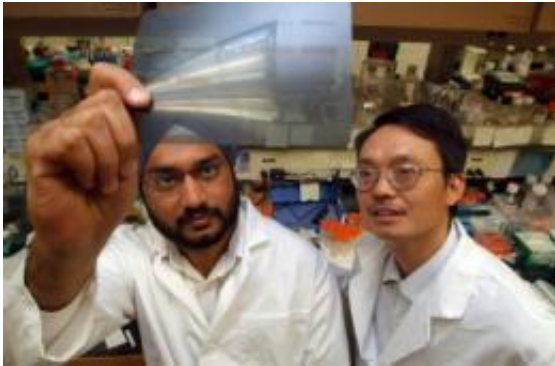


Cause and potential treatment found for cancer drug's kidney toxicity

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Drs. Navjotsingh Pabla and Zheng Dong at Georgia Health Sciences University have found a way to make the popular cancer drug cisplatin less toxic to the kidneys and more effective against some cancers. Credit: Phil Jones/GHSU photographer

Scientists may have a way to make the powerful cancer drug cisplatin less toxic to the kidneys and more effective against some cancers.

The [chemotherapeutic agent](#) used in combination with other drugs for a variety of cancers, results in [kidney damage](#) or failure in about 30 percent of users, although the mechanism has been unclear. The most physicians can do today to protect the kidneys is advise patients to drink more water.

The relatively simple, highly reactive compound tends to accumulate in

the kidneys, said Dr. Navjotsingh Pabla, postdoctoral fellow at Georgia Health Sciences University and first author on the study in *The [Journal of Clinical Investigation](#)*. "The kidneys can take it up, but they have trouble removing it, so it just accumulates," he said.

The kidneys' endless workload of filtering some substances while resorbing others leaves them vulnerable to injury, one of the reasons the kidneys are the first organ to shut down when a patient is critically ill, said Dr. Zheng Dong, GHSU cell biologist, Career Research Scientist at the Charlie Norwood Veterans Affairs Medical Center in Augusta and the study's senior author. "Any stress to the cell can injure it," Dong said.

The scientists have shown in mice with tumors as well as human [cancer cells](#) in culture that cisplatin highly activates [protein kinase C](#) delta; protein kinases regulate other proteins by adding phosphates to them that can change their function. They've further shown that protein kinase C delta is a key mediator of cell death in kidneys and important to [cancer cell survival](#).

The dichotomy appears useful because they've also shown that a drug, already in clinical trials for its potential in protecting [brain cells](#) following stroke, blocks the kidney destruction. In fact, protein kinase inhibitors in mice with tumors, enhanced breast and ovarian cancer treatment.

"Normal cells may not depend on this protein for survival and growth so if you remove it, there don't appear to be major negative consequences," Pabla said. The findings point toward using protein kinase C inhibitors as an adjunct therapy for patients experiencing kidney problems and potentially for all cancer patients treated with cisplatin if the enhanced efficacy finding continues to hold up, Dong said.

The scientists note that reducing the cisplatin dose decreases kidney

toxicity but also decreases its efficacy and may leave the patient resistant to even higher doses of the drug. In the more than 30-year history with cisplatin, related drugs, such as carboplatin, have been developed to circumvent kidney damage, but those drugs tend to have more limited use, be less effective and/or have additional side effects. In more recent years, the focus has been on trying to protect the kidneys.

Next steps include working with chemists to see if an even more effective inhibitor can be developed.

Provided by Georgia Health Sciences University

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