

Combating Chemotherapy Resistance in Cancer

Study from the University of Colorado Anschutz Medical Campus and Cedars-Sinai Cancer investigators reveals opportunities to improve effectiveness of common chemotherapy drug

January 1, 2025 By University of Colorado Cancer Center

A new study from [Cedars-Sinai Cancer](#) and the [University of Colorado Anschutz Medical Campus](#) reveals a potential way to overcome tumor resistance to a common chemotherapy drug called cisplatin.

The [study](#), published in the peer-reviewed journal Science Advances, could improve the effectiveness of the widely used platinum-based medication and reduce the required dosage, minimizing side effects.

'Enhance patient response'

"We found that by inhibiting the action of a gene that limits the importation of the drug into tumor cells, we can increase the uptake of cisplatin and thus its effectiveness," said [Dan Theodorescu, MD, PhD](#), director of Cedars-Sinai Cancer, the PHASE ONE Foundation Distinguished Chair, and co-senior author of the study. "This gives us a druggable target to enhance patient response, especially in cases of advanced disease, and we have demonstrated this in multiple cancer types. We hope these findings will make cisplatin therapy more effective and an option for more patients."

His colleague, co-senior author [James Costello, PhD](#), associate professor of Pharmacology at CU Anschutz, said the study sheds light on how platinum gets inside a cell.

"All cells have channels that sit on the cell surface and control what goes in and out of the cell. It turns out that some of these channels import platinum drugs into cells," Costello said.

Cisplatin is widely used as part of first-line therapy for many cancer types, including bladder, ovarian, cervical, testicular, lung, and breast cancer, as well as sarcomas, lymphomas, and leukemias. Nearly 50% of all patients who receive chemotherapy receive platinum-based drugs, which work by damaging the DNA of tumor cells to prevent them from multiplying. However, tumor cells are often able to "escape" the drugs' effects, so these therapies rarely cure advanced

disease.

To explore ways to overcome cancer cells' resistance to cisplatin, investigators from Cedars-Sinai, the University of Colorado Anschutz Medical Campus, and Erasmus University Medical Center, Rotterdam, The Netherlands, worked with bladder cancer cells in laboratory mice and in cell culture, and also with organoids grown from patients' bladder cancer cells. Tumor organoids are clusters of cells, grown in a petri dish, that share many characteristics with actual tumors.

'Promising target for drug development for patients with treatment-resistant cancer'

"We showed that inhibition of a gene called NPEPPS increased sensitivity to cisplatin in these cells and organoids, providing the first description of this gene's role in cisplatin resistance," Theodorescu said. "Our data have shown the importance of this pathway in various cancer types and in patients who had platinum-based therapy. Our data have clearly identified NPEPPS as a promising target for drug development for patients with treatment-resistant cancer."

Previous research has shown that platinum-based chemotherapy used along with immunotherapy can improve immunotherapy effectiveness, which further broadens the impact of these findings, Theodorescu said.

The researchers discovered that NPEPPS is the protein that gets turned up in response to platinum drugs and then blocks the channels that import them.

"So, by targeting NPEPPS therapeutically, we can prevent it from blocking these channels," Costello said. "We are continuing to study how blocking NPEPPS therapeutically affects both tumor and normal cells, including interactions with the immune system."

'Better Patient Outcomes'

Ongoing studies are aimed at more fully understanding how NPEPPS inhibits the import of cisplatin into cancer cells and at discovering drugs that can inhibit NPEPPS. Combining these drugs with cisplatin would make the cisplatin more effective at killing cancer cells, leading to better patient outcomes.

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