oncology.

In addition, Shilpi Arora, a TGen Staff Scientist and the paper's lead author, said this data, "also demonstrate the effectiveness of high-throughput RNAi screening as a tool for identifying sensitizing targets to known and established chemotherapeutic agents."

Provided by The Translational Genomics Research Institute

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