New use for a cell toxin found to inhibit survival proteins in cancer cells

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A chemically-modified version of a mitochondrial toxin long used to control species of invasive fish in lakes has been found to selectively inhibit two "survival proteins" in cancer cells. The research is a first step toward developing a molecularly-targeted drug that could eliminate cellular-level resistance to multiple types of chemotherapy and radiation therapy found in many types of cancers.

In a paper published today in the July 2007 issue of *Molecular Cancer Therapeutics*, scientists at Fred Hutchinson Cancer Research Center report that a modified version of antimycin called 2-Methoxy antimycin is selective in killing cells that have high levels of Bcl-2 and Bcl-xL proteins. The over expression of these proteins in many types of cancer cells correlates with resistance to chemotherapy and radiation therapy. Cells with normal levels of Bcl-2 or Bcl-xL are resistant to 2-Methoxy antimycin.

David M. Hockenbery, a member of the Hutchinson Center's Clinical Research Division and principal investigator for the study, and colleagues set up screening assays to look for small molecules or compounds that are selectively toxic to cells that over express Bcl-2 proteins. Higher expression of the target protein made cells more sensitive to the 2-Methoxy antimycin inhibitor. This is called a "gain of function" mechanism and is counterintuitive to the way most drugs work.

"Our compound, 2-Methoxy antimycin, is the only Bcl-2 inhibitor reported with 'gain of function' activity, which provides a therapeutic window between cancer cells with high expression of the proteins versus cells with normal expression," said Hockenbery, who is also a professor of medicine at the University of Washington Medical Center. "This effect was preserved when 2-Methoxy antimycin was used in combination with other agents, and could lead to a targeted molecular therapy to enhance the effectiveness of cancer treatments."

Hockenbery said his group's approach illustrated the need to look at how the proteins interact with everything else in the cell. "By over expressing this protein, the cell is changed in some interesting ways. It creates a situation where the cell becomes dependent upon the protein," he said. "Cancers can become addicted to certain proteins, so just by over expressing the protein the cell changes so that it can't live without that protein."

The next step in this research is to use the assays his lab developed to "cast a wider net" to find additional compounds that have similar properties to 2-Methoxy antimycin, Hockenbery said. This strategy has already yielded one additional Bcl-xL inhibitor with "gain of function" activity, reported in the Molecular Cancer Therapeutics paper. Funding for the study, "2-Methoxy antimycin reveals a unique mechanism for Bcl-xL inhibition," came from the New Technology Development Fund administered by the Hutchinson Center. Additional key investigators in Hockenbery's lab included Michael Manion, Ph.D., and Pam Schwartz, Ph.D., and John Fry.

Source: Fred Hutchinson Cancer Research Center