Challenge and promise: roles for Livin in progression and therapy of cancer

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Abstract
Livin is a member of the inhibitors of apoptosis protein gene family, which is highly expressed in a variety of human neoplasms. Several studies have shown that down-regulation of Livin expression increases the apoptotic rate, reduces tumor growth potential, and sensitizes tumor cells to chemotherapeutic drugs. Furthermore, emerging data reveal that Livin fragments cleaved by caspases restored paradoxical proapoptotic activity during the apoptotic process, suggesting that Livin cleavage will become a highly potent proapoptotic agent in the future. In this article, we review the current understanding of the versatile roles of Livin in the apoptotic cascade and exploit the promising approach to interfere with Livin as a novel strategy for cancer therapy. [Mol Cancer Ther 2008;7(12):3661–9]

Introduction
In 1972, the word “apoptosis” was formally introduced to describe a special form of cell death (1). Experimental evidence accumulated over three decades has led to the identification of many genes and gene products that regulate apoptosis (2–4). The inhibitors of apoptosis proteins (IAP) were revealed by the discovery of highly conserved expressions in organisms ranging from yeast to mammals and embarked on multiple biological activities, from carrying out apoptotic signaling, the formation of the mitotic spindle during cytokinesis to modulating receptor-mediated signal transduction (5, 6). This family is structurally similar in that they all consist of one or more baculovirus IAP repeat (BIR) domains that have been the defining module of this family. Most of these members also harbor a COOH-terminal RING finger domain. Up to now, as many as eight human family members have been identified, NAIP, c-IAP1 (MIHB, HIAP-2), c-IAP2 (MIHC, HIAP-1), XIAP (hILP, MIHA, ILP-1), Survivin, Apollon (Bruce), ILP-2, and Livin (ML-IAP, KIAP; ref. 7; Fig. 1A). They are the only confirmed endogenous proteins that counteract signaling through specific apoptosis pathways mainly on regulating the activity of both initiator and effector caspases thus far (8, 9). Livin, a recently discovered IAP, whose expression is one among a variety of malignancies and shows a strong correlation with shorter disease-free or overall survival in most cases, is identified as a candidate independent prognostic indicator of poor outcome in patients with some tumor types. Pursuing the novel functions of Livin in cancer may lead to the development of global pathway inhibitors with unique therapeutic potential. Therefore, we review the current state of therapeutic agents being tested and other considerations in an attempt to present an overview and generate discussion on Livin.

Livin Biology
Livin is a 39 kDa protein consisting of a single BIR domain and a RING finger motif, the gene of which spans 4.6 kb on chromosome 20 at band q13 composed of six introns and seven exons (10, 11). The BIR domain is supposed to be approximately 70 amino-acid zinc-binding residues and the core of it is usually wired with the conserved cysteine- and histidine-rich residues, which are traditionally required for antiapoptotic activity. Structurally, Livin-BIR forms a globular architecture conserved by four a-helices and a three-stranded anti-parallel l-sheet, as well as corresponding residues that form the hydrophobic core (11, 12). In comparing with BIR domains of other IAP family members, sequence studies reveal that it is most homologous to the NAIP-BIR3, c-IAP2-BIR3, XIAP-BIR3, and Survivin-BIR (52.9%, 51.5%, 50.0%, and 39.7%, respectively; ref. 13).

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implicated in the interaction with the cellular components of the ubiquitination machinery, controlling turnover of these proteins and other proteins with which they associate (15). In XIAP, c-IAP1, and c-IAP2, the most prominent roles of RING domains have been shown to encode ubiquitin protease ligase activity, which is preceded by ubiquitin-activating enzymes and ubiquitin-conjugating enzymes in the cascade of protein ubiquitination, and then to catalyze the transfer of ubiquitin into target proteins (16). A similar function of the RING domain has also been detected in Livin, and some studies reveal that it may play an additional role in the subcellular distribution directing apoptosis (17).

It is known that there are two alternatively similar splicing variants of Livin, Livin-α and Livin-β, except for 18 amino acids located between the BIR and RING domains, which are present in the α-isoform but not in the β-isoform (Fig. 1B). Both isoform expressions have been reported to be high in heart, placenta, lung, spleen, and ovary normal tissues and protected cells from tumor necrosis factor- and anti-CD95-induced apoptosis (11, 18). Although they are very closely similar, the two variants display different cellular and tissue distributions and antiapoptotic characteristics. For example, elevated levels of Livin-β have been identified especially in fetal tissues and adult kidney, whereas the α-isoform could only be measurable in the brain, skeletal muscle, and peripheral blood lymphocytes among adult and children organs (11). Recent experiments show that only Livin-α was positively expressed in a proportion of tumor bladder tissues with a high risk of relapse (19). In the presence of the apoptosis-inducing drugs, Livin-α possesses the property of protecting cells from staurosporine-induced apoptosis, but Livin-β protects against etoposide (11). In HeLa cells, cell growth could be blocked in clonogenic survival assays and sensitization to different proapoptotic stimuli. This is enhanced dramatically by performing RNA interference strategy to inhibit Livin-β (20). The functional and tissue distribution differences of two variants indicate that a complex regulatory balance exists, which may determine the varied responses to different stimuli in cancers. Regarding the lack of difference existing between the BIR domains of the two Livin isoforms, it is tempting to suggest that the 18 amino acids in the Livin-α BIR-RING linker region might form specific binding sites for directing different functions. Quite interestingly, a lately released report says that Livin isoform-specific functions is part of the innate immune system. The article by Nachmias et al. says that Livin-α augments natural killer cell killing, whereas Livin-β, on the contrary, moderately protects against killing by inhibition.

Figure 1. The schematic diagram of IAP family members. A, the domain arrangements of the eight known members of the IAP family are presented. BIR, RING, caspase activation recruitment domain (CARD), E2 ubiquitination enzyme motif (Ubc), and nucleotide-binding domain (NB). B, structure of two variants of Livin. The major 18 amino acids between two isoforms have been listed.
apoptosis of Jurkat cells (21). Therefore, it is perplexing to illustrate the diverse roles Livin isoforms play, but isoform-specific therapy might offer an alternative opportunity to target tumors in the near future. Taken together, this is probably not the whole story on the multiple functions of Livin variants; thus, an effort will be made to build a unifying model for introducing a more in-depth mechanism for all phenomena.

Livin and Apoptosis: Paradigms and Paradoxes

Apoptosis is a self-directed biological process of cell death that proceeds with characteristic biochemical and cytologic features, which is critical for controlling the number of cells in development throughout an organism’s life by removal of cells at the appropriate time. Hitherto, only two classic pathways for apoptosis have been clarified in detail in mammalian cells. The “extrinsic” pathway is triggered through the Fas death receptor, a member of the TNF receptor superfamily (22, 23). The “intrinsic” pathway involves the participation of the mitochondria, which responds to various noxious stimuli and releases caspases-activating proteins to trigger apoptosis (24, 25). Although commonly viewed as separate pathways and capable of functioning independently, cross-talk can occur between these pathways, which ultimately converge on downstream effector caspases.

Livin Interacts with Caspases

In recent years, it is often assumed that the BIR domain is a requirement for the suppression of apoptosis by interacting with and increasing the flexibility of caspases in IAPs (26–28). The antiapoptotic mechanism of XIAP is comparatively lucid in the IAP family. It has been clarified that BIR2 and the linker region between BIR1 and BIR2 of XIAP were critical for caspase-3 and caspase-7 inhibition, whereas only the BIR3 domain can potently inhibit active caspase-9 (29–31). The role of Livin in the inhibition of apoptosis has a similar degree of complexity, connecting to multiple parallel pathways that regulate gene expression, protein-protein interactions, and mitochondrial functions. A model summarizing these concepts is shown in Fig. 2. The antiapoptotic activity of Livin is also attributed to its single BIR domain. The current available information reveal that Livin was claimed to be a genuine apoptosis inhibitor, not only because it was associated with caspase-3 or caspase-7 directly but also because it counteracted cell death by interfering with caspase-9 processing (32). Similarly, Vucic et al. showed that Livin-BIR possessed an evolutionarily conserved fold that was necessary for a powerful inhibitor of caspase-3. Deletion and mutational analyses further verify that the integrity of the BIR domain was required for its antiapoptotic function (10). These observations suggest a significant and conservative role for Livin-BIR in apoptosis; however, selective discrepant binding capability with caspases may still exist.

Previous correlative data suggest that Livin interacts with and inhibits caspases, but other findings paint a more confusing picture. In Eckelman et al.’s article, they found the presence of an IAP-binding motif–interacting groove exosite and an inhibitory element conserved in XIAP. Therefore, XIAP is the mammalian IAP that directly inhibits caspase activity (33). Actually, Livin shows weak inhibition on caspase-3 and caspase-9 in comparison with XIAP of inhibition constant. By matching the amino acid sequence of the caspase-binding region of the BIR domains, it is the three critical amino acid residues (Ser300, Gln307, and Glu308) that render Livin a less potent inhibitor of the enzymatic activity of caspases compared with the corresponding residues of XIAP (Gly326, His333, and Leu344). However, the triple-mutant Livin protein that was replaced by three amino acid residues of XIAP inhibited caspase-9 more efficiently than native XIAP-BIR3 (34). This gives rise to the possibility that there might exist another peptide-binding site other than the three major residues responsible for conventional caspase inhibition of Livin.

The Biochemical Journal and The Journal of Biological Chemistry report further investigations that reveal the reason why low affinity exists between some IAPs and caspases (35, 36). One is ILP-2, which, similar to Livin, is a weak caspase-9 inhibitor. It was reported that a 9-residue linker from XIAP fused to the NH2 terminus of ILP-2 would dramatically gain extra-tight caspase-9 inhibition. In fact, it was the second mitochondria-derived activator of caspase/direct IAP-binding protein with low pI (Smac, also known as DIABLO) that made ILP-2 stabilized and nullified its inhibitory function. Another example is identified by Orgyia pseudotsugata protein (Op-IAP), which is a potent inhibitor of Bax-mediated apoptosis in human cells, to an extent equivalent to that of XIAP. However, there was no direct binding of Op-IAP to any caspase to exert inhibition. It probably mainly relies on the ability of Smac to interact with other free endogenous IAPs to develop further apoptosis networks. On the basis of the two examples reported here and the structure/function investigations on Livin, one conclusion not widely recognized is that although the caspase-binding sites may retain these IAP members, the potential interacting surfaces that resulted in protease inhibition might survive. Therefore, using physiologic approaches to promote Livin-Smac interaction may be an alternative mechanism to regulate apoptosis.

Alternative Mechanisms of Livin Inhibition of Apoptosis

There seems to exist with the IAPs a counterintuitive situation wherein a single protein possesses biochemically distinct mechanisms directed to the same end. While we know that most studies on Livin have focused on its role as a caspase inhibitor, there is mounting evidence that it also does so via other mechanisms (Fig. 2). It is now accepted that the selective activation of Jun NH2-terminal kinase 1 (JNK1) of mitogen-activated protein kinase is a second network for XIAP (37). There is also the case for Livin. It
has been shown that Livin is capable of activating JNK1 and the activated JNK1 is a requirement for protecting against TNF-α– and interleukin-converting enzyme–induced apoptosis. Although it is not clear what the BIR domain of Livin plays in mitogen-activated protein kinase pathway, these data indicate that the mechanisms for BIR domain function among the IAP family members may also be different in response to different signaling molecules. In this way, Livin is likely to mediate JNK1 activation by transforming growth factor β–activated kinase 1 (TAK1)/TAK1-binding protein (TAB1) signaling cascade (38). Further studies of these phenomena may provide important information for disease treatment.

A second posttranscriptional network indicates that Livin is involved in the wingless and integration site growth factor (Wnt)/β-catenin signaling pathway, the key component of which involves β-catenin activation of genes that have significant consequences on tumor development by forming a complex with the T-cell factor (TCF) transcription factor family (39). In human non–small cell lung cancer A549 and 103H cell lines, the activity of the Livin promoter was increased considerably by β-catenin activation and could be blocked by a dominant-negative TCF expression construct. Moreover, chromatin immunoprecipitation assay has confirmed that the β-catenin/TCF complex bonded to the putative TCF binding site of the Livin promoter (40). According to these data, it can be deduced that Livin is likely to be one of the targets of β-catenin/TCF in tumor, which may help us better understand the molecular mechanism of carcinogenesis.

**Versatile Roles of Livin in the Apoptotic Cascade**

Despite being acknowledged that Livin makes a definite contribution to apoptosis inhibition, little is known about its proapoptotic regulatory mechanism. Nachmias et al. recognized that Livin fragments cleaved by caspases restored paradoxical proapoptotic activity during the apoptotic process. To be specific, the effectors caspase-3 and caspase-7 cleaved Livin-α and β isoforms into 30 kDa (p30-Livin α) and 28 kDa (p28-Livin β) fragments, respectively, at the 52 amino acids at the NH2 terminus, both of which contained the full BIR and RING domains. In human embryonic kidney 293T cells, both p30-Livin α and p28-Livin β could be transiently transfected to perform

![Figure 2. Potential mechanisms by which Livin interacts with apoptosis.](https://mct.aacrjournals.org)
proapoptotic activity, and the effect of latter seemed slightly stronger. However, p30-Livin α could be stably expressed and showed significant proapoptotic activity in 721.221 EBV-transformed B-cell line but not p28-Livin β (41). Conversely, it was reported that the greater proapoptotic potency of p28-Livin β was more evident than that of p30-Livin α after transfection in the melanoma cell LB33-MEL-A-1 (42). Therefore, the data derived from the experimental model may define Livin isoforms as proapoptotic agents and lead to novel approaches for cancer treatment; however, the diverse activities between the two isoforms displayed in a wide range of cell apoptosis are still uncertain. One hypothesis is that this different effect is presumably due to spontaneous apoptosis by whatever Livin cleavage takes advantage of in the corresponding cell. A similar case has occurred to c-IAPI, but the cleavage product only possessed the spacer RING domain. In the case of XIAP, its cleavage fragment contained the BIR3-RING domain resembling the Livin COOH-terminal portion, but retained no proapoptotic activity (43). Therefore, it can be deduced that the resulting cleavage product of Livin might also play an essential role in modulating its antiapoptotic effect. Furthermore, Nachmias et al. discovered that different subcellular compartments of Livin cleavage products had different biochemical effects and might contribute to the antiapoptotic or proapoptotic activity. In their article, full-length Livin is detected exclusively in the cytoplasm, whereas the truncated form (tLivin) is located in a perinucleus with marked localization to the Golgi apparatus; the accumulation of tLivin in the nucleus showed positive correlation with the increase in apoptosis. An extensive mutation study theorized that an intact RING domain was identified as the critical residue for the proapoptotic function of tLivin (42). This may provide a possible mechanism by which the RING motif can increase the activity of caspases indirectly in the cell so that the apoptotic barrier can be lowered to allow the cell to undergo apoptosis. Because Livin-BIR is known to confer resistance to apoptosis and the intact BIR remains in the tLivin, it is speculated that the antiapoptotic activity of the BIR motif was likely to be inhibited by its adjacent NH2-terminal amino acids during the proapoptotic process. Taken together, Livin is a unique IAP family member exerting proapoptotic and antiapoptotic activities. Taking advantage of its exclusive property, the strategy to promote tLivin cleavage will probably counteract its antiapoptotic function and transform it into a highly potent proapoptotic agent. Moreover, small molecules using sequence-specific mimic tLivin can be devised as a novel therapeutic avenue against cancer to enhance chemotherapy effects.

Validating Livin as a Potential Prognostic Marker

Molecular profiling studies and retrospective analyses of patient records have consistently validated the increased expression of Livin as a risk factor for cancer progression and prognostic prediction. The study of neuroblastoma shows that Livin protein expression is higher in primary tumors and cultured cells. In addition, patients with combined high Livin expression and amplified Myc oncogene had significantly shorter median survival (44). It is worth noting that increased Livin expression might have a potential role in categorizing a subset of neuroblastoma patients with poor prognosis. Likewise, Gazzaniga et al. reported that in a proportion of superficial bladder cancer patients, median relapse-free time of Livin-positive patients was obviously shorter than that of Livin-negative patients. Further study illustrated that elevated Livin-α isoform expression was associated with the progression of cancer and could be used as a marker of early recurrence (19). Consequently, it is possible that not only the intact Livin molecule is a suitable candidate indicating adverse outcome, but its α-isof orm also counts. However, Kempensteffen found that Livin expression levels did not correlate with pathologic or clinical outcome by real-time reverse transcription-PCR and Western blot detected in renal cell carcinoma patients (45). In the same year, it was reported that Livin-α and Livin-β were unexpectedly found to be different between renal cell carcinoma and normal kidney tissues. Besides, the results showed that even if cytoplasmic Livin was presented in both renal cell carcinoma and normal kidney tissues, nuclear Livin could only be detectable in renal cell carcinoma (46). Supporting his conclusion, Nedelcu et al. successively identified that the nuclear localization of Livin was in parallel with a decreased overall survival in osteosarcoma patients (47). These observations indicated that nuclear Livin rather than the other form validated it as a promising prognostic marker in clinical diagnosis and therapy. Because the whole study contained relatively small numbers of patients and is retrospective in design, further research is necessary to identify the molecular characterization of function and localization of multiple Livin forms.

A positive correlation between Livin and response to childhood acute lymphoblastic leukemia was recently reported. In this study, Livin expression promoted apoptotic response of leukemic cells induced by chemotherapeutic agents. Additionally, a long-term survival rate was associated with the presence of Livin expression (48). Of note, it is a brand new evidence to show that Livin becomes an independent favorable prognostic factor, although it is not entirely clear why overexpression of Livin is associated with a good prognosis. It may be attributed to the theory that in response to apoptotic stimuli, the cleaved form of Livin probably acts as a strong proapoptotic regulator and the different Livin subcellular localization may play an important role in determining its antiapoptotic or proapoptotic activity. However, the age of patients is a putative interference in the study; thus, more positive correlations are expected in adult acute lymphoblastic leukemia. In brief, Livin may have additional roles that have to be defined.
Livin-Directed Cancer Therapy

Strategies for innovative therapies are beginning to emerge from the accumulating base of knowledge about IAPs and the cellular mechanisms that regulate their functions. According to its structural characteristics and its distinguishing role in apoptosis, Livin can become a proof-of-concept therapeutic target that is suitable for molecular antagonists, vaccination strategies, small-molecule inhibitors, and gene therapy. Below is a brief discussion of the portfolio of strategies to target Livin for novel cancer therapies achieved at various biological levels (Fig. 3).

Targeting Livin at the Nucleic Acid Level

One therapeutic strategy to inhibit IAPs is to use antisense oligonucleotides to decrease the target IAP mRNA and subsequently reduce protein expression. More recently, the antisense oligonucleotides specific for Survivin and XIAP already entered clinical trials in patients with advanced cancers (49–51). It was supposed that it would be a practical approach for the therapy of malignancy. Supported by the favorable safety profile, Kasof et al. reported that the antisense oligonucleotide directed against Livin rendered knockdown of its mRNA after 48 h transfection in cultured HeLa and G361 cells, in parallel with dramatically decreasing viability and inducing apoptosis (32). Encouraged by these results, Puri et al. used an oligonucleotide homologous to the telomere 3’ overhang sequence (T-oligo) specific for Livin to induce DNA damage responses in several established human melanoma cell lines. In this study, tumor growth was markedly inhibited in severe combined immunodeficient mice after administration of T-oligos (52). All data indicate that the antisense oligonucleotides may remain effective against human carcinomas even when one or more of the principal pathways mediating response to conventional chemotherapeutic agents have been compromised.

In recent years, another revitalized interest in the development of nucleic acid–based technologies for gene suppression is small interfering RNA (siRNA), which can inhibit specific gene expression significantly and open a door in cancer therapy (53, 54). In vitro proof-of-principle experiments provided the preclinical justification for the feasible development of siRNA-based approach to inhibit cancer-related genes, including Livin. Crnkovic-Mertens et al. used siRNA to repress endogenous Livin expression...
in MeWo and HeLa cells specifically (55). Sequentially, these authors continued to discover that siRNA-mediated Livin knockdown was able to reduce tumor cell proliferative potential and induce sensitization toward proapoptotic stimuli in renal cell carcinoma (56). Similar positive results were also acquired from other experiments in non–small cell lung cancer (57). Therefore, in spite of the challenges, the specific targeting of particular oncopgenes has proven to be successful in a number of different cancers (58, 59). The field is rapidly progressing with the development of chemically modified siRNAs and a variety of novel delivery strategies for future application.

**Targeting Livin by Blocking Protein Function**

Although traditionally not viewed as easy to target, there are abundant precedents of interrupting protein-protein interactions, especially those involving apoptosis regulators, creating meaningful anticancer activity, managing toxicity and drug-like properties that apply clinical testing (60). Small molecules that can specifically bind and disrupt the physical complex between Livin and other network components are another promising approach for treatment. The first and best characterized of these molecules is the endogenous short polypeptide, which is a negative regulator of Livin, such as Smac. It has been shown that the NH₂ terminus of Smac was the crucial structure that could negate the ability of overexpressed Livin to repress apoptosis in MCF7 cells (61). Experimental evidence suggested that Smac-based ligands bound to the two BIR domains of XIAP were much more potent than that which was bound to a single domain (62). We speculate that the number of BIR domains may have influence on the ability of antagonizing apoptosis in XIAP. As for Livin, the relationship between Smac and the BIR domain was very specific and could be completely abolished by single amino acid mutations in either of them (63). Therefore, small molecules that promote the Smac-Livin interaction by imitating the interaction with Smac might trigger cell cycle arrest and apoptosis.

Inspired by the hypothesis, Smac mimic, as a mimic of native parental peptides, was designed. Previous data revealed that the peptidomimetic is water soluble and nonimmunogenic (64). In comparison with Smac, Smac mimetic could cross the cell membrane and bind efficiently to its target proteins (65). It was shown that Smac mimetic possessed the ability of activating caspase-3 and caspase-7, reducing cell viability of MDA-MB-231 breast cancer cells and A2058 melanoma cells, and enhancing doxorubicin-induced apoptosis (66). Together, the development of small molecules is offering not only prospects for individualized treatment but also a valuable therapeutic window to limit unwanted side effects (67, 68).

Alternatively, using monoclonal antibodies against IAPs has been widely applied in tumor cells. In Livin-positive models, antibodies could interfere with the antiapoptotic effects and are expected to increase apoptosis rate. Actually, it was Watanabe et al. who detected anti-Livin antibody in gastrointestinal cancer patients (69). In their study, a huge range of cancer patients of different origins, e.g., breast, renal, melanoma, and lung tumors, were positive for anti-Livin antibodies, suggesting that anti-Livin antibodies could be useful for detecting these cancers and can serve as a therapeutic approach (70–72).

**Targeting Livin by Immunotherapy**

Harnessing the immune system has aroused marvelous interest in the battle against cancer during the past several decades. Indeed, several immunotherapeutic strategies for achieving this goal, including adoptive transfer of tumor-reactive T cells, systemic or localized administration of immune modulating cytokines, and the use of vaccines, have been explored. Recently, strong evidence that MHC-restricted Livin epitopes may act as important and widely applicable targets for anticancer immunotherapeutic strategies has been collected and the clinical trials using Livin-based vaccines aim to prove its efficacy. The investigation was undertaken by Andersen et al. in an effort to learn that Livin-derived peptides were recognized specifically by T cells not only infiltrating the tumor but also circulating in the peripheral blood in a large proportion of melanoma patients. Further investigation validated Livin as an appropriate immunologic target in that Livin-reactive T cells isolated by magnetic beads coated with peptide/HLA-A2 or HLA-A3 complexes were cytotoxic against HLA-matched malignant cell lines (73, 74). Moreover, the CTL induced by Livin7 (amino acid sequence KWFPSCQFLL) peptide showed high cytotoxicity against Livin-positive lung cancer cell lines in an HLA-A24–restricted manner (75). In conclusion, these series data provided a rational basis for targeting Livin aimed at an excellent target antigen in immunotherapy and Livin7 may become a candidate peptide vaccine favoring the collapse of tumor-associated angiogenesis. However, despite the efficacy and specificity that Livin-directed immunotherapeutic approaches displayed, consequences of prolonged Livin disruption in normal cells, particularly those associated with continuous renewal, need to be delineated. Understanding the role of Livin in normal versus malignant cells will be important in identifying strategies that maximally disrupt Livin in cancer cells with minimal effect on normal tissues.

**Future Trends**

A large body of evidence now supports important functions of Livin expression in the pathogenesis and progression of cancer. Although the details of the multiple pathways emanating from Livin networks are yet to be fully elucidated, there is a consensus that Livin is an appropriate therapeutic target for effective cancer therapy. However, full verification of Livin application will come from preclinical and clinical trials in view of both biological as well as clinical efficacy end points in wider populations. Hopefully, these potential approaches will bring more blessing to the patients with malignancy.
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No potential conflicts of interest were disclosed.

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