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Cancer: Trapping the escape artist

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Cancer uses devious means to evade treatment and survive. One prime example is the way tumors express anti-cell death (anti-apoptotic) proteins to resist chemotherapy and radiation. However, the Pellecchia laboratory at Sanford-Burnham Medical Research Institute (Sanford-Burnham) has made two recent discoveries that may help curb these anti-apoptotic proteins and make current treatments more effective.

In a paper published online in the journal *Cell Death and Disease* on May 6, Maurizio Pellecchia, Ph.D., and colleagues outline how the six anti-apoptotic proteins in the Bcl-2 family are expressed differently in different cancers. As a result, any therapy designed to defeat these proteins, and thus enhance the cell death caused by most cancer treatments, must target the exact anti-apoptotic protein the cancer is expressing to be effective. However, even targeting the right protein might not be enough, as cancers often express more than one and can select for an "escape" protein and continue to thrive.

"You need to inhibit all six of the anti-apoptotic proteins members of the Bcl-2 family to have a compound with therapeutic potential," says Dr. Pellecchia.

Related research may have solved that problem. The Pellecchia laboratory, in collaboration with Coronado Biosciences and Virginia Commonwealth University, has been working on just such a pan-Bcl-2 inhibitor, and may have found it in a compound called BI-97C1. A paper published online on May 5 in the Journal of Medicinal Chemistry describes how BI-97C1, an optically pure derivative of a cottonseed

extract called gossypol, inhibits all six anti-apoptotic Bcl -2 family proteins. This broad spectrum approach could make current cancer treatments more effective by controlling all six of these proteins and allowing malignant cells to die.

"When we tested BI-97C1 against human prostate cancer in mice, the cancer was completely wiped out, even with one tenth the dose we had used with previous compounds," says Dr. Pellecchia.

BI-97C1 is currently licensed to Coronado Biosciences, a private, clinical stage biotech company focused on new cancer treatments. Coronado's pan Bcl-2 inhibitor program is expected to enter clinical trials soon. "We have a very productive collaboration with Dr. Pellecchia," says R.J. Tesi, M.D., president and CEO of Coronado Biosciences. "His work demonstrates the importance of inhibiting all six Bcl-2 pro-survival proteins and demonstrates how rational drug design can optimize the development of targeted therapies to treat cancer. We are anxious to move BI-97C1 from pre-clinical development into patients."

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