Scientists create extremely potent and improved derivatives of successful anticancer drug

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Scientists at The Scripps Research Institute (TSRI) have found a way to make dramatic improvements to the cancer cell-killing power of vinblastine, one of the most successful chemotherapy drugs of the past few decades. The team's modified versions of vinblastine showed 10 to 200 times greater potency than the clinical drug. Even more significantly, these new compounds overcome the drug resistance that emerges upon treatment relapse, which renders continued or subsequent vinblastine treatment ineffective in some patients.

The TSRI researchers expect that similar modifications will boost the effectiveness of vincristine, a closely related drug that is commonly used against childhood leukemias and Hodgkin's disease.

"These new compounds should improve on what are already superb anticancer drugs," said Dale L. Boger, who is the Richard and Alice Cramer Professor and Chair of the Department of Chemistry at TSRI. Boger and members of his laboratory reported the discovery in a paper recently published online ahead of print by the journal *ACS Medicinal Chemistry Letters*.

Anticancer Agents

Vinblastine and vincristine are natural products of a pink-flowered herb known as the Madagascar periwinkle. Although the leaves of the plant

had been used in traditional medicines for a range of other conditions, from diabetes to hemorrhoids, drug researchers at Eli Lilly found in the 1960s that the two compounds showed excellent potential as anticancer agents.

Both were found to selectively kill cancer cells by a mechanism that many other cancer drugs, including taxol, epothilones, and colchicine, have followed since—they bind a cellular protein called tubulin in a way that interferes with the buildup and breakdown of tubulin-containing chains called microtubules—structural elements of cells that play a key role in cell division. When the normal dynamics of their microtubules are disrupted, fast-dividing cancer cells stop dividing and die.

Since the 1960s, vinblastine has been used successfully in combination with other chemotherapy drugs against lymphomas as well as testicular, ovarian, breast, bladder and lung cancers. Vincristine is routinely used in combination regimes against childhood acute lymphoblastic leukemia and non-Hodgkin lymphomas. Both compounds are presently isolated from cultivated fields of the plants that make them naturally, but in trace amounts (0.0001% of the dry leaf weight).

Since they are plant-derived natural products, they cannot be accessed using existing biotechnology or genetic engineering methods and, prior to the TSRI efforts, they were viewed as far too complex to be prepare by laboratory organic chemistry techniques. The authors developed a remarkable three-step preparation from commercially available chemicals using chemistry that they invented specifically for this purpose.

A significant limitation of vinblastine and vincristine is that, with extended treatment, they may evoke a powerful form of drug resistance. This resistance comes from a doorkeeper-type molecule called P-glycoprotein (Pgp), which transports infiltrating drug molecules out of

the cancer cells. As cancer cells evolve to produce more and more Pgp, drugs fail to reach effective concentrations in cells and cancerous growth resumes. For years, medicinal chemists have tried to find modified versions—"analogues"—of these drugs that would overcome Pgp-mediated resistance, but without success.

Developing Extraordinary Potency

Last year, however, in a landmark paper in Organic Letters, Boger and his colleagues described a broad new method for modifying organic compounds like vinblastine, and demonstrated the method by making previously inaccessible variants of the drug. "Although it is a versatile method, we developed it specifically so that we could start making these vinblastine analogues that couldn't be made before," Boger said.

As his team used the method to make more new vinblastine analogues, the scientists discovered a type of modification to the drug that limits its usual drop in potency against resistant, Pgp-overproducing cancer cells as compared to non-resistant cancer cells. For the new study, the team explored variations of that modification and eventually found several analogues that were as good at killing resistant cells as ordinary vinblastine is at killing non-resistant cancer cells.

These new analogues were also many times more potent than vinblastine against non-resistant cells—which are the kinds of cancer cells almost all patients have at diagnosis.

The laboratory of a major drug company, Bristol-Myers Squibb, was able to repeat these results in a larger set of clinically important human tumor cell lines, and Boger's team confirmed that the new analogues' greater potency corresponds to their greater ability to bind to tubulin.

"The potency of these analogues is extraordinary—they show activity

down at the 100 picomolar level [100 trillionths of a mole] against some cell lines," said Boger. "So we have something here that's really unique, and we discovered it only because of the novel chemistry we developed."

More information: "Potent Vinblastine C20' Ureas Displaying Additionally Improved Activity Against a Vinblastine-Resistant Cancer Cell Line," *ACS Medicinal Chemistry Letters.*

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