

# [Targeting apoptosis signaling pathways for anticancer therapy](https://assignbuster.com/targeting-apoptosis-signaling-pathways-for-anticancer-therapy/)

[](https://assignbuster.com/)[Health & Medicine](https://assignbuster.com/essay-subjects/health-n-medicine/)

## Introduction

Tissue homeostasis is the result of a delicate balance of proliferation on one side and cell death on the other side ( [Evan and Vousden, 2001](#B19) ). Tipping this balance can contribute to either tumor formation or inappropriate tissue loss via too little or too much apoptosis ( [Fulda, 2009b](#B24) ). Apoptosis (also called programmed cell death) is a cellular death program that is inherent to all mammalian cells and plays an important role in the regulation of various physiological and pathological conditions ( [Taylor et al., 2008](#B86) ). For example, deregulation of apoptosis programs can lead to resistance of cancers to current treatment strategies, since the ability to activate cell death programs in cancer cells critically determines the efficacy of current cancer therapies ( [Makin and Dive, 2001](#B57) ; [Johnstone et al., 2002](#B38) ; [Fulda and Debatin, 2006](#B25) ). Furthermore, apoptosis of circulating tumor cells can have an impact on the metastatic process ( [Larson et al., 2004](#B48) ; [Fehm et al., 2006](#B20) ). This calls for a better understanding of the regulatory mechanisms that control cell death and survival pathways in human cancers, since this knowledge is expected to translate into the development of new approaches to rationally and selectively target deregulated signaling pathways in cancer cells. This strategy will likely pave the avenue to an innovative approach to bypass treatment resistance in various human cancers.

## Apoptosis Pathways

The central apoptotic machinery can be divided into two major signaling pathways, comprising the death receptor (extrinsic) and the mitochondrial (intrinsic) pathway ( [Fulda and Debatin, 2006](#B25) ). Both pathways eventually fuel into a common effector phase that is characterized by the activation of caspases ( [Fulda and Debatin, 2006](#B25) ). Caspases are a family of proteases that act as common death effector molecules in various forms of cell death ( [Logue and Martin, 2008](#B54) ).

In the extrinsic pathway, the ligation of death receptors by their ligands including tumor necrosis factor (TNF) receptor, CD95 (APO-1/Fas), or TNF-related apoptosis-inducing ligand (TRAIL) receptors, initiates the formation of a multimeric protein complex called the death-inducing signaling complex (DISC) that drives activation of caspase-8 ( [Ashkenazi, 2008b](#B4) ). Caspase-8 can transmit the apoptosis signal directly by cleaving other caspases such as caspase-3 ( [Ashkenazi, 2008b](#B4) ). Alternatively, caspase-8 indirectly transfers the signal to apoptosis via mediators, for example Bid, a proapoptotic, BH3-only domain containing protein of the Bcl-2 family ( [Adams and Cory, 2007](#B1) ). Once Bid is cleaved by caspase-8, the resulting cleaved form tBid translocates to mitochondrial membranes to engage mitochondrial outer membrane permeabilization ( [Adams and Cory, 2007](#B1) ).

In the mitochondrial pathway, the release of apoptogenic factors such as cytochrome *c* or second mitochondrial activator of caspases (Smac) from the mitochondrial intermembrane space constitutes a key event that controls the activation of downstream apoptosis pathways ( [Fulda et al., 2010](#B26) ). To this end, mitochondrial proteins that are released from the mitochondrial intermembrane space in the course of mitochondrial outer membrane permeabilization are critical mediators ( [Kroemer et al., 2007](#B42) ). For example, cytochrome *c* initiates caspase-3 activation via the cytochrome *c* /Apaf-1/caspase-9-containing apoptosome complex following its release into the cytosol ( [Kroemer et al., 2007](#B42) ). Smac, another mitochondrial intermembrane space protein, antagonizes “ inhibitor of apoptosis” (IAP) proteins via binding to these proteins, thereby releasing their inhibitory effect on caspases ( [Fulda et al., 2010](#B26) ).

Apoptosis pathways are tightly regulated by antiapoptotic factors to prevent their accidental activation. The same mechanisms that dampen the inappropriate initiation of cell death can also confer resistance in cancer cells, for example in the context of drug resistance. Therefore, these mechanisms of apoptosis resistance can be exploited as therapeutic targets to elicit cell death in cancer cells as discussed in more detail in the following chapters.

## Exploiting Apoptosis Pathways for Cancer Therapy

Since the escape of apoptosis presents a characteristic feature of a variety of human cancers that plays an important role in promoting tumor formation and progression, there has been much interest to design strategies to target the apoptotic machinery in cancer cells. In principle, cell death pathways can be activated by agents that directly trigger apoptosis pathways. Alternatively, apoptosis-targeted therapies can be used to increase the responsiveness of human cancers toward classical treatment approaches that are currently used in clinical therapies, e. g., chemo-, radio-, or immunotherapy, as these therapies primarily exert their antitumor activity by inducing apoptosis in cancer cells.

### Exploiting the Death Receptor (Extrinsic) Pathway

#### Alterations in the death receptor (extrinsic) pathway in human cancers

As far as the extrinsic pathway is concerned, alterations that interfere with signal transduction to apoptosis have been identified at various levels within the pathway. For example, surface expression of death receptors may simply be reduced or even completely absent in apoptosis-resistant cancers. Accordingly, downregulation of CD95 expression was detected in drug-resistant leukemia or neuroblastoma cells, linking CD95 signaling to drug sensitivity ( [Friesen et al., 1997](#B21) ; [Fulda et al., 1998](#B29) ). Furthermore, the transport of death receptors, i. e., TRAIL receptors TRAIL-R1 and -R2, from intracellular stores such as the endoplasmatic reticulum to the cell surface may be defective resulting in resistance toward TRAIL as described in colon carcinoma ( [Jin et al., 2004](#B37) ). Moreover, genetic alterations may disturb death receptor expression or function. For example, mutations of the CD95 gene were reported in solid cancers and in hematological malignancies ( [Fulda, 2009a](#B23) ). Also, the chromosomal location of the two agonistic TRAIL receptors on chromosome 8p is frequently altered in human cancers, e. g., by loss of heterozygosity (LOH; [Ashkenazi, 2008a](#B3) ). Deletions or mutations resulting in loss of both copies of TRAIL-R1 or -R2 have been detected in several cancers, e. g., non-Hodgkin’s lymphoma, colorectal, breast, head and neck cancer, osteosarcoma, or lung carcinoma ( [Pai et al., 1998](#B62) ; [Dechant et al., 2004](#B15) ). Another mechanism of resistance is due to the expression of decoy receptors that interfere with death receptor signaling. To give one example, genetic amplification or overexpression of decoy receptor 3 (DcR3) has been reported as a resistance mechanism in CD95-triggered apoptosis in lung or colon carcinoma as well as glioblastoma, as DcR3 competes with CD95 for CD95 ligand binding ( [Pitti et al., 1998](#B67) ; [Roth et al., 2001](#B71) ). As far as decoy receptors in the TRAIL system are concerned, TRAIL-R3 has been shown to be overexpressed in gastric carcinoma ( [Sheikh et al., 1999](#B72) ).

In addition to genetic modifications, also epigenetic alterations can perturb death receptor signaling. Accordingly, hypermethylation of gene promoters of death receptors may impair their expression levels and may also contribute to immune escape ( [Van Noesel et al., 2002](#B92) ; [Petak et al., 2003](#B64) ). Expression of epigenetically silenced CD95 could be restored upon treatment with histone deacetylase inhibitors, thereby enhancing NK cell-dependent cytotoxicity ( [Maecker et al., 2002](#B56) ).

Next, death receptor signaling may be disturbed because of insufficient formation of the DISC that is critical to drive caspase-8 activation. Overexpression of antiapoptotic molecules such as cFLIP or phosphoprotein enriched in diabetes/phosphoprotein enriched in astrocytes-15 kDa (PED/PEA-15) that block the recruitment of caspase-8 to the DISC ( [Hao et al., 2001](#B32) ; [Krueger et al., 2001](#B43) ) frequently occurs in tumors and has been correlated with resistance to death receptor- and also to chemotherapy-induced apoptosis ( [Fulda et al., 2000](#B28) ; [Longley et al., 2006](#B55) ). Caspase-8 expression can also be impaired by epigenetic silencing as reported in a variety of cancers including Ewing tumor, neuroblastoma, medulloblastoma, retinoblastoma, rhabdomyosarcoma, or small lung cell carcinoma both in cell lines as well as in primary tumor specimens ( [Teitz et al., 2000](#B87) ; [Fulda et al., 2001](#B27) ; [Harada et al., 2002](#B33) ; [Hopkins-Donaldson et al., 2003](#B35) ; [Pingoud-Meier et al., 2003](#B66) ).

#### Strategies to target the death receptor pathway

Since the TRAIL ligand/receptor system presents the most promising target for therapeutic intervention and clinical translation among the death receptors, the following paragraph will focus on the use of TRAIL receptor agonists for the treatment of cancer. Intravenous infusion of even high doses of TRAIL showed no toxicity in chimpanzees and cynomolgus monkeys that were used as non-human primates ( [Ashkenazi et al., 1999](#B5) ). Similarly, TRAIL exerted no detectable cytotoxic activity against various non-malignant human cells of different lineages including fibroblasts, endothelial cells, smooth muscle cells, epithelial cells, or astrocytes ( [Lawrence et al., 2001](#B49) ). It is still not exactly known what determines the differential sensitivity of malignant versus normal cells toward TRAIL.

Recombinant soluble TRAIL proved to be a potent apoptosis-inducer in a large panel of preclinical studies both *in vitro* as well as *in vivo* ( [Ashkenazi, 2008a](#B3) ). Similarly, monoclonal TRAIL receptor antibodies targeting the proapoptotic TRAIL receptors TRAIL-R1 or -R2 resulted in suppression of tumor growth ( [Chuntharapai et al., 2001](#B13) ; [Ichikawa et al., 2001](#B36) ). Of note, TRAIL-R2 antibody-based therapy also stimulated tumor-specific T cell memory, leading to protection from tumor relapse ( [Takeda et al., 2004](#B83) ). Further, several gene therapy approaches have been developed to deliver TRAIL specifically to tumor cells. Adenovirally expressed TRAIL yielded high expression levels of TRAIL resulting in tumor-specific induction of apoptotic cell death with little transgene expression in non-malignant human primary mammary epithelial cells ( [Lin et al., 2002](#B52) ). Proof-of-concept studies were also performed using intralesional injection of adenoviral TRAIL, which led to growth inhibition of human breast cancer xenografts and tumor-free survival of mice ( [Lin et al., 2002](#B52) ).

Since TRAIL may not exert sufficient antitumor activity as monotherapy in most cancers for long-term suppression of tumor growth, various TRAIL-based combination therapies together with chemo-, radio-, or immunotherapy or targeted therapeutics have been developed. Cooperativity between TRAIL receptor agonists and DNA-damaging chemo- or radiotherapy occurred in a multitude of solid cancers as well as leukemia in cell lines and in mouse cancer models ( [Gliniak and Le, 1999](#B31) ; [Chinnaiyan et al., 2000](#B11) ; [Keane et al., 2000](#B39) ; [Nagane et al., 2000](#B60) ; [Belka et al., 2001](#B6) ; [Rohn et al., 2001](#B70) ; [Ray and Almasan, 2003](#B69) ; [Singh et al., 2003](#B74) ). This synergism combining TRAIL and DNA-damaging insults may involve various mechanisms of action, e. g., transcriptional upregulation of the agonistic TRAIL receptors TRAIL-R1 and -R2 upon DNA damage in a p53-dependent or -independent manner ( [Takimoto and El-Deiry, 2000](#B84) ; [Meng and El-Deiry, 2001](#B58) ) or increased formation of the CD95 or TRAIL DISC ( [Lacour et al., 2003](#B47) ). Recombinant TRAIL and TRAIL receptor antibodies are evaluated in early clinical trials as mono- or combination therapy, for example with chemotherapeutics ( [Younes and Aggarwall, 2003](#B96) ; [Mom et al., 2005](#B59) ; [Chow et al., 2006](#B12) ; [Herbst et al., 2006](#B34) ; [Patnaik et al., 2006](#B63) ; [Tolcher et al., 2007](#B89) ).

In addition to triggering apoptosis, TRAIL has also been reported to stimulate proliferation and survival, at least under certain conditions. For example in TRAIL-resistant cancers, the addition of TRAIL was shown to result in proliferation in a NF-κB-dependent manner ( [Ehrhardt et al., 2003](#B18) ). Thus, TRAIL might not only be ineffective in resistant forms of cancers, but may paradoxically even enhance tumor growth.

### Exploiting the Mitochondrial (Intrinsic) Pathway

#### Defects in the mitochondrial (intrinsic) pathway in human cancers

Apoptosis pathways can also be altered at the level of mitochondria in human cancers, leading to tumor formation and treatment resistance. For example, overexpression of antiapoptotic proteins of the Bcl-2 family such as Bcl-2 frequently occurs in various tumors. In follicular lymphoma, Bcl-2 is expressed at high levels because of chromosomal translocation of the Bcl-2 oncogene into the immunoglobulin heavy chain gene locus ( [Tsujimoto et al., 1984](#B90) ). Besides genetic alterations, aberrant Bcl-2 expression may also be caused by oncogenic activation of survival pathways, e. g., PI3K/Akt signaling. Another possible cause for the disturbed balance between pro- and antiapoptotic Bcl-2 family proteins are somatic mutations of the *bax* gene, a proapoptotic protein of the Bcl-2 family that plays a key role in the regulation of mitochondrial cytochrome *c* release. Colon cancer or hematopoietic malignancies that are mismatch repair-deficient were reported to harbor frameshift mutations or single nucleotide substitution of the *bax* gene ( [Rampino et al., 1997](#B68) ; [Kitada et al., 2002](#B40) ). Furthermore, genetic alterations in BH3-only proteins, which also belong to the Bcl-2 family and harbor a BH3 domain only, have been detected in malignant tumors, e. g., homozygous deletions of the *bim* gene in mantle cell lymphoma ( [Tagawa et al., 2005](#B81) ). The observation that *bid-* deficient mice spontaneously develop a myeloproliferative disease and subsequently a chronic myelomonocytic form of leukemia ( [Zinkel et al., 2003](#B97) ) further supports the notion that proapoptotic Bcl-2 proteins may exert tumor suppressive functions.

Moreover, the mitochondrial pathway of apoptosis can also be impaired in human cancers at the postmitochondrial level, for example by decreased or absent activity of Apaf-1 in melanoma and leukemia that contributes to caspase-3 activation via formation of the apoptosome complex ( [Soengas et al., 2001](#B75) ; [Fu et al., 2003](#B22) ). Abnormal expression of IAP proteins can impair effector caspase activation, thereby interfering with the common effector phase of both the death receptor and the mitochondrial pathway. Factors that can contribute to aberrant expression of IAP proteins include increased mRNA or protein expression ( [Tamm et al., 2000](#B85) ), enhanced protein stability, e. g., due to phosphorylation by Akt ( [Dan et al., 2004](#B14) ) or chromosomal translocation, for the *t* (11; 18; q21; q21) translocation that leads to aberrant *cIAP2* gene expression that frequently occurs in mucosa-associated lymphoid tissue (MALT) lymphoma ( [Dierlamm et al., 1999](#B16) ). Alternatively, loss of endogenous antagonists such as XAF1 can result in unrestrained signaling of IAP proteins ( [Tamm et al., 2000](#B85) ; [Chakravarti et al., 2002](#B9) ; [Byun et al., 2003](#B8) ). Overexpression of survivin can antagonize apoptosis by binding to Smac, thereby releasing XIAP to block caspase activation ( [Song et al., 2003](#B76) ; [Dohi et al., 2004](#B17) ).

#### Cancer therapeutics targeting Bcl-2 family proteins

A variety of approaches have been developed over the years to neutralize antiapoptotic Bcl-2 proteins. A prototype example is the design of small molecule inhibitors that interfere with the protein–protein interaction site of antiapoptotic Bcl-2 proteins (i. e., Bcl-2, Bcl-X L , Bcl-w) and the multidomain proteins Bax or Bak ( [Oltersdorf et al., 2005](#B61) ). The first generation compound originating from this development program is ABT-737 ( [Oltersdorf et al., 2005](#B61) ), which has been reported to either directly trigger apoptosis or enhance the sensitivity to apoptosis in combination treatments ( [Oltersdorf et al., 2005](#B61) ). To this end, ABT-737 acted together with various classical anticancer drugs to trigger apoptosis ( [Oltersdorf et al., 2005](#B61) ; [Konopleva et al., 2006](#B41) ; [Van Delft et al., 2006](#B91) ). High levels of Mcl-1 expression have been associated with resistance to ABT-737, as ABT-737 does not antagonize Mcl-1, another antiapoptotic member of the Bcl-2 family ( [Konopleva et al., 2006](#B41) ; [Van Delft et al., 2006](#B91) ). This Mcl-1-mediated resistance can be overcome by combination strategies, e. g., using proteasome inhibitors that trigger upregulation of Noxa, a BH3-only domain protein that specifically antagonizes Mcl-1, or alternatively CDK inhibitors (e. g., roscovitine, flavopiridol, seliciclib) or Raf/Mek inhibitors such as sorafenib, which all proved to augment the cytotoxicity following treatment with ABT-737 ( [Chen et al., 2001](#B10) ; [Konopleva et al., 2006](#B41) ; [Van Delft et al., 2006](#B91) ; [Lin et al., 2007](#B53) ; [Tahir et al., 2007](#B82) ).

Besides small molecule inhibitors, antisense strategies against antiapoptotic Bcl-2 proteins were developed ( [Tolcher et al., 2005](#B88) ). The most prominent example are Bcl-2 antisense oligonucleotides, which have been evaluated both as single agents as well as in combination with chemotherapy ( [Tolcher et al., 2005](#B88) ). Furthermore, BH3 peptides mimicking BH3-only domain proteins have been designed to directly engage the multidomain proapoptotic Bax and Bak proteins ( [Letai et al., 2002](#B50) ). Together, these tools to neutralize antiapoptotic Bcl-2 proteins are considered as promising strategies to engage the mitochondrial pathway of apoptosis in cancer cells.

### Exploiting “ Inhibitor of Apoptosis” Proteins

“ Inhibitor of apoptosis” proteins comprise a family of endogenous caspase inhibitors highly conserved in evolution ( [Lacasse et al., 2008](#B46) ). The human analogs include eight members, i. e., neuronal apoptosis inhibitory protein (NAIP/BIRC1/NLRB) cellular IAP1 (cIAP1)/human IAP2 (HIAP2)/BIRC2, cellular IAP2 (cIAP2)/human IAP1 (HIAP1)/BIRC3, X-linked IAP (XIAP)/BIRC4, survivin/BIRC5, BIR-containing ubiquitin conjugating enzyme (BRUCE)/apollon/BIRC6, livin/melanoma-IAP (ML-IAP)/BIRC7/KIAP, and testis-specific IAP (Ts-IAP)/hILP-2/BIRC8; [Lacasse et al., 2008](#B46) ). To be classified as IAP proteins, they contain at least one baculoviral IAP repeat (BIR) domain of 70–80 amino acids. Additional domains include the really interesting new gene (RING) domain harboring E3 ubiquitin ligase activity and the caspase activating and recruitment domain (CARD) domain, a motif for protein–protein interaction ( [Lacasse et al., 2008](#B46) ).

### Cancer Therapeutics Targeting “ Inhibitor of Apoptosis” Proteins

In order to design inhibitors that mimic the apoptosis-inducing properties of the endogenous IAP antagonist Smac, the groove of the BIR3 domain of XIAP has served as a scaffold that binds the native Smac protein upon its release into the cytosol ( [Shiozaki and Shi, 2004](#B73) ). For example, Smac peptides comprising the N-terminal amino acid stretch of Smac that is critical for its interaction with XIAP proved to trigger caspase activation and to prime cancer cells for apoptosis together with other cytotoxic stimuli ( [Fulda et al., 2002](#B30) ). For enhanced intracellular uptake such Smac peptides were coupled to various forms of carrier proteins ( [Arnt et al., 2002](#B2) ; [Fulda et al., 2002](#B30) ; [Yang et al., 2003](#B95) ). Furthermore, the design of Smac peptidomimetics binding to XIAP-BIR3, cIAP1-BIR3, cIAP2-BIR3, or livin-BIR domains resulted in potent apoptosis sensitizers in combination therapies, e. g., together with TRAIL, TNFα, or chemotherapeutics ( [Li et al., 2004](#B51) ; [Sun et al., 2004a](#B79) , [b](#B80) , [2005](#B77) , [2006](#B78) ; [Bockbrader et al., 2005](#B7) ; [Zobel et al., 2006](#B98) ). IAP antagonists also engage cell death pathways by initiating autoubiquitination of cIAPs leading to activation of non-canonical NF-κB and TNFα-mediated apoptosis ( [Petersen et al., 2007](#B65) ; [Varfolomeev et al., 2007](#B93) ; [Vince et al., 2007](#B94) ). Furthermore, antisense oligonucleotides targeting XIAP demonstrated antitumor activity in preclinical models both as monotherapy as well as in combination with anticancer drugs ( [Lacasse et al., 2005](#B45) , [2006](#B44) ). Taken together, strategies to antagonize IAP proteins present promising novel approaches to induce apoptotic cell death in cancer cells or to lower the threshold for the induction of apoptosis.

## Conclusion

Intact apoptosis programs are critically required for the antitumor activity of most current cancer therapies that are used in clinical oncology. However, apoptosis signaling pathways are frequently disturbed at various levels in human cancers. Further insights into the regulation of apoptosis signaling pathways in response to anticancer drug treatment will likely have important implications for the development of molecular targeted therapies. In addition, targeting apoptosis pathways in circulating tumor cells may present a means to interfere with metastasis. Several strategies to target elements of the apoptotic machinery in cancer cells have already progressed up to clinical evaluation. Such strategies may pave the avenue to more effective cancer treatments.

## Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Acknowledgments

Work in the author’s laboratory is supported by grants from the Deutsche Forschungsgemeinschaft, the Deutsche Krebshilfe, the Bundesministerium für Forschung und Technologie, Wilhelm-Sander-Stiftung, Else-Kröner-Fresenius Stiftung, Novartis Stiftung für therapeutische Forschung, the European Community (ApopTrain, APO-SYS), and IAP6/18.

## References

Adams, J. M., and Cory, S. (2007). The Bcl-2 apoptotic switch in cancer development and therapy. *Oncogene* 26, 1324–1337.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17322918) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17322918) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1210220)

Arnt, C. R., Chiorean, M. V., Heldebrant, M. P., Gores, G. J., and Kaufmann, S. H. (2002). Synthetic Smac/DIABLO peptides enhance the effects of chemotherapeutic agents by binding XIAP and cIAP1 in situ. *J. Biol. Chem.* 277, 44236–44243.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12218061) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12218061) | [CrossRef Full Text](http://dx.doi.org/10.1074/jbc.M207578200)

Ashkenazi, A. (2008a). Directing cancer cells to self-destruct with pro-apoptotic receptor agonists. *Nat. Rev. Drug Discov.* 7, 1001–1012.

[CrossRef Full Text](http://dx.doi.org/10.1038/nrd2637)

Ashkenazi, A. (2008b). Targeting the extrinsic apoptosis pathway in cancer. *Cytokine Growth Factor Rev.* 19, 325–331.

[CrossRef Full Text](http://dx.doi.org/10.1016/j.cytogfr.2008.04.001)

Ashkenazi, A., Pai, R. C., Fong, S., Leung, S., Lawrence, D. A., Marsters, S. A., Blackie, C., Chang, L., Mcmurtrey, A. E., Hebert, A., Deforge, L., Koumenis, I. L., Lewis, D., Harris, L., Bussiere, J., Koeppen, H., Shahrokh, Z., and Schwall, R. H. (1999). Safety and antitumor activity of recombinant soluble Apo2 ligand. *J. Clin. Invest.* 104, 155–162.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10411544) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=10411544) | [CrossRef Full Text](http://dx.doi.org/10.1172/JCI6926)

Belka, C., Schmid, B., Marini, P., Durand, E., Rudner, J., Faltin, H., Bamberg, M., Schulze-Osthoff, K., and Budach, W. (2001). Sensitization of resistant lymphoma cells to irradiation-induced apoptosis by the death ligand TRAIL. *Oncogene* 20, 2190–2196.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11360204) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11360204) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1204318)

Bockbrader, K. M., Tan, M., and Sun, Y. (2005). A small molecule Smac-mimic compound induces apoptosis and sensitizes TRAIL- and etoposide-induced apoptosis in breast cancer cells. *Oncogene* 24, 7381–7388.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16044155) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=16044155) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1208888)

Byun, D. S., Cho, K., Ryu, B. K., Lee, M. G., Kang, M. J., Kim, H. R., and Chi, S. G. (2003). Hypermethylation of XIAP-associated factor 1, a putative tumor suppressor gene from the 17p13. 2 locus, in human gastric adenocarcinomas. *Cancer Res.* 63, 7068–7075.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=14612497) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=14612497)

Chakravarti, A., Noll, E., Black, P. M., Finkelstein, D. F., Finkelstein, D. M., Dyson, N. J., and Loeffler, J. S. (2002). Quantitatively determined survivin expression levels are of prognostic value in human gliomas. *J. Clin. Oncol.* 20, 1063–1068.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11844831) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11844831) | [CrossRef Full Text](http://dx.doi.org/10.1200/JCO.20.4.1063)

Chen, Q., Gong, B., Mahmoud-Ahmed, A. S., Zhou, A., Hsi, E. D., Hussein, M., and Almasan, A. (2001). Apo2L/TRAIL and Bcl-2-related proteins regulate type I interferon-induced apoptosis in multiple myeloma. *Blood* 98, 2183–2192.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11568006) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11568006) | [CrossRef Full Text](http://dx.doi.org/10.1182/blood.V98.1.156)

Chinnaiyan, A. M., Prasad, U., Shankar, S., Hamstra, D. A., Shanaiah, M., Chenevert, T. L., Ross, B. D., and Rehemtulla, A. (2000). Combined effect of tumor necrosis factor-related apoptosis-inducing ligand and ionizing radiation in breast cancer therapy. *Proc. Natl. Acad. Sci. U. S. A.* 97, 1754–1759.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10677530) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=10677530) | [CrossRef Full Text](http://dx.doi.org/10.1073/pnas.030545097)

Chow, L. Q., Eckhardt, S. G., Gustafson, D. L., O’bryant, C., Hariharan, S., Diab, S., Fox, N. L., Corey, A., Padavic, K., and Brown, M. (2006). HGS-ETR1, an antibody targeting TRAIL-R1, in combination with paclitaxel and carboplatin in patients with advanced solid malignancies: results of a phase 1 and PK study. *J. Clin. Oncol.* 24, 2515.

[CrossRef Full Text](http://dx.doi.org/10.1200/JCO.2006.05.6879)

Chuntharapai, A., Dodge, K., Grimmer, K., Schroeder, K., Marsters, S. A., Koeppen, H., Ashkenazi, A., and Kim, K. J. (2001). Isotype-dependent inhibition of tumor growth in vivo by monoclonal antibodies to death receptor 4. *J. Immunol.* 166, 4891–4898.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11290766) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11290766)

Dan, H. C., Sun, M., Kaneko, S., Feldman, R. I., Nicosia, S. V., Wang, H. G., Tsang, B. K., and Cheng, J. Q. (2004). Akt phosphorylation and stabilization of X-linked inhibitor of apoptosis protein (XIAP). *J. Biol. Chem.* 279, 5405–5412.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=14645242) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=14645242) | [CrossRef Full Text](http://dx.doi.org/10.1074/jbc.M312044200)

Dechant, M. J., Fellenberg, J., Scheuerpflug, C. G., Ewerbeck, V., and Debatin, K. M. (2004). Mutation analysis of the apoptotic “ death-receptors” and the adaptors TRADD and FADD/MORT-1 in osteosarcoma tumor samples and osteosarcoma cell lines. *Int. J. Cancer* 109, 661–667.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=14999771) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=14999771) | [CrossRef Full Text](http://dx.doi.org/10.1002/ijc.20008)

Dierlamm, J., Baens, M., Wlodarska, I., Stefanova-Ouzounova, M., Hernandez, J. M., Hossfeld, D. K., De Wolf-Peeters, C., Hagemeijer, A., Van Den Berghe, H., and Marynen, P. (1999). The apoptosis inhibitor gene API2 and a novel 18q gene, MLT, are recurrently rearranged in the t(11; 18)(q21; q21) associated with mucosa-associated lymphoid tissue lymphomas. *Blood* 93, 3601–3609.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10339464) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=10339464)

Dohi, T., Okada, K., Xia, F., Wilford, C. E., Samuel, T., Welsh, K., Marusawa, H., Zou, H., Armstrong, R., Matsuzawa, S., Salvesen, G. S., Reed, J. C., and Altieri, D. C. (2004). An IAP-IAP complex inhibits apoptosis. *J. Biol. Chem.* 279, 34087–34090.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15218035) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15218035) | [CrossRef Full Text](http://dx.doi.org/10.1074/jbc.C400236200)

Ehrhardt, H., Fulda, S., Schmid, I., Hiscott, J., Debatin, K. M., and Jeremias, I. (2003). TRAIL induced survival and proliferation in cancer cells resistant towards TRAIL-induced apoptosis mediated by NF-kappaB. *Oncogene* 22, 3842–3852.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12813457) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12813457) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1206520)

Evan, G. I., and Vousden, K. H. (2001). Proliferation, cell cycle and apoptosis in cancer. *Nature* 411, 342–348.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11357141) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11357141) | [CrossRef Full Text](http://dx.doi.org/10.1038/35077213)

Fehm, T., Becker, S., Becker-Pergola, G., Sotlar, K., Gebauer, G., Durr-Storzer, S., Neubauer, H., Wallwiener, D., and Solomayer, E. F. (2006). Presence of apoptotic and nonapoptotic disseminated tumor cells reflects the response to neoadjuvant systemic therapy in breast cancer. *Breast Cancer Res.* 8, R60.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17062129) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17062129) | [CrossRef Full Text](http://dx.doi.org/10.1186/bcr1611)

Friesen, C., Fulda, S., and Debatin, K. M. (1997). Deficient activation of the CD95 (APO-1/Fas) system in drug-resistant cells. *Leukemia* 11, 1833–1841.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=9369415) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=9369415) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.leu.2400827)

Fu, W.-N., Bertoni, F., Kelsey, S. M., Mcelwaine, S. M., Cotter, F. E., Newland, A. C., and Jia, L. (2003). Role of DNA methylation in the suppression of Apaf-1 protein in human leukaemia. *Oncogene* 22, 451–455.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12545166) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12545166) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1206147)

Fulda, S. (2009a). Inhibitor of apoptosis proteins in hematological malignancies. *Leukemia* 23, 467–476.

[CrossRef Full Text](http://dx.doi.org/10.1038/leu.2008.329)

Fulda, S. (2009b). Tumor resistance to apoptosis. *Int. J. Cancer* 124, 511–515.

[CrossRef Full Text](http://dx.doi.org/10.1002/ijc.24064)

Fulda, S., and Debatin, K. M. (2006). Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy. *Oncogene* 25, 4798–4811.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16892092) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=16892092) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1209608)

Fulda, S., Galluzzi, L., and Kroemer, G. (2010). Targeting mitochondria for cancer therapy. *Nat. Rev. Drug Discov.* 9, 447–464.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20467424) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=20467424) | [CrossRef Full Text](http://dx.doi.org/10.1038/nrd3137)

Fulda, S., Kufer, M. U., Meyer, E., Van Valen, F., Dockhorn-Dworniczak, B., and Debatin, K. M. (2001). Sensitization for death receptor- or drug-induced apoptosis by re-expression of caspase-8 through demethylation or gene transfer. *Oncogene* 20, 5865–5877.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11593392) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11593392) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1204750)

Fulda, S., Meyer, E., and Debatin, K. M. (2000). Metabolic inhibitors sensitize for CD95 (APO-1/Fas)-induced apoptosis by down-regulating Fas-associated death domain-like interleukin 1-converting enzyme inhibitory protein expression. *Cancer Res.* 60, 3947–3956.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10919673) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=10919673)

Fulda, S., Scaffidi, C., Susin, S. A., Krammer, P. H., Kroemer, G., Peter, M. E., and Debatin, K. M. (1998). Activation of mitochondria and release of mitochondrial apoptogenic factors by betulinic acid. *J. Biol. Chem.* 273, 33942–33948.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=9852046) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=9852046) | [CrossRef Full Text](http://dx.doi.org/10.1074/jbc.273.51.33942)

Fulda, S., Wick, W., Weller, M., and Debatin, K. M. (2002). Smac agonists sensitize for Apo2L/TRAIL- or anticancer drug-induced apoptosis and induce regression of malignant glioma in vivo. *Nat. Med.* 8, 808–815.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12118245) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12118245)

Gliniak, B., and Le, T. (1999). Tumor necrosis factor-related apoptosis-inducing ligand’s antitumor activity in vivo is enhanced by the chemotherapeutic agent CPT-11. *Cancer Res.* 59, 6153–6158.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10626806) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=10626806)

Hao, C., Beguinot, F., Condorelli, G., Trencia, A., Van Meir, E. G., Yong, V. W., Parney, I. F., Roa, W. H., and Petruk, K. C. (2001). Induction and intracellular regulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) mediated apotosis in human malignant glioma cells. *Cancer Res.* 61, 1162–1170.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11221847) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11221847)

Harada, K., Toyooka, S., Shivapurkar, N., Maitra, A., Reddy, J. L., Matta, H., Miyajima, K., Timmons, C. F., Tomlinson, G. E., Mastrangelo, D., Hay, R. J., Chaudhary, P. M., and Gazdar, A. F. (2002). Deregulation of caspase 8 and 10 expression in pediatric tumors and cell lines. *Cancer Res.* 62, 5897–5901.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12384554) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12384554)

Herbst, R. S., Mendolson, D. S., Ebbinghaus, S., Gordon, M. S., O’dwyer, P., Lieberman, G., Ing, J., Kurzrock, R., Novotny, W., and Eckhardt, G. (2006). A phase I safety and pharmacokinetic (PK) study of recombinant Apo2L/TRAIL, an apoptosis-inducing protein in patients with advanced cancer. *J. Clin. Oncol.* 24, 3013.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16769985) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=16769985) | [CrossRef Full Text](http://dx.doi.org/10.1200/JCO.2005.04.9114)

Hopkins-Donaldson, S., Ziegler, A., Kurtz, S., Bigosch, C., Kandioler, D., Ludwig, C., Zangemeister-Wittke, U., and Stahel, R. (2003). Silencing of death receptor and caspase-8 expression in small cell lung carcinoma cell lines and tumors by DNA methylation. *Cell Death Differ.* 10, 356–364.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12700635) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12700635) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.cdd.4401157)

Ichikawa, K., Liu, W., Zhao, L., Wang, Z., Liu, D., Ohtsuka, T., Zhang, H., Mountz, J. D., Koopman, W. J., Kimberly, R. P., and Zhou, T. (2001). Tumoricidal activity of a novel anti-human DR5 monoclonal antibody without hepatocyte cytotoxicity. *Nat. Med.* 7, 954–960.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11479629) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11479629) | [CrossRef Full Text](http://dx.doi.org/10.1038/91000)

Jin, Z., Mcdonald, E. R. III, Dicker, D. T., and El-Deiry, W. S. (2004). Deficient tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) death receptor transport to the cell surface in human colon cancer cells selected for resistance to TRAIL-induced apoptosis. *J. Biol. Chem.* 279, 35829–35839.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15155747) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15155747) | [CrossRef Full Text](http://dx.doi.org/10.1074/jbc.M401056200)

Johnstone, R. W., Ruefli, A. A., and Lowe, S. W. (2002). Apoptosis: a link between cancer genetics and chemotherapy. *Cell* 108, 153–164.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11832206) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11832206) | [CrossRef Full Text](http://dx.doi.org/10.1016/S0092-8674(02)00625-6)

Keane, M. M., Rubinstein, Y., Cuello, M., Ettenberg, S. A., Banerjee, P., Nau, M. M., and Lipkowitz, S. (2000). Inhibition of NF-kappaB activity enhances TRAIL mediated apoptosis in breast cancer cell lines. *Breast Cancer Res. Treat.* 64, 211–219.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11194457) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11194457) | [CrossRef Full Text](http://dx.doi.org/10.1023/A: 1006458407515)

Kitada, S., Pedersen, I. M., Schimmer, A. D., and Reed, J. C. (2002). Dysregulation of apoptosis genes in hematopoietic malignancies. *Oncogene* 21, 3459–3474.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12032782) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12032782) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1205327)

Konopleva, M., Contractor, R., Tsao, T., Samudio, I., Ruvolo, P. P., Kitada, S., Deng, X., Zhai, D., Shi, Y.-X., Sneed, T., Verhaegen, M., Soengas, M., Ruvolo, V. R., Mcqueen, T., Schober, W. D., Watt, J. C., Jiffar, T., Ling, X., Marini, F. C., Harris, D., Dietrich, M., Estrov, Z., Mccubrey, J., May, W. S., Reed, J. C., and Andreeff, M. (2006). Mechanisms of apoptosis sensitivity and resistance to the BH3 mimetic ABT-737 in acute myeloid leukemia. *Cancer Cell* 10, 375–388.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17097560) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17097560) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.ccr.2006.10.006)

Kroemer, G., Galluzzi, L., and Brenner, C. (2007). Mitochondrial membrane permeabilization in cell death. *Physiol. Rev.* 87, 99–163.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17237344) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17237344) | [CrossRef Full Text](http://dx.doi.org/10.1152/physrev.00013.2006)

Krueger, A., Baumann, S., Krammer, P. H., and Kirchhoff, S. (2001). FLICE-inhibitory proteins: regulators of death receptor-mediated apoptosis. *Mol. Cell. Biol.* 21, 8247–8254.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11713262) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11713262) | [CrossRef Full Text](http://dx.doi.org/10.1128/MCB.21.24.8247-8254.2001)

Lacasse, E. C., Cherton-Horvat, G. G., Hewitt, K. E., Jerome, L. J., Morris, S. J., Kandimalla, E. R., Yu, D., Wang, H., Wang, W., Zhang, R., Agrawal, S., Gillard, J. W., and Durkin, J. P. (2006). Preclinical characterization of AEG35156/GEM 640, a second-generation antisense oligonucleotide targeting X-linked inhibitor of apoptosis. *Clin. Cancer Res.* 12, 5231–5241.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16951243) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=16951243) | [CrossRef Full Text](http://dx.doi.org/10.1158/1078-0432.CCR-06-0608)

Lacasse, E. C., Kandimalla, E. R., Winocour, P., Sullivan, T., Agrawal, S., Gillard, J. W., and Durkin, J. (2005). Application of XIAP antisense to cancer and other proliferative disorders: development of AEG35156/GEM640. *Ann. N. Y. Acad. Sci.* 1058, 215–234.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16394139) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=16394139) | [CrossRef Full Text](http://dx.doi.org/10.1196/annals.1359.032)

Lacasse, E. C., Mahoney, D. J., Cheung, H. H., Plenchette, S., Baird, S., and Korneluk, R. G. (2008). IAP-targeted therapies for cancer. *Oncogene* 27, 6252–6275.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18931692) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=18931692) | [CrossRef Full Text](http://dx.doi.org/10.1038/onc.2008.302)

Lacour, S., Micheau, O., Hammann, A., Drouineaud, V., Tschopp, J., Solary, E., and Dimanche-Boitrel, M. T. (2003). Chemotherapy enhances TNF-related apoptosis-inducing ligand DISC assembly in HT29 human colon cancer cells. *Oncogene* 22, 1807–1816.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12660816) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12660816) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1206127)

Larson, C. J., Moreno, J. G., Pienta, K. J., Gross, S., Repollet, M., O’hara S, M., Russell, T., and Terstappen, L. W. (2004). Apoptosis of circulating tumor cells in prostate cancer patients. *Cytometry A* 62, 46–53.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15472900) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15472900) | [CrossRef Full Text](http://dx.doi.org/10.1002/cyto.a.20073)

Lawrence, D., Shahrokh, Z., Marsters, S., Achilles, K., Shih, D., Mounho, B., Hillan, K., Totpal, K., Deforge, L., Schow, P., Hooley, J., Sherwood, S., Pai, R., Leung, S., Khan, L., Gliniak, B., Bussiere, J., Smith, C. A., Strom, S. S., Kelley, S., Fox, J. A., Thomas, D., and Ashkenazi, A. (2001). Differential hepatocyte toxicity of recombinant Apo2L/TRAIL versions. *Nat. Med.* 7, 383–385.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11283636) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11283636) | [CrossRef Full Text](http://dx.doi.org/10.1038/86397)

Letai, A., Bassik, M. C., Walensky, L. D., Sorcinelli, M. D., Weiler, S., and Korsmeyer, S. J. (2002). Distinct BH3 domains either sensitize or activate mitochondrial apoptosis, serving as prototype cancer therapeutics. *Cancer Cell* 2, 183–192.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12242151) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12242151) | [CrossRef Full Text](http://dx.doi.org/10.1016/S1535-6108(02)00127-7)

Li, L., Thomas, R. M., Suzuki, H., De Brabander, J. K., Wang, X., and Harran, P. G. (2004). A small molecule Smac mimic potentiates TRAIL- and TNFalpha-mediated cell death. *Science* 305, 1471–1474.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15353805) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15353805) | [CrossRef Full Text](http://dx.doi.org/10.1126/science.1098674)

Lin, T., Huang, X., Gu, J., Zhang, L., Roth, J. A., Xiong, M., Curley, S. A., Yu, Y., Hunt, K. K., and Fang, B. (2002). Long-term tumor-free survival from treatment with the GFP-TRAIL fusion gene expressed from the hTERT promoter in breast cancer cells. *Oncogene* 21, 8020–8028.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12439752) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12439752) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1205518)

Lin, X., Morgan-Lappe, S., Huang, X., Li, L., Zakula, D. M., Vernetti, L. A., Fesik, S. W., and Shen, Y. (2007). “ Seed” analysis of off-target siRNAs reveals an essential role of Mcl-1 in resistance to the small-molecule Bcl-2/Bcl-XL inhibitor ABT-737. *Oncogene* 26, 3972–3979.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17173063) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17173063) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1210166)

Logue, S. E., and Martin, S. J. (2008). Caspase activation cascades in apoptosis. *Biochem. Soc. Trans.* 36, 1–9.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18208375) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=18208375) | [CrossRef Full Text](http://dx.doi.org/10.1042/BST0360001)

Longley, D. B., Wilson, T. R., Mcewan, M., Allen, W. L., Mcdermott, U., Galligan, L., and Johnston, P. G. (2006). c-FLIP inhibits chemotherapy-induced colorectal cancer cell death. *Oncogene* 25, 838–848.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16247474) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=16247474) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1209122)

Maecker, H. L., Yun, Z., Maecker, H. T., and Giaccia, A. J. (2002). Epigenetic changes in tumor Fas levels determine immune escape and response to therapy. *Cancer Cell* 2, 139–148.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12204534) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12204534) | [CrossRef Full Text](http://dx.doi.org/10.1016/S1535-6108(02)00095-8)

Makin, G., and Dive, C. (2001). Apoptosis and cancer chemotherapy. *Trends Cell Biol.* 11, S22–S26.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11684438) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11684438) | [CrossRef Full Text](http://dx.doi.org/10.1016/S0962-8924(01)02124-9)

Meng, R. D., and El-Deiry, W. S. (2001). p53-independent upregulation of KILLER/DR5 TRAIL receptor expression by glucocorticoids and interferon-gamma. *Exp. Cell Res.* 262, 154–169.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11139340) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11139340) | [CrossRef Full Text](http://dx.doi.org/10.1006/excr.2000.5073)

Mom, C. H., Sleijfer, S., Gietema, J. A., Sneller, V., Fox, N. L., Lo, L., Uges, D. R. A., Loos, W., De Vries, E. G. E., and Verweij, J. (2005). A phase 1 study of HGS-ETR1, a fully human agonistic monoclonal antibody to the TRAIL-R1 in combination with gemcitabine and cisplatin in subjects with advanced solid malignancies [abstract C74]. *Clin. Cancer Res.* 11, 9117S.

Nagane, M., Pan, G., Weddle, J. J., Dixit, V. M., Cavenee, W. K., and Huang, H. J. (2000). Increased death receptor 5 expression by chemotherapeutic agents in human gliomas causes synergistic cytotoxicity with tumor necrosis factor-related apoptosis-inducing ligand in vitro and in vivo. *Cancer Res.* 60, 847–853.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10706092) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=10706092)

Oltersdorf, T., Elmore, S. W., Shoemaker, A. R., Armstrong, R. C., Augeri, D. J., Belli, B. A., Bruncko, M., Deckwerth, T. L., Dinges, J., Hajduk, P. J., Joseph, M. K., Kitada, S., Korsmeyer, S. J., Kunzer, A. R., Letai, A., Li, C., Mitten, M. J., Nettesheim, D. G., Ng, S., Nimmer, P. M., O’connor, J. M., Oleksijew, A., Petros, A. M., Reed, J. C., Shen, W., Tahir, S. K., Thompson, C. B., Tomaselli, K. J., Wang, B., Wendt, M. D., Zhang, H., Fesik, S. W., and Rosenberg, S. H. (2005). An inhibitor of Bcl-2 family proteins induces regression of solid tumours. *Nature* 435, 677–681.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15902208) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15902208) | [CrossRef Full Text](http://dx.doi.org/10.1038/nature03579)

Pai, S. I., Wu, G. S., Ozoren, N., Wu, L., Jen, J., Sidransky, D., and El-Deiry, W. S. (1998). Rare loss-of-function mutation of a death receptor gene in head and neck cancer. *Cancer Res.* 58, 3513–3518.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=9721851) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=9721851)

Patnaik, A., Wakelee, H., Mita, M., Fitzgerald, A., Hill, M., Fox, N., Howard, T., Ullrich, S., Tolcher, A., and Sikic, B. (2006). HGS-ETR2 – a fully human monoclonal antibody to TRAIL-R2: results of a phase I trial in patients with advanced solid tumors. *J. Clin. Oncol.* 24, 3012.

Petak, I., Danam, R. P., Tillman, D. M., Vernes, R., Howell, S. R., Berczi, L., Kopper, L., Brent, T. P., and Houghton, J. A. (2003). Hypermethylation of the gene promoter and enhancer region can regulate Fas expression and sensitivity in colon carcinoma. *Cell Death Differ.* 10, 211–217.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12700649) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12700649) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.cdd.4401132)

Petersen, S. L., Wang, L., Yalcin-Chin, A., Li, L., Peyton, M., Minna, J., Harran, P., and Wang, X. (2007). Autocrine TNFalpha signaling renders human cancer cells susceptible to Smac-mimetic-induced apoptosis. *Cancer Cell* 12, 445–456.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17996648) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17996648) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.ccr.2007.08.029)

Pingoud-Meier, C., Lang, D., Janss, A. J., Rorke, L. B., Phillips, P. C., Shalaby, T., and Grotzer, M. A. (2003). Loss of caspase-8 protein expression correlates with unfavorable survival outcome in childhood medulloblastoma. *Clin. Cancer Res.* 9, 6401–6409.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=14695141) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=14695141)

Pitti, R. M., Marsters, S. A., Lawrence, D. A., Roy, M., Kischkel, F. C., Dowd, P., Huang, A., Donahue, C. J., Sherwood, S. W., Baldwin, D. T., Godowski, P. J., Wood, W. I., Gurney, A. L., Hillan, K. J., Cohen, R. L., Goddard, A. D., Botstein, D., and Ashkenazi, A. (1998). Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer. *Nature* 396, 699–703.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=9872321) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=9872321) | [CrossRef Full Text](http://dx.doi.org/10.1038/25387)

Rampino, N., Yamamoto, H., Ionov, Y., Li, Y., Sawai, H., Reed, J. C., and Perucho, M. (1997). Somatic frameshift mutations in the BAX gene in colon cancers of the microsatellite mutator phenotype. *Science* 275, 967–969.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=9020077) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=9020077) | [CrossRef Full Text](http://dx.doi.org/10.1126/science.275.5302.967)

Ray, S., and Almasan, A. (2003). Apoptosis induction in prostate cancer cells and xenografts by combined treatment with Apo2 ligand/tumor necrosis factor-related apoptosis-inducing ligand and CPT-11. *Cancer Res.* 63, 4713–4723.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12907654) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12907654)

Rohn, T. A., Wagenknecht, B., Roth, W., Naumann, U., Gulbins, E., Krammer, P. H., Walczak, H., and Weller, M. (2001). CCNU-dependent potentiation of TRAIL/Apo2L-induced apoptosis in human glioma cells is p53-independent but may involve enhanced cytochrome c release. *Oncogene* 20, 4128–4137.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11464279) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11464279) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1204534)

Roth, W., Isenmann, S., Nakamura, M., Platten, M., Wick, W., Kleihues, P., Bahr, M., Ohgaki, H., Ashkenazi, A., and Weller, M. (2001). Soluble decoy receptor 3 is expressed by malignant gliomas and suppresses CD95 ligand-induced apoptosis and chemotaxis. *Cancer Res.* 61, 2759–2765.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11289159) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11289159)

Sheikh, M. S., Huang, Y., Fernandez-Salas, E. A., El-Deiry, W. S., Friess, H., Amundson, S., Yin, J., Meltzer, S. J., Holbrook, N. J., and Fornace, A. J. Jr. (1999). The antiapoptotic decoy receptor TRID/TRAIL-R3 is a p53-regulated DNA damage-inducible gene that is overexpressed in primary tumors of the gastrointestinal tract. *Oncogene* 18, 4153–4159.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10435597) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=10435597) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1202763)

Shiozaki, E. N., and Shi, Y. (2004). Caspases, IAPs and Smac/DIABLO: mechanisms from structural biology. *Trends Biochem. Sci.* 29, 486–494.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15337122) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15337122) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.tibs.2004.07.003)

Singh, T. R., Shankar, S., Chen, X., Asim, M., and Srivastava, R. K. (2003). Synergistic interactions of chemotherapeutic drugs and tumor necrosis factor-related apoptosis-inducing ligand/Apo-2 ligand on apoptosis and on regression of breast carcinoma in vivo. *Cancer Res.* 63, 5390–5400.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=14500373) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=14500373)

Soengas, M. S., Capodieci, P., Polsky, D., Mora, J., Esteller, M., Opitz-Araya, X., Mccombie, R., Herman, J. G., Gerald, W. L., Lazebnik, Y. A., Cordon-Cardo, C., and Lowe, S. W. (2001). Inactivation of the apoptosis effector Apaf-1 in malignant melanoma. *Nature* 409, 207–211.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11196646) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11196646) | [CrossRef Full Text](http://dx.doi.org/10.1038/35051606)

Song, Z., Yao, X., and Wu, M. (2003). Direct interaction between survivin and Smac/DIABLO is essential for the anti-apoptotic activity of survivin during taxol-induced apoptosis. *J. Biol. Chem.* 278, 23130–23140.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12660240) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12660240) | [CrossRef Full Text](http://dx.doi.org/10.1074/jbc.M308983200)

Sun, H., Nikolovska-Coleska, Z., Chen, J., Yang, C. Y., Tomita, Y., Pan, H., Yoshioka, Y., Krajewski, K., Roller, P. P., and Wang, S. (2005). Structure-based design, synthesis and biochemical testing of novel and potent Smac peptido-mimetics. *Bioorg. Med. Chem. Lett.* 15, 793–797.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15664859) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15664859) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.bmcl.2005.03.088)

Sun, H., Nikolovska-Coleska, Z., Lu, J., Qiu, S., Yang, C. Y., Gao, W., Meagher, J., Stuckey, J., and Wang, S. (2006). Design, synthesis, and evaluation of a potent, cell-permeable, conformationally constrained second mitochondria derived activator of caspase (Smac) mimetic. *J. Med. Chem.* 49, 7916–7920.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17181177) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17181177) | [CrossRef Full Text](http://dx.doi.org/10.1021/jm051141k)

Sun, H., Nikolovska-Coleska, Z., Yang, C. Y., Xu, L., Liu, M., Tomita, Y., Pan, H., Yoshioka, Y., Krajewski, K., Roller, P. P., and Wang, S. (2004a). Structure-based design of potent, conformationally constrained Smac mimetics. *J. Am. Chem. Soc.* 126, 16686–16687.

[CrossRef Full Text](http://dx.doi.org/10.1021/ja038756w)

Sun, H., Nikolovska-Coleska, Z., Yang, C. Y., Xu, L., Tomita, Y., Krajewski, K., Roller, P. P., and Wang, S. (2004b). Structure-based design, synthesis, and evaluation of conformationally constrained mimetics of the second mitochondria-derived activator of caspase that target the X-linked inhibitor of apoptosis protein/caspase-9 interaction site. *J. Med. Chem.* 47, 4147–4150.

[CrossRef Full Text](http://dx.doi.org/10.1021/jm0499108)

Tagawa, H., Karnan, S., Suzuki, R., Matsuo, K., Zhang, X., Ota, A., Morishima, Y., Nakamura, S., and Seto, M. (2005). Genome-wide array-based CGH for mantle cell lymphoma: identification of homozygous deletions of the proapoptotic gene BIM. *Oncogene* 24, 1348–1358.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15608680) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15608680) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1208300)

Tahir, S. K., Yang, X., Anderson, M. G., Morgan-Lappe, S. E., Sarthy, A. V., Chen, J., Warner, R. B., Ng, S.-C., Fesik, S. W., Elmore, S. W., Rosenberg, S. H., and Tse, C. (2007). Influence of Bcl-2 family members on the cellular response of small-cell lung cancer cell lines to ABT-737. *Cancer Res.* 67, 1176–1183.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17283153) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17283153) | [CrossRef Full Text](http://dx.doi.org/10.1158/0008-5472.CAN-06-2203)

Takeda, K., Yamaguchi, N., Akiba, H., Kojima, Y., Hayakawa, Y., Tanner, J. E., Sayers, T. J., Seki, N., Okumura, K., Yagita, H., and Smyth, M. J. (2004). Induction of tumor-specific T cell immunity by anti-DR5 antibody therapy. *J. Exp. Med.* 199, 437–448.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=14769851) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=14769851) | [CrossRef Full Text](http://dx.doi.org/10.1084/jem.20031457)

Takimoto, R., and El-Deiry, W. S. (2000). Wild-type p53 transactivates the KILLER/DR5 gene through an intronic sequence-specific DNA-binding site. *Oncogene* 19, 1735–1743.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10777207) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=10777207) | [CrossRef Full Text](http://dx.doi.org/10.1038/sj.onc.1203489)

Tamm, I., Kornblau, S. M., Segall, H., Krajewski, S., Welsh, K., Kitada, S., Scudiero, D. A., Tudor, G., Qui, Y. H., Monks, A., Andreeff, M., and Reed, J. C. (2000). Expression and prognostic significance of IAP-family genes in human cancers and myeloid leukemias. *Clin. Cancer Res.* 6, 1796–1803.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10815900) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=10815900)

Taylor, R. C., Cullen, S. P., and Martin, S. J. (2008). Apoptosis: controlled demolition at the cellular level. *Nat. Rev. Mol. Cell Biol.* 9, 231–241.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18073771) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=18073771) | [CrossRef Full Text](http://dx.doi.org/10.1038/nrg2311)

Teitz, T., Wei, T., Valentine, M. B., Vanin, E. F., Grenet, J., Valentine, V. A., Behm, F. G., Look, A. T., Lahti, J. M., and Kidd, V. J. (2000). Caspase 8 is deleted or silenced preferentially in childhood neuroblastomas with amplification of MYCN. *Nat. Med.* 6, 529–535.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10802708) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=10802708) | [CrossRef Full Text](http://dx.doi.org/10.1038/75007)

Tolcher, A. W., Chi, K., Kuhn, J., Gleave, M., Patnaik, A., Takimoto, C., Schwartz, G., Thompson, I., Berg, K., D’aloisio, S., Murray, N., Frankel, S. R., Izbicka, E., and Rowinsky, E. (2005). A phase II, pharmacokinetic, and biological correlative study of oblimersen sodium and docetaxel in patients with hormone-refractory prostate cancer. *Clin. Cancer Res.* 11, 3854–3861.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15897586) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15897586) | [CrossRef Full Text](http://dx.doi.org/10.1158/1078-0432.CCR-04-2145)

Tolcher, A. W., Mita, M., Meropol, N. J., Von Mehren, M., Patnaik, A., Padavic, K., Hill, M., Mays, T., Mccoy, T., Fox, N. L., Halpern, W., Corey, A., and Cohen, R. B. (2007). Phase I pharmacokinetic and biologic correlative study of mapatumumab, a fully human monoclonal antibody with agonist activity to tumor necrosis factor-related apoptosis-inducing ligand receptor-1. *J. Clin. Oncol.* 25, 1390–1395.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17416859) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17416859) | [CrossRef Full Text](http://dx.doi.org/10.1200/JCO.2006.08.8898)

Tsujimoto, Y., Finger, L. R., Yunis, J., Nowell, P. C., and Croce, C. M. (1984). Cloning of the chromosome breakpoint of neoplastic B cells with the t(14; 18) chromosome translocation. *Science* 226, 1097–1099.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=6093263) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=6093263) | [CrossRef Full Text](http://dx.doi.org/10.1126/science.6093263)

Van Delft, M. F., Wei, A. H., Mason, K. D., Vandenberg, C. J., Chen, L., Czabotar, P. E., Willis, S. N., Scott, C. L., Day, C. L., Cory, S., Adams, J. M., Roberts, A. W., and Huang, D. C. (2006). The BH3 mimetic ABT-737 targets selective Bcl-2 proteins and efficiently induces apoptosis via Bak/Bax if Mcl-1 is neutralized. *Cancer Cell* 10, 389–399.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17097561) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17097561) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.ccr.2006.08.027)

Van Noesel, M. M., Van Bezouw, S., Salomons, G. S., Voute, P. A., Pieters, R., Baylin, S. B., Herman, J. G., and Versteeg, R. (2002). Tumor-specific down-regulation of the tumor necrosis factor-related apoptosis-inducing ligand decoy receptors DcR1 and DcR2 is associated with dense promoter hypermethylation. *Cancer Res.* 62, 2157–2161.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11929838) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11929838)

Varfolomeev, E., Blankenship, J. W., Wayson, S. M., Fedorova, A. V., Kayagaki, N., Garg, P., Zobel, K., Dynek, J. N., Elliott, L. O., Wallweber, H. J., Flygare, J. A., Fairbrother, W. J., Deshayes, K., Dixit, V. M., and Vucic, D. (2007). IAP antagonists induce autoubiquitination of c-IAPs, NF-kappaB activation, and TNFalpha-dependent apoptosis. *Cell* 131, 669–681.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18022362) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=18022362) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.cell.2007.10.030)

Vince, J. E., Wong, W. W., Khan, N., Feltham, R., Chau, D., Ahmed, A. U., Benetatos, C. A., Chunduru, S. K., Condon, S. M., Mckinlay, M., Brink, R., Leverkus, M., Tergaonkar, V., Schneider, P., Callus, B. A., Koentgen, F., Vaux, D. L., and Silke, J. (2007). IAP antagonists target cIAP1 to induce TNFalpha-dependent apoptosis. *Cell* 131, 682–693.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18022363) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=18022363) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.cell.2007.10.037)

Yang, L., Mashima, T., Sato, S., Mochizuki, M., Sakamoto, H., Yamori, T., Oh-Hara, T., and Tsuruo, T. (2003). Predominant suppression of apoptosome by inhibitor of apoptosis protein in non-small cell lung cancer H460 cells: therapeutic effect of a novel polyarginine-conjugated Smac peptide. *Cancer Res.* 63, 831–837.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12591734) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12591734)

Younes, A., and Aggarwall, B. B. (2003). Clinical implications of the tumor necrosis factor family in benign and malignant hematologic disorders. *Cancer* 98, 458–467.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12879461) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12879461) | [CrossRef Full Text](http://dx.doi.org/10.1002/cncr.11524)

Zinkel, S. S., Ong, C. C., Ferguson, D. O., Iwasaki, H., Akashi, K., Bronson, R. T., Kutok, J. L., Alt, F. W., and Korsmeyer, S. J. (2003). Proapoptotic BID is required for myeloid homeostasis and tumor suppression. *Genes Dev.* 17, 229–239.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12533511) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12533511) | [CrossRef Full Text](http://dx.doi.org/10.1101/gad.1045603)

Zobel, K., Wang, L., Varfolomeev, E., Franklin, M. C., Elliott, L. O., Wallweber, H. J., Okawa, D. C., Flygare, J. A., Vucic, D., Fairbrother, W. J., and Deshayes, K. (2006). Design, synthesis, and biological activity of a potent Smac mimetic that sensitizes cancer cells to apoptosis by antagonizing IAPs. *ACS Chem. Biol.* 1, 525–533.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17168540) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17168540) | [CrossRef Full Text](http://dx.doi.org/10.1021/cb600276q)