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Marked for destruction: Newly developed compound triggers cancer cell death

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The BCL-2 protein family plays a large role in determining whether cancer cells survive in response to therapy or undergo a form of cell death known as apoptosis. Cells are pressured toward apoptosis by expression of pro-apoptotic BCL-2 proteins. However, cancer cells respond to therapy by increasing expression of anti-apoptotic proteins, which bind and neutralize pro-apoptotic family members and mediate therapeutic resistance. Therefore, development of therapeutic strategies to neutralize resistance to apoptosis will be critical to clinical improvements.

A research group from the Dana-Farber Cancer Institute, led by Dr. Loren Walensky, developed a compound modeled directly from the pro-apoptotic the death domain of BCL-2, the BIM BH3 domain. This compound, known as a stapled BIM BH3 peptide, was found to competitively bind with anti-apoptotic proteins and led to enhanced apoptosis in cancer cells. They also showed that tumor growth in mice was suppressed by the stapled BIM BH3 compound and that the new compound worked synergistically with other with pharmaceutical agents that promote apoptosis. The potential therapeutic effects of stapled BIM BH3 were further shown by activation of cell death in an acute myeloid leukemia tumor model in mice with little side effects on surrounding tissue.

Their study presents a new formulation of a BH3 mimetic that has broad BCL-2 family targeting and may provide significant clinical benefit.