New type of drug leads to hope against resistant ovarian cancer

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Scientists at USC have discovered a new type of drug for the treatment of ovarian cancer that works in a way that should not only decrease the number of doses that patients need to take, but also may make it effective for patients whose cancer has become drug-resistant.

The drug, which so far has been tested in the lab on ovarian cancer cells and on mice tumors, was unveiled last month in the Proceedings of the National Academy of Sciences (*PNAS*).

"We need a new generation of drugs," said Shili Xu, a USC graduate student and lead author of the *PNAS* paper. "We need to overcome the drug-resistance issue."

The drug is a member of a new class of cytotoxic agents abbreviated as PACMA that was discovered by testing roughly 10,000 chemical compounds on cancer cells in the lab of Nouri Neamati, professor of pharmacology and pharmaceutical sciences at the USC School of Pharmacy, and a co-corresponding author of the paper.

These initial findings led to a collaboration with Nicos Petasis, co-corresponding author of the paper and professor of chemistry at the USC Dornsife College of Letters, Arts and Sciences, with appointments at the School of Pharmacy and the USC Norris Comprehensive Cancer Center of the Keck School of Medicine of USC. This joint effort led to a study of PACMA compounds that was reported last year in the Journal of Medicinal Chemistry.

In order to investigate and optimize the anticancer properties of PACMAs, co-author Alexey Butkevich, a graduate student in the Petasis lab, synthesized more than 80 newly designed compounds. One of these, called PACMA31, was eventually found to be very toxic to ovarian cancer cells and was shown to be a potentially effective drug.

In the PNAS paper, Xu and his co-authors reported that PACMA31 is a potent and selective inhibitor of a protein called Protein Disulfide Isomerase (PDI) that is highly expressed in ovarian cancer.

PACMA31 can be taken orally and accumulates in cancer cells, which means that it is less likely to cause harmful side effects in normal tissues. It is also what is known as an "irreversible" drug, meaning that it permanently latches on to its target, PDI, and refuses to wear off until the protein is degraded.

That irreversibility may result in prolonged duration of drug action that could translate into giving the patients lower doses of drugs.

"We are exploring combination studies in order to find synergy between our drug and first-line therapy for ovarian cancer," Neamati said.

Currently, there are two major types of drugs in the first-line treatment of ovarian cancer: paclitaxel, which hinders cancer cell division by inhibiting the disassembly of microtubules; and carboplatin, which binds to and causes crosslinking of DNA that results in the death of cancer cells.

PACMA31 attacks cancer cells in yet a different way, targeting PDI and thus interrupting the folding process during which proteins assume the shapes that allow them to function properly. Accumulation of misfolded proteins in a cell causes cellular stress and eventually cancer cell death.

Because PACMA31's strategy is different than that of current anticancer drugs, it has the potential to help patients who do not respond to paclitaxel or cisplatin.

"When the patient has no other choice, we could potentially treat them with our drug," Neamati said.

Other co-authors of the PNAS paper included Roppei Yamada, Yu Zhou, Bikash Debnath and Professors Roger Duncan and Ebrahim Zandi. Additional contributors to the PACMA project and co-authors to the team's first paper included Xuefei Cao, Melissa Millard, Srinivas Odde, Nick Mordwinkin, Rambabu Gundla and Professor Stan Louie.

"The discovery of this new drug and its novel mechanism of action is a great example of the power of interdisciplinary collaborations between chemists, biologists, pharmacologists and other biomedical researchers," Petasis said.

The drug will still require additional testing, but so far it appears to be nontoxic and effective at halting tumor growth. It may also have potential for treating other types of cancer, Neamati noted.

"Obviously, we think that it will go beyond ovarian cancer," he said.

Provided by University of Southern California