

## **Survivin: Key Regulator of Mitosis and Apoptosis and Novel Target for Cancer Therapeutics**

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**Abstract** Survivin, a member of the family of inhibitor of apoptosis proteins, functions as a key regulator of mitosis and programmed cell death. Initially, survivin was described as an inhibitor of caspase-9. However, over the last years, research studies have shown that the role of survivin in cancer pathogenesis is not limited to apoptosis inhibition but also involves the regulation of the mitotic spindle checkpoint and the promotion of angiogenesis and chemoresistance. Survivin gene expression is transcriptionally repressed by wild-type p53 and can be deregulated in cancer by several mechanisms, including gene amplification, hypomethylation, increased promoter activity, and loss of p53 function. This article reviews the multiple functions of survivin in the regulation of apoptosis, the promotion of tumorigenesis, and the development of survivin inhibitors as a novel anticancer therapeutic strategy.

### **Background**

Apoptosis, or programmed cellular death, results from the activation of elements belonging to a family of 14 cysteine proteases called caspases, enzymes that cleave cellular proteins, including other caspases, at aspartic acid residues (1). Caspases are initially synthesized as zymogens and undergo a cascade of proteolysis activation classically triggered by two distinct pathways termed the intrinsic and extrinsic pathways. The two pathways converge at caspase-3 and follow a common process of activating the "executioner" caspases. The final result is the cleavage of essential substrates for cell survival, such as cytoskeletal proteins, DNA repair proteins, and inhibitory subunits of endonucleases, and, subsequently, cell death (2). Apoptosis is tightly regulated by a fine-tuned balance between proapoptotic and antiapoptotic factors. One class of molecules that block apoptosis by direct binding to caspases is the inhibitor of apoptosis proteins (IAP; reviewed in ref. 3).

Targeting the apoptotic pathways for cancer treatment is supported by several findings emphasizing the role of aberrant apoptosis in tumorigenesis and also resistance to anticancer treatment. Evasion from apoptosis is critical for tumor growth and a hallmark of cancer cells (4). Some conventional antitumor therapies, including DNA-damaging and antimicrotubule agents, exert their function by activating the intrinsic apoptosis pathway (5). It was also shown that the mutation

of p53, the most frequent gene mutation in solid tumors, may render the cells resistant to the activation of the intrinsic apoptotic pathway. The dysregulation of apoptosis, including the overexpression of antiapoptotic *Bcl-2* homologues (6, 7), the diminished expression of apoptotic protease activating factor 1(8), and the overexpression of survivin (9) have all been reported to contribute to drug resistance. Therefore, targeting apoptotic pathways may have a direct role in inducing tumor cell death, circumventing drug resistance, and sensitizing cancer cells to apoptosis induced by other therapies.

### **Pathway Overview**

IAPs constitute a class of regulatory proteins with nine family members: X-linked IAP, cIAP1, cIAP2, neuronal apoptosis inhibitor protein, melanoma IAP, IAP-like protein 2, livin, apollon, and survivin (10–12). IAPs are inhibited by Smac/DIABLO, which is released from the mitochondria along with the cytochrome *c*. Survivin, the smallest member of the IAP family, is a 142-amino acid, 16.5-kDa protein coded by a single-copy gene located on the human 17q25 chromosome. Structurally, survivin contains a single repeat of the characteristic baculovirus–inhibitor of apoptosis domains that are essential for the caspase-inhibitory function (13–15) as well as an extended carboxy-terminal  $\alpha$ -helical coiled coil but no RING finger or other identifiable domain (13). X-ray crystallography studies showed that survivin molecules are identified as homodimers in solution (16). The synthesis and degradation of survivin in normal tissues is modulated in a cell-cycle–dependent manner. Survivin transcription is controlled by specific sequences in the promoter region, increases during G<sub>1</sub>, and reaches a peak in G<sub>2</sub>-M (17, 18). The regulation of survivin expression and function is complex and can occur at various levels, including transcription, differential splicing, protein degradation, and intracellular sequestration via different ligands. The expression of survivin is up-regulated at a transcriptional level by the nuclear factor- $\kappa$ B, which, in turn,

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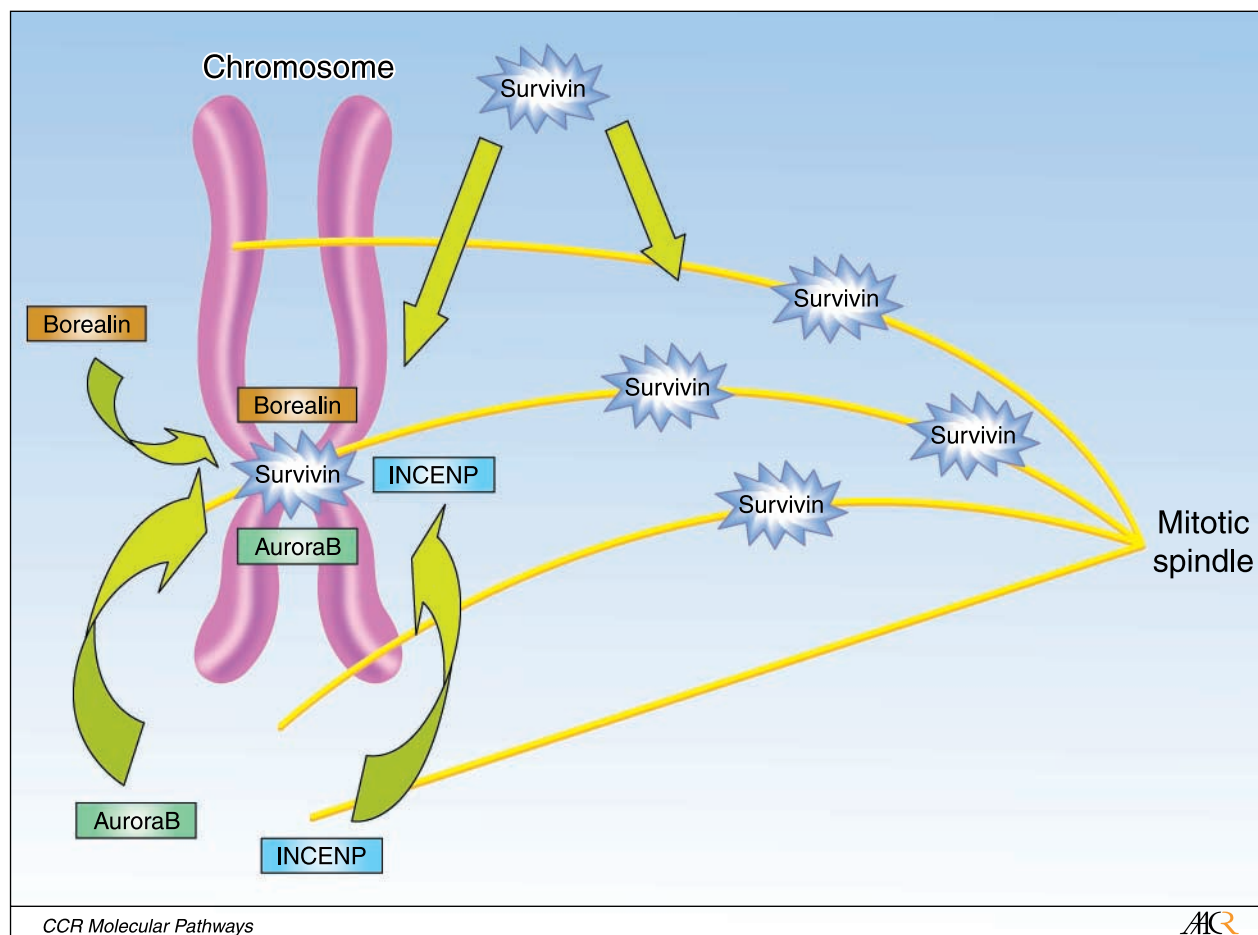
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can be activated indirectly by growth factors via the phosphatidylinositol 3-kinase/Akt pathway (19). Additionally, insulin-like growth factor I/mTOR signaling has been reported to up-regulate survivin via rapid changes in mRNA translation (20). Other factors involved in survivin up-regulation are members of the *Ras* oncogene family, signal transducer and activator of transcription 3, and the antiapoptotic factor Wnt-2 (21–23). On the other hand, survivin is one of the genes repressed at the transcriptional level by wild-type p53 and p75 (24–26). Following transcription, the alternative splicing of survivin mRNA in at least four distinct regions yields isoforms with different expression patterns and abilities to prevent apoptosis, which produces an additional level of complexity in the regulation of survivin function (27). Finally, survivin degradation occurs via the ubiquitin-proteasome pathway in the G<sub>1</sub> phase of the cell cycle and is stabilized when bound to heat shock protein 90 (28–30).

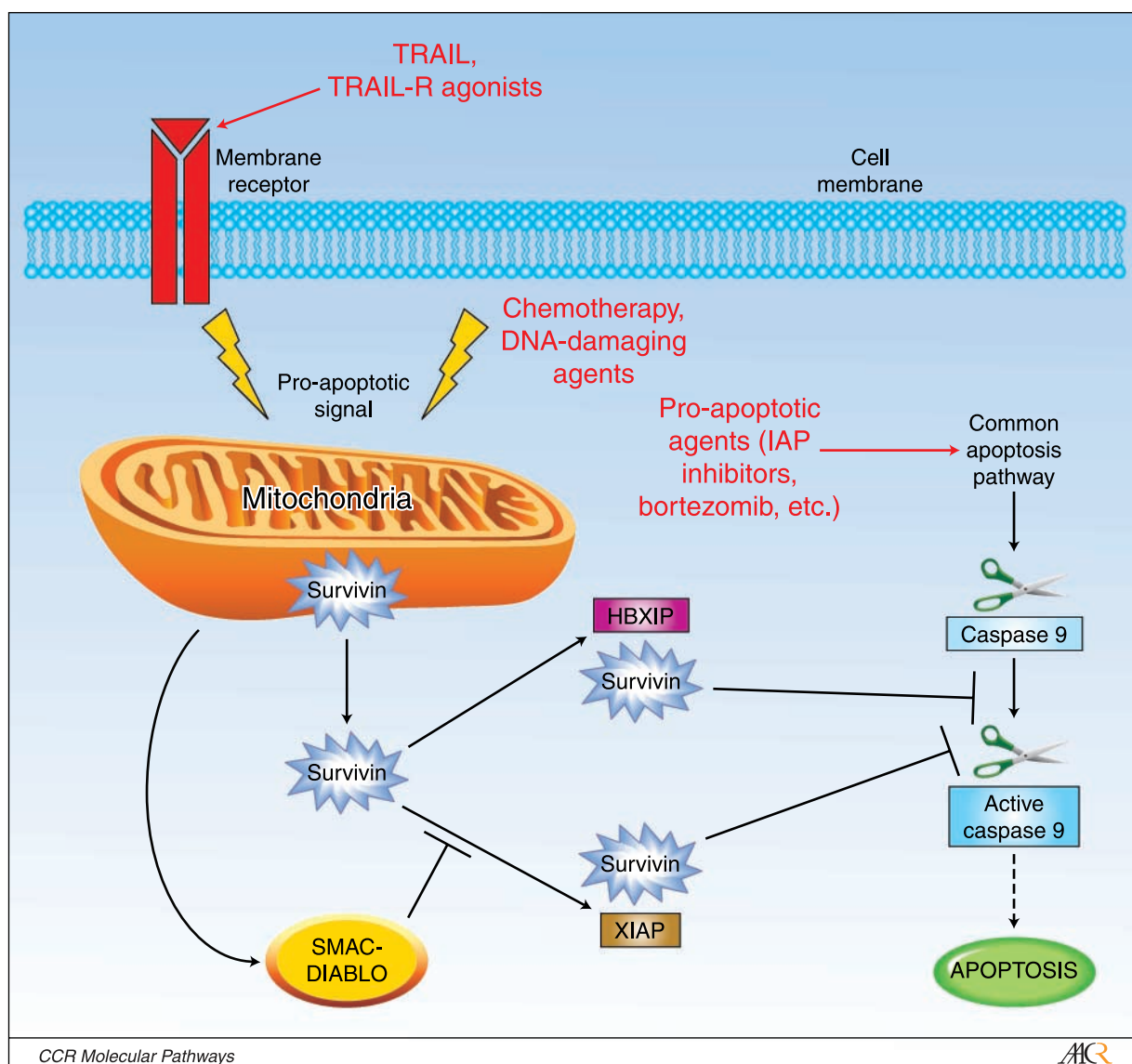
The main established functions of survivin are the regulation of cell division and the inhibition of apoptosis (Figs. 1 and 2). The role of survivin in cell division is unanimously accepted. The tightly cell-cycle-dependent control of the synthesis and degradation of survivin in normal tissues strongly supports its role in mitotic regulation. During mitosis, survivin functions in a narrow time window at metaphase and anaphase and localizes to two main subcellular pools. One pool of survivin

is directly associated with polymerized tubulin. This pool involves centrosomes, microtubules of the metaphase and anaphase spindle, and the remnants of the mitotic apparatus, and suggests a regulation of microtubule dynamics (15, 31–33). A second pool of survivin localizes to the kinetochores of metaphase chromosomes. In this pool, survivin is associated with regulators of cytokinesis, such as Aurora B kinase, INCENP, and Borealin/Dasra (34–37), which supports a role for survivin as a subunit of the chromosomal passenger complex that is essential for proper chromosome segregation and cytokinesis (reviewed in ref. 38). Although the functions of survivin as a regulator of microtubule dynamics and chromosomal passenger protein may seem incompatible, a recently proposed theory of survivin as a central regulator of spindle formation may reconcile the two. According to this model, survivin mediates the proper targeting of chromosomal passenger proteins to kinetochores and, in addition, stabilizes the microtubules, thus contributing to bipolar spindle formation (33).

The role of survivin in apoptosis inhibition has been the subject of controversy. Initially, survivin and other IAPs were postulated to selectively bind to and promote the degradation of active caspase-3, caspase-7, and caspase-9 (14). In support of this model, it was shown that survivin is inhibited by Smac/DIABLO, thus placing survivin in a central position in the



**Fig. 1.** Function of survivin in mitosis. Survivin is a component of the chromosomal passenger complex that is essential for proper chromosome segregation and cytokinesis. Additionally, a distinct pool of survivin is directly associated with polymerized tubulin and contributes to the regulation of microtubule dynamics.



**Fig. 2.** Function of survivin as inhibitor of apoptosis. Upon activation of proapoptotic cell signaling, survivin is released from the mitochondria in the cytosol and inhibits active caspase-9. This function requires association with the hepatitis B X-interacting protein and/or with X-linked IAP and is inhibited by Smac/Diablo.

dynamic balance of proapoptotic and antiapoptotic factors (39). However, this model was challenged by the observations that survivin lacks the structural motifs that mediate binding to caspases that are present in other IAPs and that the role of survivin-like orthologues in *Caenorhabditis elegans* and other organisms seemed exclusively involved in cell division but not in cytoprotection (40). Later experiments indicated that survivin inhibits active caspase-9 but not active caspase-3 and caspase-7 and that the inhibition of caspase-9 requires a co-factor, the hepatitis B X-interacting protein (41). Additionally, it was suggested that the antiapoptotic role of survivin could be mediated by its association with X-linked IAP via their conserved baculovirus-inhibitor of apoptosis domain, thus increasing X-linked IAP stability and leading to the synergistic inhibition of caspase-9 activation (42). Therefore, the ability of survivin to inhibit apoptosis seems likely although its mechanism of action may be more sophisticated than direct caspase inhibition and could involve cooperation with

other molecules (such as hepatitis B X-interacting protein and X-linked IAP).

### Role of Survivin in Cancer

Survivin is a unique inhibitor of apoptosis usually expressed in the embryonic lung and fetal organs in the developmental stages but undetectable in normal adult tissues other than the thymus, placenta, CD34<sup>+</sup> stem cells, and basal colonic epithelial cells (13, 43–46). However, survivin seems to be selectively expressed in transformed cells and in most human cancers, including lung, breast, pancreatic, and colon carcinomas, soft tissue sarcomas, brain tumors, melanoma, neuroblastoma, and hematologic malignancies, among others (43, 47–54). Genome-wide searches confirmed the differential expression of survivin in tumors versus normal tissues (53). Survivin expression can be deregulated in cancer by several mechanisms, including amplification of the survivin locus on

chromosome 17q25 (53), demethylation of survivin exons (55), increased promoter activity (56), and increased upstream signaling in the phosphatidylinositol 3-kinase or mitogen-activated protein kinase pathways (20). Additionally, the up-regulation of survivin expression in cancer cells seems to be independent of the cell cycle, suggesting an increase of its antiapoptotic role compared with normal cells, in which its mitotic regulation functions may be predominant. Finally, the dynamic intracellular localization of survivin in tumors (i.e., cytoplasmic and nuclear) may serve as an indicator of survivin activity and as a predictive marker in several tumor types, including oropharynx carcinoma and astrocytoma (57, 58).

Overall, increased survivin expression in cancer patients is an unfavorable prognostic marker correlating with decreased overall survival in several malignancies, including non-small cell lung, gastric, colorectal, and breast carcinomas, neuroblastoma, and hematologic malignancies. Increased survivin expression was also associated with increased risk of recurrence, locoregional lymph node invasion, and metastasis (59, 60). As an example, in a series of 222 consecutive patients who underwent radical cystectomy, survivin was not expressed in any of the normal bladder specimens but was present in 64% of bladder tumors and 94% of malignant lymph nodes (61). In the same study, survivin expression correlated with disease recurrence and disease-specific mortality, suggesting that survivin expression may represent a diagnosis marker of occult malignancy. Indeed, the detection of urinary survivin by immunochemistry or reverse transcription-PCR seems to be a promising assay to detect both newly diagnosed and recurrent bladder cancer (62, 63). Finally, survivin overexpression may be a predictive factor to determine response to chemotherapy and radiotherapy in patients with bladder cancer (64), breast cancer (65), multiple myeloma (66), and lymphoma (67–69).

It is clear that the role of survivin in cancer biology far exceeds the simple inhibition of apoptosis. Because survivin has been implicated in the regulation of the mitotic spindle checkpoint, from kinetocore to spindle assembly, its overexpression in cancer may allow cells with spindle defects or misaligned kinetochores to continue through cell division (14, 70). In addition to its direct role in carcinogenesis, survivin may also play a key role in tumor angiogenesis because it is strongly expressed in endothelial cells during the remodeling and proliferative phase of angiogenesis (71, 72). Moreover, the antisense-mediated suppression of survivin during angiogenesis stimulates capillary involution *in vitro* (73). Recent studies also suggest that survivin plays a role in tumor progression and chemoresistance (13, 42, 43, 68, 74). Survivin has been shown to inhibit cell death induced by several anticancer agents, including paclitaxel, etoposide, and tumor necrosis factor- $\alpha$ -related apoptosis-inducing ligand. In addition, NIH 3T3 fibroblasts treated with paclitaxel are protected from apoptosis when they express recombinant survivin (75). *In vitro* and *in vivo* studies showed that inhibiting survivin reduces tumor growth potential and sensitizes tumor cells to chemotherapeutic agents, such as paclitaxel, cisplatin, etoposide, gamma irradiation, and immunotherapy (75).

### Clinical-Translational Advances

Several novel experimental therapeutic strategies have been developed to target survivin. These include vaccination strategies to generate an antigen-specific immune response

against survivin-bearing tumor cells; the development of antisense oligonucleotides, ribozymes, or siRNA molecules targeting survivin; and small molecule inhibitors of survivin function (52, 54, 76, 77). Two of these strategies, antisense oligonucleotides and small-molecule inhibitors, have entered clinical development. YM155 (Astellas Pharma) is a small-molecule survivin suppressant selected via a high-throughput screening assay with a survivin-promoter luciferase assay. It selectively inhibits survivin mRNA transcription and protein expression in several tumor cell lines and has shown potent (nmol/L) antiproliferative activity in a broad spectrum of preclinical models, including prostate, breast, ovarian, and non-small cell lung carcinomas and melanoma as well as non-Hodgkin's lymphoma and leukemia. Tumor regressions, including complete responses, have been observed in xenograft models of non-Hodgkin's lymphoma and prostate carcinoma. In a phase I study, 41 patients were treated with a 168-hour continuous infusion of YM155 at doses ranging from 1.8 to 6 mg/m<sup>2</sup>/d (78). Dose-limiting toxicities were encountered at 6.0 mg/m<sup>2</sup> per day, with reversible renal tubular necrosis and grade 3 mucositis in one patient and increased serum creatinine in another patient. The maximum tolerated dose was 4.8 mg/m<sup>2</sup>/d, the most frequent adverse events being pyrexia, arthralgias, nausea, fatigue, and diarrhea. Activity has been reported with three partial responses in non-Hodgkin's lymphoma, two prostate-specific antigen responses in hormone-refractory prostate cancer patients, and one minor response in non-small cell lung cancer (78). A second phase I study done in Japan with a similar dosing schedule but with i.v. hydration support reported a slightly higher maximum tolerated dose at 8 mg/m<sup>2</sup>/d (79). Dose-limiting toxicities were similar with the U.S. study, with 2 patients experiencing increases in creatinine levels and 1 experiencing lymphopenia. Although no objective responses were observed, 9 of the 33 evaluable patients showed stable disease, and 5 of them experienced minor responses. The favorable safety profile of YM155 at the recommended dose as well as its provocative antitumor efficacy prompted the phase II evaluation of this compound in melanoma, prostate carcinoma, and non-Hodgkin's lymphoma. One of these phase II studies reported two prostate-specific antigen responses in 32 patients with hormone-refractory prostate cancer as well as an acceptable toxicity profile for YM155 (80). In the melanoma study, 1 partial response and 1 minor response were observed in the 34 patients, with 2 additional patients experiencing stable disease. The non-Hodgkin's lymphoma study is ongoing, and several combination trials of YM155 with cytotoxics as well as with targeted therapies are either planned or under way. Another transcriptional repressor of survivin, EM-1421 (Erimos Pharmaceuticals) showed promising results as a topical application for cervical intraepithelial neoplasia and is currently undergoing early clinical trials. LY2181308 (ISIS 23722; Eli Lilly and Co. and ISIS Pharmaceuticals Inc.), a second-generation antisense oligonucleotide targeting survivin, is also being evaluated in phase I trials.

Because survivin inhibitors have shown only modest anti-tumor activity in clinical trials, these agents may be best used in combination with conventional chemotherapy. Due to the complexity of the proapoptotic and antiapoptotic pathways, with multiple players involved, redundant signaling networks, and multifaceted interactions between the involved elements, blocking only one antiapoptotic factor may not result in robust



antitumor activity. Therefore, the rather disappointing results of survivin inhibitors administered as a single agent in unselected populations in phase II studies are not surprising. A molecular-based enrichment of the treated populations with subjects more likely to respond to survivin inhibition could overcome, at least in part, these caveats. It was suggested that, in diffuse large-cell lymphoma, survivin may be the primary mechanism for apoptosis abrogation in a significant subset of patients, with another subset being dependent on *bcl-2* overexpression and a smaller distinct population possibly relying on both (81). Alternatively, the combination of survivin with other proapoptotic factors seems to be an attractive strategy with potentially broad clinical applications. There are multiple lines of evidence indicating that survivin inhibition potentializes the antitumor activity of several cytotoxic and targeted therapies, including topoisomerase inhibitors (82), alkylating agents (83), tumor necrosis factor- $\alpha$ -related apoptosis-inducing ligand (84), and UCN-01 (85).

### Conclusion and Perspectives

Increases in survivin expression have been implicated in tumor growth, progression, and resistance to conventional and targeted anticancer agents. Interestingly, survivin is not usually expressed in normal tissues in contrast to malignant

tissues, thus making it an ideal target for cancer therapy. Several antagonizing modalities have already been developed, and several molecules are currently in clinical trials. YM155, a small-molecule survivin suppressant, is currently in phase II clinical development. Although antitumor activity was observed in single-agent studies, there is clear evidence that combination strategies with chemotherapy or other targeted therapies would not only improve the objective response but also possibly circumvent drug resistance. Considering this approach, combination therapy studies with biological or chemotherapeutic agents are currently being planned or are ongoing. Strategically designing clinical trials and selecting patients that are the most susceptible to survivin inhibition will hopefully provide improved antitumor activity and survival.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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