Vitamin D metabolite helps stop drug-resistant cancer

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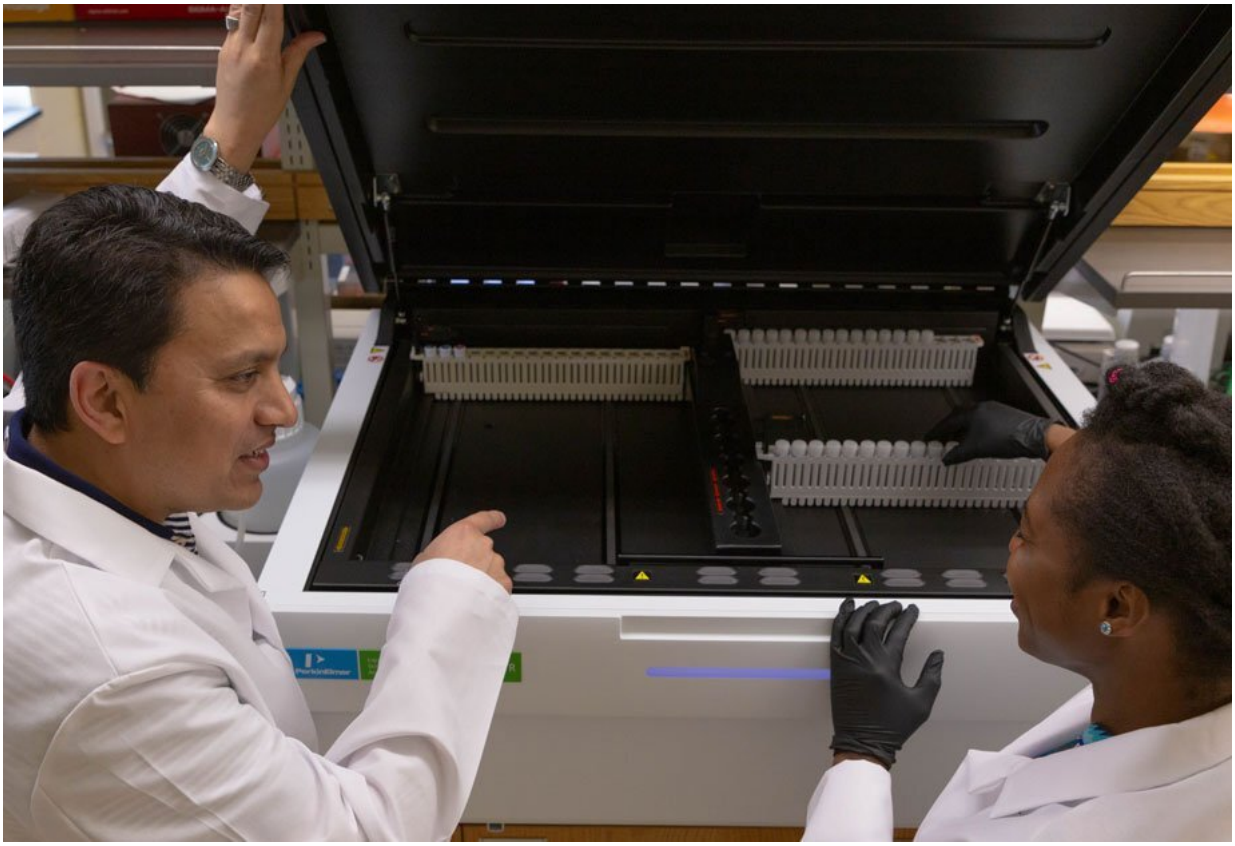

Assistant Professor Surtaj H. Iram and doctoral student Angelina Sampson of the SDSU Department of Chemistry and Biochemistry measure the isotope tritium to determine which compounds interact with drug transporter proteins. Overexpression of drug transporter proteins is the most frequent mechanism through which cancer cells gain resistance. Credit: South Dakota State University

What's good for our bones may also help stop cancer cells that develop resistance to multiple chemotherapy drugs.

The vitamin D metabolite calcitriol and its analog calcipotriol can block one of the mechanisms through which cancer cells gain resistance to chemotherapy drugs—and can selectively kill those drug-resistant cells, according to Assistant Professor Surtaj Iram of the South Dakota State University Department of Chemistry and Biochemistry.

His research focuses on drug transporter proteins, which are the key determinants of drug absorption, distribution and excretion from the body. Overexpression of drug transporter proteins is the most frequent mechanism through which cancer cells gain resistance.

"Several epidemiologic and preclinical studies show the positive effect of vitamin D in reducing cancer risk and progression, but we are the first to discover its interaction with drug transporter protein and its ability to selectively kill drug-resistant cancer cells," Iram said.

Furthermore, most drug discovery projects focus on killing cancer cells but eventually they gain resistance to chemotherapy drugs, he explained. "The vitamin D metabolite and its analog cannot kill the naive cancer cells, but when those cells develop resistance, calcitriol and calcipotriolcan kill them."

The study results were published in *Drug Metabolism and Disposition*, a journal of the American Society of Pharmacology and Experimental Therapeutics. "The paper was picked as the best of the issue and was featured on the cover," Iram said. "This is an extraordinary experience for an assistant professor. We are getting the SDSU name out there."

Postdoctoral researcher Kee W. Tan and doctoral students Bremansu Osa-Andrews and Angelina Sampson also worked on the study.

"Collateral sensitivity is the idea behind the discovery of drugs that can selectively kill MRP1-overexpressing multidrug resistant cancer cells," Iram explained. "Gaining strength in one area usually creates weakness in another area—everything in nature comes at a price. Our approach is to target the Achilles' heel of drug-resistant cancer cells through exploiting the fitness cost of resistance."

The project was supported by South Dakota Board of Regents, South Dakota's National Science Fundation Experimental Program to Stimulate Competitive Research (EPSCoR) Program, the SDSU Research and Scholarship Support Fund, the SDSU Scholarly Excellence Fund and Iram's laboratory startup funding.

Multidrug resistant protein 1, known as MRP1, is a protein on the cell surface that serves as a gatekeeper, Iram explained. "Any drug needs to go past these gatekeepers." MRP1 protects the cell by pumping out harmful molecules to prevent toxin buildup in organs, including lungs, kidneys and the gastrointestinal tract.

However, overexpression of MRP1 causes the protein to pump out chemotherapy drugs, thereby protecting cancer cells and making them resistant to multiple therapeutic drugs. MRP1 overexpression has been associated with multidrug resistance in lung, breast and prostate cancer.

In addition to anticancer agents, MRP1 can reduce the efficacy of a wide variety of drugs commonly used for various metabolic diseases and neurological disorders, as well as anti-virals, antibiotics, antidepressants, anti-inflammatory and antiHIV drugs, so this discovery has implications for a wide range of diseases, Iram explained. "If we can get a better handle on these transporters, we can improve drug efficacy. Patients can take less medication yet get the same effect because the drugs are not being pumped out so much." The lower dosage will then reduce drug side effects.

"We can make drugs which are now being used successfully even better," said Iram, who does research through South Dakota's Biosystems Networks and Translational Research Center (BioSNTR). He is applying for NIH funding to continue this work.

"This knowledge opens a new doorway to identify what pathway vitamin D is hitting and expose more targets, new avenues of research to selectively kill multidrug-resistant cancer cells," Iram said. "Now we must go back to understand exactly how this molecule kills these cells. We want to understand those mechanisms so we can find different ways to kill these cells and then find an agent which is very potent."

Furthermore, MRP1 is part of a larger family of proteins called ABC transporters that move things around in animals and plants, Iram noted. "Plants have the most." In future, Iram plans to apply the lessons learned from human ABC transporters to food products and precision agriculture.

Provided by South Dakota State University