studies of these agents, carefully conducted phase II studies will need to be performed to identify predictive biomarkers, direct subsequent pivotal studies to the population that has tumors that express these biomarkers, and thereby enhance the likelihood that these agents will be successfully developed.

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464 INVITED

Regulation of apoptosis by synthetic helices of the BCL-2 family

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Defects in "apoptosis" or programmed cell death are a hallmark of cancer. The BCL-2 family of pro- and anti-apoptotic intracellular proteins constitutes a critical decisional control point in the intrinsic cell death pathway. Protein interaction between BCL-2 members is a prominent mechanism of regulation and is mediated through the amphipathic alpha-helical BH3 segment, which functions as an essential death domain. The manufacture of small molecules to activate cell death pathways has been complicated by the extensive, shallow and hydrophobic interface of apoptotic protein targets. The *in vivo* utility of specific peptides to inhibit or activate these signaling pathways has been compromised by their lack of secondary structure, susceptibility to proteolytic degradation, and difficulty penetrating cells. We developed a chemical strategy, termed hydrocarbon stapling, to generate BH3 peptides with dramatically improved pharmacologic properties. The stapled peptides, entitled "Stabilized Alpha-Helix of BCL-2 domains" or SAHBs, proved to be helical, protease resistant, and cell permeable molecules that bound with increased affinity to multidomain BCL-2 member pockets. A SAHB of the BH3 domain from BID, for example, activated the genetic pathway of apoptosis to kill leukemia cells. In addition, SAHB effectively inhibited human leukemia xenografts *in vivo*. Synthetic approaches such as hydrocarbon stapling that reinforce native peptide sequences provide an alternative strategy to manipulate protein-protein interactions and target cell death pathways in cancer.

465 INVITED

Targeting Bcl-2 using antisense molecules

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Abnormal expression of Bcl-2 protects malignant cells from apoptosis, and is implicated in the aetiology of non-Hodgkin's lymphoma and in chemoresistance of several tumour types. Oligonucleotides (ONT) complementary to a region of the *bcl-2* mRNA can specifically down-regulate Bcl-2 expression, leading *in vitro* to increased rates of apoptosis and enhanced chemosensitivity. Oblimersen (Genasense, GS), the lead Bcl-2-targeted antisense ONT is an 18-base phosphorothioate ONT targeting the first 6 codons of the Bcl-2 open reading frame. Clinical trials of GS as a single agent or with chemotherapy have demonstrated the