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Investigations of survivin: the past, present and future

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1. ABSTRACT

Survivin is a member of the inhibitors-of-apoptosis protein (IAPs) family. It promotes cell survival through interference with multiple cell cycle-related proteins such as INCENP and Aurora B kinase. Survivin also inhibits cell death through interference with both caspase-dependent and -independent cell apoptosis. Interestingly, recent evidence suggests that survivin may also play a role in the regulation of cancer cell autophagy. At the clinical level, studies on clinical specimens have shown that survivin expression is up-regulated in various human cancers and its up-regulation is associated with tumour resistance to both chemotherapy and radiation therapy. On the basis of these findings, survivin has been proposed as an attractive target for new anti-cancer interventions. However, despite the role that survivin plays in cancer cell survival and anti-drug response, the development of survivin inhibitors is relatively slow as compared to other therapeutic inhibitors for cancer treatment. In this review, the relationships between survivin expression and the causation of drug resistance in cancers are re-addressed. This review also summarizes the recent development of survivin inhibitors for clinical usage.

2. INTRODUCTION

Members of the inhibitor of apoptosis protein (IAP) family are important for inhibiting caspase activity and cell death in response to apoptotic stimuli. Eight IAPs are identified in humans: Apollon (Bruce) (1), cIAP-1 (HIAP-2/MIHB) (2), cIAP-2 (HIAP-1/MIHC) (3), ILP-2 (Ts-IAP) (4), NIAP (5), survivin (TIAP) (6), XIAP (ILP-1/MIHA) (7) and the recently identified livin (alternatively called ML-IAP or KIAP) (8). They are characterized by the possession of one or more baculoviral IAP repeat (BIR) domains of ~70 amino acid residues and structure-function studies of IAPs have demonstrated that IAPs require at least one BIR domain in order to suppress cell apoptosis. Although IAPs are widely expressed in normal tissues, their expression is significantly increased in various tumour tissues (9-13). The only exception is survivin, which is primarily expressed in fetal and cancerous tissues, but not in normal, developed adult tissues (14). Originally, survivin was thought to be able to inhibit caspase-dependent apoptosis and at the same time promote cell division by interfering with Aurora-B kinase. However, recent literature reveals that survivin plays multiple roles in the process of tumorigenesis and the causation of drug-

resistance. In this review, the underlying mechanism of survivin function is discussed. Furthermore, the relationships between survivin expression and the causation of drug resistance in cancers are re-addressed. This review also summarizes the recent development of survivin inhibitors for clinical usage.

3. SURVIVIN

3.1. The expression of survivin in human cancers

Survivin is a member of the IAP family, which is expressed during embryonic and fetal development. In fact, it has been demonstrated that survivin plays essential roles in both neurogenesis and hematopoiesis (15, 16). Unlike other IAPs, survivin is also expressed in various cancers, but not in differentiated normal tissue. In clinical situations, survivin was found to be expressed in various oral cancers. A study from Lin *et al.* in Taiwan has observed the expression of survivin in 97% (60/62) of oral epithelial dysplasia specimens (17). In addition, 98% (94/96) of oral squamous cell carcinoma specimens showed increased survivin expression (17). In contrast, the expression of survivin was not observed in adjacent normal oral mucosal tissues (17). Another study from Hsu *et al.*, also in Taiwan, demonstrated that survivin was over-expressed in esophageal squamous cell carcinoma (18). In this study, the percentage of survivin expression in well differentiated (n=7), moderately differentiated (n=15) and poorly differentiated (n=24) esophageal squamous carcinomas was 60%, 74% and 80% respectively. In contrast, only 25% of normal esophageal epithelia specimens (n=8) expressed survivin (18). In addition, high survivin expression level was significantly associated with a shorter survival period (18). Another study performed by Preuss *et al.* revealed a correlation between survivin expression and survival period in patients with oropharyngeal cell carcinoma (19). In this study, patients with higher cytoplasmic survivin expression levels were shown to have a lower 5-year disease-free survival rate (19).

Besides being overexpressed in oral cancers, survivin was found to be over-expressed in patients with colorectal carcinoma and lymphoma (20). Two studies revealed that expression of survivin was significantly higher in adenomatous polyps and adenocarcinoma as compared to normal colorectal mucosa (21, 22). Survivin expression was also correlated with overall survival in patients with stage II colorectal carcinoma in the above independent studies (21, 22). On the other hand, survivin seems to play an important role in the transition of adenoma with low dysplasia to high dysplasia during human colorectal tumorigenesis (23). In one study, Kawasaki *et al.* demonstrated that only two percent of cases with adenoma with low dysplasia (n=171) were positive for survivin expression. In comparison, more than 50% of cases with adenoma with high dysplasia (n=42) and with carcinoma (n=60) were positive for survivin expression (23). Therefore, survivin over-expression seems to play important roles in the pathogenesis and the progression of some cancers.

3.2. Molecular functions of survivin

Since survivin is over-expressed in different cancers under clinical situations, various studies have been carried out to determine its underlying molecular mechanisms. At the molecular level, survivin is a bi-functional protein that acts as a suppressor of apoptosis and plays a central role in cell division (Figure 1). It has been suggested that survivin, possibly the mitochondrial fraction instead of the cytosol fraction, inhibits apoptosis through interference with caspases (24-26). A study using surface plasmon resonance spectroscopy showed that survivin directly binds to caspase-3 and caspase-7 with nanomolar affinity (24). In addition, myc-tagged survivin bound caspase-3 and caspase-7 in immunoprecipitation studies (24). It is not surprising that survivin is able to interfere with the activity of caspases, given that survivin contains a single baculoviral IAP repeat (BIR) domain and that the BIR domain was shown to be important in targeting caspases in various IAP family members (27). Interestingly, recent evidence indicates that survivin may also interfere with caspase-independent apoptosis. For example, it has been demonstrated that survivin interferes with the translocation of the apoptosis-inducing-factor (AIF). AIF is a flavoprotein that is normally confined to the mitochondrial intermembrane space, but induces chromatin condensation and fragmentation of DNA into high molecular weight forms of >50 kb when it translocates to the nucleus (28, 29). Interestingly, down-regulation of survivin induces the translocation of AIF in various cancer cell lines (30-32).

Besides interfering with both caspase-dependent and -independent apoptosis, survivin also promotes cell survival through interference with cell cycle-related kinases and microtubule networks (Figure 1). Survivin appears to function as a subunit of the chromosomal passenger complex (CPC) for the regulation of cell division. It has been demonstrated that survivin binds to the Aurora-B kinase, Borealin and INCENP (33-36). During mitosis, survivin locates to centromeres on a para-polar axis during prophase/metaphase, relocates to the spindle midzone during anaphase/telophase and disappears at the end of telophase (37). Over-expression of survivin has been shown to reduce centrosomal microtubule nucleation and suppress both microtubule dynamics instability in mitotic spindles and bidirectional growth of microtubules in midbodies during cytokinesis (38). In addition, it has been shown that intracellular loading of a polyclonal antibody to survivin induced microtubule defects and resulted in the formation of multipolar mitotic spindles (39).

Recently, it has been suggested that survivin may also play a role in the regulation of cancer cell autophagy (Figure 1). Results from Roca *et al.*'s study indicated that CCL2 (Chemokine (C-C motif) ligand 2, MCP-1, monocyte chemo-attractant protein-1) protects human prostate cancer PC3 cells from autophagic cell death via the phosphatidylinositol 3-kinase/Akt/survivin pathway (40, 41). Taken together, survivin appears to be a master molecule that regulates multiple survival pathways in cancer cells.

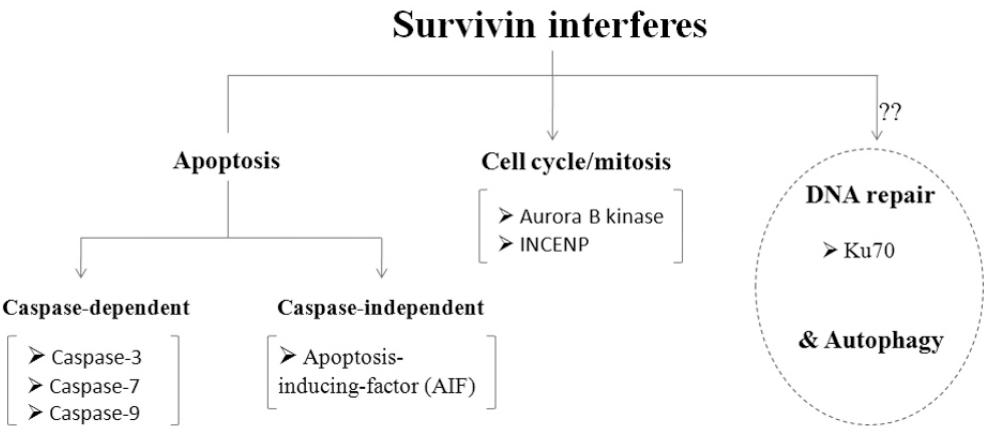

Figure 1. Molecular functions of survivin.

3.3. Survivin and drug resistance

Considering the direct interactions between survivin and various apoptotic/mitotic-related molecules, over-expression of survivin should enhance cancer cell survival and anti-drug ability under chemotherapeutic stress. In fact, over-expression of survivin has been connected to the causation of cancer-drug resistance in various studies (42-44). It has been demonstrated that the inhibition of apoptosis mediated by survivin contributed to cisplatin-resistance in lung cancers and possibly in gastric cancers (45, 46). Survivin expression was shown to be up-regulated in the gastric cancer cell line, MKN-45, in response to cisplatin treatment *in vitro***.** In addition, the level of resistance was correlated to the amount of survivin over-expressed in the treated cells (46). On the other hand, targeting survivin with shRNA induces caspase-dependent apoptosis and enhances cisplatin sensitivity in squamous cell carcinoma of the tongue (47). Expression of survivin also interferes with the sensitivity to various anti-mitotic compounds and pro-apoptotic chemokines in cancer cells. Zaffaroni *et al.* showed that stable transfection of human ovarian carcinoma cells with survivin cDNA caused a four to six-fold increase in cell resistance to taxotere and taxol (48). A recent study from our laboratory also suggests that the over-expression of survivin counteracts the therapeutic effect of anti-mitotic compounds (microtubule de-stabilizing agents) BPR0L075 and colchicine possibly through the stabilization of tubulin polymers in human oral cancer cells (30). On the other hand, survivin may play a role in tumor cell resistance to TRAIL-induced apoptosis through cell cycle regulation. Transfection of a survivin anti-sense construct enhanced the sensitivity to TRAIL in human hepatocellular carcinoma both *in vitro* and *in vivo* (49). Survivin also plays an important role in inducing therapeutic resistance to endocrine therapy in both breast and prostate cancers. Tamoxifen has been widely used in endocrine therapy for estrogen receptor-positive breast cancer. A study demonstrated that targeting survivin by siRNA enhanced tamoxifen-induced apoptosis in MCF-7 breast cancer cells *in vitro* (50). In addition, over-expression of survivin is able to mediate resistance to anti-androgen therapy in human prostate cancer cells possibly through the inhibition of apoptosis (51).

Interestingly, a few reports suggest that the over-expression of survivin may induce drug-resistance through indirect mechanisms. It has been demonstrated that the over-expression of survivin induced the up-regulation of multi-drug resistance P-glycoprotein (Pgp) and subsequently reduced drug accumulation in MCF-7 breast cancer cells *in vitro* (52). Thus, survivin may modulate the turnover of Pgp or transport by Pgp in cells, resulting in anti-apoptosis and drug resistance. Furthermore, growing evidence indicates that transient up-regulation of survivin by VEGF and bFGF in normal endothelial cells of blood vessels is partly responsible for tumour angiogenesis and tumour resistance against chemotherapeutic drugs (53, 54). Up-regulation of survivin is also able to counteract the pro-apoptotic effect induces by TNF-α in blood vessel endothelial cells (55). Interestingly, a recent report suggests that the translocation of survivin into the nucleus may enhance DNA double strand breaks (DBD) repair capability in radiation-treated oral cancer cells by up-regulating the molecular sensor of DNA damage, Ku70 (56). This observation is indeed important as it indicates that besides the over-expression of survivin, the translocation of survivin into the nucleus may also play an important role in the interference with therapeutic efficiency in cancers.

3.4. Targeting survivin by anti-sense, siRNA and dominant-negative constructs

In the past decade, most targeted-therapies did not show great therapeutic advantages over traditional chemotherapies in clinical situations. This is due to the fact that cancer cells acquire anti-apoptotic properties through up-regulation or alteration of various pro-survival mechanisms simultaneously and targeting a single pathway by targeted-therapy is insufficient to induce cancer cell death. Furthermore, cancer cells are known to acquire drug resistance properties after prolonged treatment through both drug-target mutations and changes in the intracellular signaling pathways. Since survivin interferes with various cancer-related pathways, targeting survivin may intersect multiple cancer survival pathways simultaneously (instead of a singularly targeted pathway) and may give a better

therapeutic outcome as compared to other targeted-therapies in clinical situations.

Under laboratory conditions, it has been widely demonstrated that targeting survivin induces cancer cell death and restores drug sensitivity to different chemotherapeutic compounds. Down-regulation of survivin by liposomal/adenoviral-delivered siRNA has been shown effective in inducing cell death of various cancers such as gastric carcinoma (57), esophageal carcinoma (58), renal clear cell carcinoma (59), bladder cancer (60) and cervical cancer (61). Interestingly, a recent study demonstrates that the delivery of survivin siRNA using a micro-bubble contrast agent combined with ultrasound exposure can effectively inhibit survivin expression and induce apoptosis in ovarian carcinoma cells (62). Targeting survivin by an anti-sense oligonucleotide was also successful in inducing cancer cell death. SPC3042 is a 16-mer locked nucleic acid (LNA) oligonucleotide that targets the expression of survivin. A pre-clinical study revealed that SPC3042 was able to reduce the amount of survivin protein present in PC3 prostate cancer cells and subsequently induce cell apoptosis (63). The same study also revealed that SPC3042 is capable of sensitizing prostate cancer cells to taxol treatment *in vivo* (63). On the other hand, targeting survivin by gene transfection of a dominant-negative construct (either T34A or C84A mutant) is able to induce the apoptosis of melanoma (64), lymphoma (65) and prostate cancer cells (66) *in vitro* and *in vivo*. The C84A dominant-negative mutant form of survivin was constructed on the basis of the finding that mutation of Cys84 to Ala in the extreme C-terminal region of the BIR domain disrupts the Zn^{2+} coordination sphere and subsequently abrogates survivin's ability to inhibit apoptosis. On the other hand, phosphorylation of survivin on Thr34 is critical for the stability of survivin, and hence for its role in promoting cell cycle progression and caspase inhibition (67). Mutation of Thr34 to Ala completely abolished the phosphorylation of survivin, resulting in the dissociation of the survivin-caspase-9 complex (67). Recently, it has been demonstrated that proteins fused with cell-permeable domains such as TAT and R9 are able to penetrate cells without the use of transfection reagents. Targeting survivin by a recombinant cell-permeable (TAT or R9-tagged) dominant-negative survivin (T34A or C84A) protein was also shown to be effective in inducing cancer cell death as compared to traditional gene therapy (68, 69). Interestingly, Khan *et al.* reveals that a T34A dominant-negative mutant of survivin, without coupling to a cell-permeable domain or the use of transfection reagent, was able to be taken up by HeLa cells and subsequently induced caspase-dependent apoptosis (70). It is widely believed that cancer cells over-express survivin endogenously. Then the endogenously expressed survivin interferes with various intracellular survival-related molecules within the cell. However, results of Khan *et al*'s study indicate that cancer cells may be capable of taking up survivin that is located in the extracellular space and subsequently promote the ability of cell survival.

3.5 Recent developments of the survivin-specific small molecule inhibitors

Despite previous success in the use of both anti-sense, siRNA and dominant-negative constructs to target survivin, the development of survivin-specific pharmacological (small molecule) inhibitors is relatively slow as compared to other cancer-related kinase inhibitors. For example, more than twenty aurora kinase-specific inhibitors have been developed for cancer treatment and more than six of such inhibitors have undergone various clinical trials in the last five years (71, 72). In contrast, only a few small molecule survivin inhibitors have been developed in the past ten years and only one survivin inhibitor, YM155, has successfully reached stage II clinical trials (63, 73-78). YM155 (1-(2-Methoxyethyl)-2-methyl-4,9-dioxo-3-(pyrazin-2-ylmethyl)-4,9-dihydro -1H-naphtho[2,3-d]imidazolium bromide) is an inhibitor that functions in inhibiting the transcription of survivin in cells (78). In pre-clinical models, the application of YM155 was shown to be effective in inducing apoptosis in various types of cancers such as prostate cancer, lung cancer and lymphoma (74, 77, 78). It has been demonstrated that YM155 induces the regression of human hormone-refractory prostate tumor *in vivo* (78). In a PC-3 prostate tumor xenograft animal model, a weekly three-day continuous infusion schedule of YM155 at dosages of 3 and 10 mg/kg inhibited tumor growth and induced massive tumor regression. In addition, administration of YM155 at dosages of 1 and 5 mg/kg induced 47% and 80% inhibition of tumor growth, respectively, in PC-3 orthotopic xenografts (78). YM155 was also shown to be able to sensitize human non-small cell lung cancer (NSCLC) cells to both platinum compounds and radiotherapy *in vitro* and *in vivo* (77, 79). The pharmacokinetics and the maximum tolerance dose (MTD) of YM155 have been evaluated in patients with non-Hodgkin's lymphoma, docetaxel-refractory prostate cancer and non-small cell lung cancer. Phase I clinical trials did not reveal any significant toxicity related to the use of YM155 as a single agent (73, 75, 76). In studies by Tolcher *et al.* and Satoh *et al.*, patients were treated with YM155 on a schedule of 168-hour continuous infusion every 3 weeks and the maximal tolerated dose (MTD) was defined as 4.8 and 8.0 mg/m2/d, respectively (73, 76). The non-hematological adverse events observed in these patients included stomatitis, pyrexia, nausea, arthralgia, urine microalbumin present, injection-site phlebitis, abnormal liver function test and decreased serum albumin level. Most adverse events were classified as Grade 1/2, with only one patient developing Grade 3 adverse effect (abnormal liver function). Increased level of serum creatinine was also noted as dose-limiting toxicity (DLT) in both trials, occurring only in the highest dose level. In Tolcher *et al.*'s trial, image responses occurred in three patients with non-Hodgkin's lymphoma, while two patients with heavily-treated prostate cancer experienced prostate-specific antigen response. One patient with non-small cell lung cancer had a minor response to the YM155 treatment. In addition, nine patients achieved stable disease in Satoh *et al.*'s trial.

Even though various pre-clinical and phase I clinical studies indicated that YM155 could be an effective anti-cancer reagent, phase II clinical trials showed disappointing results. Giaccone *et al.*'s study revealed that

the objective tumor response rate (ORR) to YM155 treatment (168-hour continuous infusion at a dose of 4.8 mg/m2/d) was approximately 5% in patient with advanced refractory non-small-cell lung carcinoma (75). In addition, around 70% of patients discontinued the regimen because of adverse effects (AE). In another study conducted by Lewis *et al.*, similar administration schedule was prescribed for melanoma chemotherapy-naive patients (80). The result of ORR in this study was even more disappointing: the response rate was approximately 3%. Notably, four patients experienced severe adverse events (SAE) that were possibly related to the drug. The trial has also focused on the determination of YM155-related cardio-toxicity. In this study, four subjects had been reported to exhibit cardiac rhythm AEs. This issue is not yet confirmed to be drug-related, but it should be noted in future studies.

Besides direct survivin inhibitors, indirect survivin inhibitors have also undergone various developments and investigations. However, the therapeutic effectiveness of these inhibitors is still questionable. For example, the heat shock protein 90 (Hsp90) inhibitors such as 17-AAG and shepherdin have been developed and were claimed to down-regulate survivin as one of their most important therapeutic effects (81-83). Base on the fact that Hsp90 physically binds to survivin and prevents the degradation of survivin by the proteasome, it is expected that interference of the physical interaction between Hsp90 and survivin with Hsp90-specific inhibitor will promote survivin degradation through the proteasome (84). Surprisingly, our recent study reveals that targeting Hsp90 by pharmacological inhibitors, geldanamycin and 17-AAG, induces the expression of survivin in A549, HT-29 and HONE-1 cancer cells through both transcriptional and post-transcriptional mechanisms (85). Since Hsp90 interferes with multiple molecules such as Sp1, Sp3 (both transcriptional factors and positive regulators of survivin), p53 (negative regulator of survivin transcription) and 26S proteasome (negative regulator of survivin protein level) simultaneously (86, 87), down-regulation of survivin may not be a definite therapeutic effect of Hsp90 inhibitors as we previously thought. In fact, a recent study from Stingl *et al.* also demonstrates that two novel Hsp90 inhibitors, NVP-AUY922 and NVP-BEP800, induce the up-regulation of survivin in the human HT1080 fibrosarcoma cells *in vitro* (88).

The effectiveness of another indirect survivin inhibitor, terameprocol, has also been investigated in various pre-clinical and clinical studies (89, 90). At the molecular level, terameprocol competes with the transcriptional factor Sp1 for specific Sp1 DNA binding domains within gene promoter regions during DNA synthesis. By suppressing Sp1-regulated transcription of the survivin gene (and other genes such as VEGF and cdk1), terameprocol may induce tumor cell apoptosis (89). However, detailed effectiveness and safety profiles of the use of terameprocol in clinical situations are still under evaluation. Furthermore, it is hard to know whether the down-regulation of survivin plays the major role in inducing cancer cells death during terameprocol treatment. On the other hand, a tubulin-targeted compound, EM011, has shown the ability to down-regulate survivin expression and subsequently induce survivin-related cancer cell death. It has been demonstrated that EM011 suppresses the proliferation of various human lung cancer cells such as A549, H460 and H157 *in vitro* (91). At the cellular level, EM011 induces mitotic arrest at the G_2/M phase by the activation of the spindle checkpoint. It is not surprising to know that EM011 is able to induce cell cycle arrest at the G_2/M phase because most anti-mitotic compounds such as vincristine, colchicine and palcitaxel are capable of inducing similar cellular and molecular responses (92). However, it is interesting to note that this compound could down-regulate the expression of survivin in cancer cells, given that survivin expression was previously shown to be increased in cells treated with other anti-mitotic compounds *in vitro* (30). The underlying mechanism of this effect has not yet been determined and it is hard to know whether the down-regulation of survivin plays a major role in inducing cancer cells death during EM011 treatment. Importantly, whether the down-regulation of survivin is a non-specific therapeutic effect of EM011 or the result of reduced metabolic rate (reduced rate of protein synthesis) in cells during the pro-apoptotic stage would also require further investigation.

4. SUMMARY AND PERSPECTIVE

Survivin plays multiple roles in the promotion of cancer cell survival and the causation of cancer anti-drug responses. The advancement of survivin biology in the past decade did not, however, translate immediately to the successful development of clinically applicable survivin-inhibitors, as the availability of survivin inhibitors is still limited at this stage. Therefore, further development of the survivin-specific small molecule inhibitors is required and may be important for future cancer treatments. On the other hand, optimized survivin-targeting macromolecules may be used as an alternative way to treat cancers that express survivin. As we have mentioned that survivin plays different roles in different organelles in cancer cells, organelle transduction domain (PTD)-mediated survivin-specific macromolecular therapy may be useful in combination with different organelle-specific chemotherapeutic compounds in future clinical settings. More investment and investigation is needed to develop better survivin-targeted treatments.

5. ACKNOWLEDGEMENTS

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6. REFERENCES

1. K. W. Sung, J. Choi, Y. K. Hwang, S. J. Lee, H. J. Kim, S. H. Lee, K. H. Yoo, H. L. Jung and H. H. Koo:

Overexpression of Apollon, an antiapoptotic protein, is associated with poor prognosis in childhood de novo acute myeloid leukemia. *Clin Cancer Res*, 13(17), 5109-14 (2007)

2. S. Qi, S. Mogi, H. Tsuda, Y. Tanaka, K. Kozaki, I. Imoto, J. Inazawa, S. Hasegawa and K. Omura: Expression of cIAP-1 correlates with nodal metastasis in squamous cell carcinoma of the tongue. *Int J Oral Maxillofac Surg*, 37(11), 1047-53 (2008)

3. J. W. Tichelaar, Y. Zhang, J. C. leRiche, P. W. Biddinger, S. Lam and M. W. Anderson: Increased staining for phospho-Akt, p65/RELA and cIAP-2 in pre-neoplastic human bronchial biopsies. *BMC Cancer*, 5, 155 (2005)

4. B. W. Richter, S. S. Mir, L. J. Eiben, J. Lewis, S. B. Reffey, A. Frattini, L. Tian, S. Frank, R. J. Youle, D. L. Nelson, L. D. Notarangelo, P. Vezzoni, H. O. Fearnhead and C. S. Duckett: Molecular cloning of ILP-2, a novel member of the inhibitor of apoptosis protein family. *Mol Cell Biol*, 21(13), 4292-301 (2001)

5. J. G. Chang, Y. J. Jong, S. P. Lin, B. W. Soong, C. H. Tsai, T. Y. Yang, C. P. Chang and W. S. Wang: Molecular analysis of survival motor neuron (SMN) and neuronal apoptosis inhibitory protein (NAIP) genes of spinal muscular atrophy patients and their parents. *Hum Genet*, 100(5-6), 577-81 (1997)

6. P. Gazzaniga, A. Gradilone, L. Giuliani, O. Gandini, I. Silvestri, I. Nofroni, G. Saccani, L. Frati and A. M. Agliano: Expression and prognostic significance of LIVIN, SURVIVIN and other apoptosis-related genes in the progression of superficial bladder cancer. *Ann Oncol*, 14(1), 85-90 (2003)

7. D. E. Burstein, M. T. Idrees, G. Li, M. Wu and T. Kalir: Immunohistochemical detection of the X-linked inhibitor of apoptosis protein (XIAP) in cervical squamous intraepithelial neoplasia and squamous carcinoma. *Ann Diagn Pathol*, 12(2), 85-9 (2008)

8. G. M. Kasof and B. C. Gomes: Livin, a novel inhibitor of apoptosis protein family member. *J Biol Chem*, 276(5), 3238-46 (2001)

9. W. Wang, H. Luo and A. Wang: Expression of survivin and correlation with PCNA in osteosarcoma. *Journal of Surgical Oncology*, 93(7), 578-84 (2006)

10. I. Esposito, J. Kleeff, I. Abiatari, X. Shi, N. Giese and P. Schirmacher: cIAP2 Overexpression is an early event in pancreatic cancer progression. *Journal of Clinical Pathology* (2006)

11. H. Takeuchi, J. Kim, A. Fujimoto, N. Umetani, T. Mori, A. Bilchik, R. Turner, A. Tran, C. Kuo and D. S. Hoon: X-Linked inhibitor of apoptosis protein expression level in colorectal cancer is regulated by hepatocyte growth factor/C-met pathway via Akt signaling. *Clinical Cancer Research*, 11(21), 7621-8 (2005)

12. T. Samuel, K. Okada, M. Hyer, K. Welsh, J. M. Zapata and J. C. Reed: cIAP1 Localizes to the nuclear compartment and modulates the cell cycle. *Cancer Research*, 65(1), 210-8 (2005)

13. S. Lu, B. Zhang and Z. Wang: Expression of survivin, cyclinD1, p21(WAF1), caspase-3 in cervical cancer and its relation with prognosis. *Journal of Huazhong University of Science and Technology. Medical Sciences*, 25(1), 78-81 (2005)

14. M. E. Johnson and E. W. Howerth: Survivin: a bifunctional inhibitor of apoptosis protein. *Veterinary Pathology*, 41(6), 599-607 (2004)

15. M. Delvaeye, A. De Vriese, F. Zwerts, I. Betz, M. Moons, M. Autiero and E. M. Conway: Role of the 2 zebrafish survivin genes in vasculo-angiogenesis, neurogenesis, cardiogenesis and hematopoiesis. *BMC Dev Biol*, 9, 25 (2009)

16. Y. Jiang, A. de Bruin, H. Caldas, J. Fangusaro, J. Hayes, E. M. Conway, M. L. Robinson and R. A. Altura: Essential role for survivin in early brain development. *J Neurosci*, 25(30), 6962-70 (2005)

17. C. Y. Lin, H. C. Hung, R. C. Kuo, C. P. Chiang and M. Y. Kuo: Survivin expression predicts poorer prognosis in patients with areca quid chewing-related oral squamous cell carcinoma in Taiwan. *Oral Oncol*, 41(6), 645-54 (2005)

18. K. F. Hsu, C. K. Lin, C. P. Yu, C. Tzao, S. C. Lee, Y. Y. Lee, W. C. Tsai and J. S. Jin: Cortactin, fascin, and survivin expression associated with clinicopathological parameters in esophageal squamous cell carcinoma. *Dis Esophagus*, 22(5), 402-8 (2009)

19. S. F. Preuss, A. Weinell, M. Molitor, M. Stenner, R. Semrau, U. Drebber, S. J. Weissenborn, E. J. Speel, C. Wittekindt, O. Guntinas-Lichius, T. K. Hoffmann, G. D. Eslick and J. P. Klussmann: Nuclear survivin expression is associated with HPV-independent carcinogenesis and is an indicator of poor prognosis in oropharyngeal cancer. *Br J Cancer*, 98(3), 627-32 (2008)

20. X. Gu and H. L. Lin: [Analysis of survivin expression in subtypes of lymphoma]. *Ai Zheng*, 23(6), 655-61 (2004)

21. A. A. Sahasrabuddhe, R. C. Nayak and C. M. Gupta: Ancient Leishmania coronin (CRN12) is involved in microtubule remodeling during cytokinesis. *J Cell Sci*, 122(Pt 10), 1691-9 (2009)

22. A. I. Sarela, R. C. Macadam, S. M. Farmery, A. F. Markham and P. J. Guillou: Expression of the antiapoptosis gene, survivin, predicts death from recurrent colorectal carcinoma. *Gut*, 46(5), 645-50 (2000)

23. H. Kawasaki, M. Toyoda, H. Shinohara, J. Okuda, I. Watanabe, T. Yamamoto, K. Tanaka, T. Tenjo and N. Tanigawa: Expression of survivin correlates with apoptosis,

proliferation, and angiogenesis during human colorectal tumorigenesis. *Cancer*, 91(11), 2026-32 (2001)

24. S. Shin, B. J. Sung, Y. S. Cho, H. J. Kim, N. C. Ha, J. I. Hwang, C. W. Chung, Y. K. Jung and B. H. Oh: An anti-apoptotic protein human survivin is a direct inhibitor of caspase-3 and -7. *Biochemistry*, 40(4), 1117-23 (2001)

25. I. Tamm, Y. Wang, E. Sausville, D. A. Scudiero, N. Vigna, T. Oltersdorf and J. C. Reed: IAP-family protein survivin inhibits caspase activity and apoptosis induced by Fas (CD95), Bax, caspases, and anticancer drugs. *Cancer Res*, 58(23), 5315-20 (1998)

26. T. Dohi, E. Beltrami, N. R. Wall, J. Plescia and D. C. Altieri: Mitochondrial survivin inhibits apoptosis and promotes tumorigenesis. *J Clin Invest*, 114(8), 1117-27 (2004)

27. L. Chantalat, D. A. Skoufias, J. P. Kleman, B. Jung, O. Dideberg and R. L. Margolis: Crystal structure of human survivin reveals a bow tie-shaped dimer with two unusual alpha-helical extensions. *Mol Cell*, 6(1), 183-9 (2000)

28. X. Wang, C. Yang, J. Chai, Y. Shi and D. Xue: Mechanisms of AIF-mediated apoptotic DNA degradation in Caenorhabditis elegans. *Science*, 298(5598), 1587-92 (2002)

29. C. Cande, I. Cohen, E. Daugas, L. Ravagnan, N. Larochette, N. Zamzami and G. Kroemer: Apoptosis-inducing factor (AIF): a novel caspase-independent death effector released from mitochondria. *Biochimie*, 84(2-3), 215-22 (2002)

30. C. H. Cheung, H. H. Chen, C. C. Kuo, C. Y. Chang, M. S. Coumar, H. P. Hsieh and J. Y. Chang: Survivin counteracts the therapeutic effect of microtubule de-stabilizers by stabilizing tubulin polymers. *Mol Cancer*, 8, 43 (2009)

31. M. Okuya, H. Kurosawa, J. Kikuchi, Y. Furukawa, H. Matsui, D. Aki, T. Matsunaga, T. Inukai, H. Goto, R. A. Altura, K. Sugita, O. Arisaka, A. T. Look and T. Inaba: Up-regulation of Survivin by the E2A-HLF Chimera Is Indispensable for the Survival of t(17;19)-positive Leukemia Cells. *Journal of Biological Chemistry*, 285(3), 1850-1860 (2010)

32. D. O. Croci, I. S. Cogno, N. B. Vittar, E. Salvatierra, F. Trajtenberg, O. L. Podhajcer, E. Osinaga, G. A. Rabinovich and V. A. Rivarola: Silencing survivin gene expression promotes apoptosis of human breast cancer cells through a caspase-independent pathway. *J Cell Biochem*, 105(2), 381-90 (2008)

33. G. Vader, J. J. Kauw, R. H. Medema and S. M. Lens: Survivin mediates targeting of the chromosomal passenger complex to the centromere and midbody. *EMBO Rep*, 7(1), 85-92 (2006)

34. M. A. Bolton, W. Lan, S. E. Powers, M. L. McCleland, J. Kuang and P. T. Stukenberg: Aurora B kinase exists in a complex with survivin and INCENP and its kinase activity is stimulated by survivin binding and phosphorylation. *Mol Biol Cell*, 13(9), 3064-77 (2002)

35. S. P. Wheatley, A. Carvalho, P. Vagnarelli and W. C. Earnshaw: INCENP is required for proper targeting of Survivin to the centromeres and the anaphase spindle during mitosis. *Curr Biol*, 11(11), 886-90 (2001)

36. A. A. Jeyaprakash, U. R. Klein, D. Lindner, J. Ebert, E. A. Nigg and E. Conti: Structure of a Survivin-Borealin-INCENP core complex reveals how chromosomal passengers travel together. *Cell*, 131(2), 271-85 (2007)

37. A. G. Uren, L. Wong, M. Pakusch, K. J. Fowler, F. J. Burrows, D. L. Vaux and K. H. Choo: Survivin and the inner centromere protein INCENP show similar cell-cycle localization and gene knockout phenotype. *Current Biology*, 10(21), 1319-28 (2000)

38. J. Rosa, P. Canovas, A. Islam, D. C. Altieri and S. J. Doxsey: Survivin modulates microtubule dynamics and nucleation throughout the cell cycle. *Mol Biol Cell*, 17(3), 1483-93 (2006)

39. P. Fortugno, N. R. Wall, A. Giodini, D. S. O'Connor, J. Plescia, K. M. Padgett, S. Tognin, P. C. Marchisio and D. C. Altieri: Survivin exists in immunochemically distinct subcellular pools and is involved in spindle microtubule function. *J Cell Sci*, 115(Pt 3), 575-85 (2002)

40. H. Roca, Z. Varsos and K. J. Pienta: CCL2 protects prostate cancer PC3 cells from autophagic death via phosphatidylinositol 3-kinase/AKT-dependent survivin up-regulation. *J Biol Chem*, 283(36), 25057-73 (2008)

41. H. Roca, Z. S. Varsos, K. Mizutani and K. J. Pienta: CCL2, survivin and autophagy: new links with implications in human cancer. *Autophagy*, 4(7), 969-71 (2008)

42. M. Pennati, M. Folini and N. Zaffaroni: Targeting survivin in cancer therapy: fulfilled promises and open questions. *Carcinogenesis*, 28(6), 1133-9 (2007)

43. H. Kojima, M. Iida, Y. Yaguchi, R. Suzuki, N. Hayashi, H. Moriyama and Y. Manome: Enhancement of Cisplatin sensitivity in squamous cell carcinoma of the head and neck transfected with a survivin antisense gene. *Arch Otolaryngol Head Neck Surg*, 132(6), 682-5 (2006)

44. M. Zhang, N. Mukherjee, R. S. Bermudez, D. E. Latham, M. A. Delaney, A. L. Zietman, W. U. Shipley and A. Chakravarti: Adenovirus-mediated inhibition of survivin expression sensitizes human prostate cancer cells to paclitaxel *in vitro* and *in vivo*. *Prostate*, 64(3), 293-302 (2005)

45. T. Nomura, M. Yamasaki, Y. Nomura and H. Mimata: Expression of the inhibitors of apoptosis proteins in cisplatin-resistant prostate cancer cells. *Oncol Rep*, 14(4), 993-7 (2005)

46. M. Ikeguchi, J. Liu and N. Kaibara: Expression of survivin mRNA and protein in gastric cancer cell line

(MKN-45) during cisplatin treatment. *Apoptosis*, 7(1), 23-9 (2002)

47. J. H. Xu, A. X. Wang, H. Z. Huang, J. G. Wang, C. B. Pan and B. Zhang: Survivin shRNA induces caspase-3-dependent apoptosis and enhances cisplatin sensitivity in squamous cell carcinoma of the tongue. *Oncol Res*, 18(8), 377-85 (2010)

48. N. Zaffaroni, M. Pennati, G. Colella, P. Perego, R. Supino, L. Gatti, S. Pilotti, F. Zunino and M. G. Daidone: Expression of the anti-apoptotic gene survivin correlates with taxol resistance in human ovarian cancer. *Cell Mol Life Sci*, 59(8), 1406-12 (2002)

49. S. Q. He, H. Rehman, M. G. Gong, Y. Z. Zhao, Z. Y. Huang, C. H. Li, W. G. Zhang and X. P. Chen: Inhibiting survivin expression enhances TRAIL-induced tumoricidal activity in human hepatocellular carcinoma via cell cycle arrest. *Cancer Biol Ther*, 6(8), 1247-57 (2007)

50. R. Moriai, N. Tsuji, M. Moriai, D. Kobayashi and N. Watanabe: Survivin plays as a resistant factor against tamoxifen-induced apoptosis in human breast cancer cells. *Breast Cancer Res Treat*, 117(2), 261-71 (2009)

51. M. Zhang, D. E. Latham, M. A. Delaney and A. Chakravarti: Survivin mediates resistance to antiandrogen therapy in prostate cancer. *Oncogene*, 24(15), 2474-82 (2005)

52. F. Liu, Z. H. Xie, G. P. Cai and Y. Y. Jiang: The effect of survivin on multidrug resistance mediated by P-glycoprotein in MCF-7 and its adriamycin resistant cells. *Biol Pharm Bull*, 30(12), 2279-83 (2007)

53. J. Tran, Z. Master, J. L. Yu, J. Rak, D. J. Dumont and R. S. Kerbel: A role for survivin in chemoresistance of endothelial cells mediated by VEGF *Proceedings of the National Academy of Sciences of the United States of America*, 99(7), 4349-4354 (2002)

54. D. S. O' Connor, J. S. Schechner, C. Adida, M. Mesri, A. L. Rothermel, F. Li, A. K. Nath, J. S. Pober and D. C. Altieri: Control of Apoptosis during Angiogenesis by Survivin Expression in Endothelial Cells. *The American Journal of Pathology*, 156(2), 393-398 (2000)

55. D. S. O'Connor, J. S. Schechner, C. Adida, M. Mesri, A. L. Rothermel, F. Li, A. K. Nath, J. S. Pober and D. C. Altieri: Control of apoptosis during angiogenesis by survivin expression in endothelial cells. *Am J Pathol*, 156(2), 393-8 (2000)

56. G. Jiang, B. Ren, L. Xu, S. Song, C. Zhu and F. Ye: Survivin may enhance DNA double-strand break repair capability by up-regulating Ku70 in human KB cells. *Anticancer Res*, 29(1), 223-8 (2009)

57. G. Y. Miao, Q. M. Lu and X. L. Zhang: Downregulation of survivin by RNAi inhibits growth of human gastric carcinoma cells. *World J Gastroenterol*, 13(8), 1170-4 (2007)

58. Y. Wang, H. Zhu, L. Quan, C. Zhou, J. Bai, G. Zhang, Q. Zhan and N. Xu: Downregulation of survivin by RNAi inhibits the growth of esophageal carcinoma cells. *Cancer Biol Ther*, 4(9), 974-8 (2005)

59. Y. Zhang, Z. D. Chen, C. J. Du, G. Xu and W. Luo: siRNA targeting survivin inhibits growth and induces apoptosis in human renal clear cell carcinoma 786-O cells. *Pathol Res Pract*, 205(12), 823-7 (2009)

60. S. Ning, S. Fuessel, M. Kotzsch, K. Kraemer, M. Kappler, U. Schmidt, H. Taubert, M. P. Wirth and A. Meye: siRNA-mediated down-regulation of survivin inhibits bladder cancer cell growth. *Int J Oncol*, 25(4), 1065-71 (2004)

61. Q. X. Li, J. Zhao, J. Y. Liu, L. T. Jia, H. Y. Huang, Y. M. Xu, Y. Zhang, R. Zhang, C. J. Wang, L. B. Yao, S. Y. Chen and A. G. Yang: Survivin stable knockdown by siRNA inhibits tumor cell growth and angiogenesis in breast and cervical cancers. *Cancer Biol Ther*, 5(7), 860-6 (2006)

62. J. J. Wang, Y. Zheng, F. Yang, P. Zhao and H. F. Li: Survivin small interfering RNA transfected with a microbubble and ultrasound exposure inducing apoptosis in ovarian carcinoma cells. *Int J Gynecol Cancer*, 20(4), 500-6 (2010)

63. J. B. Hansen, N. Fisker, M. Westergaard, L. S. Kjaerulff, H. F. Hansen, C. A. Thrue, C. Rosenbohm, M. Wissenbach, H. Orum and T. Koch: SPC3042: a proapoptotic survivin inhibitor. *Mol Cancer Ther*, 7(9), 2736-45 (2008)

64. T. Liu, B. Brouha and D. Grossman: Rapid induction of mitochondrial events and caspase-independent apoptosis in Survivin-targeted melanoma cells. *Oncogene*, 23(1), 39-48 (2004)

65. J. R. Kanwar, W. P. Shen, R. K. Kanwar, R. W. Berg and G. W. Krissansen: Effects of survivin antagonists on growth of established tumors and B7-1 immunogene therapy. *J Natl Cancer Inst*, 93(20), 1541-52 (2001)

66. L. Pan, X. C. Peng, F. Leng, Q. Z. Yuan, Y. Shan, D. D. Yu, Z. Y. Li, X. Chen, W. J. Xiao, Y. Wen, T. T. Ma, L. Yang, Y. Q. Mao, H. S. Yang, Y. Q. Wei and C. T. Wang: Therapeutic effects of survivin dominant negative mutant in a mouse model of prostate cancer. *J Cancer Res Clin Oncol* (2010)

67. D. S. O'Connor, D. Grossman, J. Plescia, F. Li, H. Zhang, A. Villa, S. Tognin, P. C. Marchisio and D. C. Altieri: Regulation of apoptosis at cell division by p34cdc2 phosphorylation of survivin. *Proc Natl Acad Sci U S A*, 97(24), 13103-7 (2000)

68. C. H. A. Cheung, J. Kanwar and G. W. Krissansen: A cell-permeable dominant-negative Survivin protein as a tool to understand how Survivin maintains tumour cell survival. *Ejc Supplements*, 4(12), 488 (2006)

69. C. Shen, W. Liu, A. K. Buck and S. N. Reske: Pro-apoptosis and anti-proliferation effects of a recombinant dominant-negative survivin-T34A in human cancer cells. *Anticancer Res*, 29(4), 1423-8 (2009)

70. S. Khan, J. R. Aspe, M. G. Asumen, F. Almaguel, O. Odumosu, S. Acevedo-Martinez, M. De Leon, W. H. Langridge and N. R. Wall: Extracellular, cell-permeable survivin inhibits apoptosis while promoting proliferative and metastatic potential. *Br J Cancer*, 100(7), 1073-86 (2009)

71. M. S. Coumar, C. H. Cheung, J. Y. Chang and H. P. Hsieh: Advances in Aurora kinase inhibitor patents. *Expert Opin Ther Pat*, 19(3), 321-56 (2009)

72. C. H. Cheung, M. S. Coumar, H. P. Hsieh and J. Y. Chang: Aurora kinase inhibitors in preclinical and clinical testing. *Expert Opin Investig Drugs*, 18(4), 379-98 (2009)

73. T. Satoh, I. Okamoto, M. Miyazaki, R. Morinaga, A. Tsuya, Y. Hasegawa, M. Terashima, S. Ueda, M. Fukuoka, Y. Ariyoshi, T. Saito, N. Masuda, H. Watanabe, T. Taguchi, T. Kakihara, Y. Aoyama, Y. Hashimoto and K. Nakagawa: Phase I study of YM155, a novel survivin suppressant, in patients with advanced solid tumors. *Clin Cancer Res*, 15(11), 3872-80 (2009)

74. T. Minematsu, M. Iwai, K. Sugimoto, N. Shirai, T. Nakahara, T. Usui and H. Kamimura: Carrier-mediated uptake of 1-(2-methoxyethyl)-2-methyl-4,9-dioxo-3-(pyrazin-2-ylmethyl)-4,9-dihydro-1 H-naphtho[2,3-d]imidazolium bromide (YM155 monobromide), a novel small-molecule survivin suppressant, into human solid tumor and lymphoma cells. *Drug Metab Dispos*, 37(3), 619-28 (2009)

75. G. Giaccone, P. Zatloukal, J. Roubec, K. Floor, J. Musil, M. Kuta, R. J. van Klaveren, S. Chaudhary, A. Gunther and S. Shamsili: Multicenter phase II trial of YM155, a small-molecule suppressor of survivin, in patients with advanced, refractory, non-small-cell lung cancer. *J Clin Oncol*, 27(27), 4481-6 (2009)

76. A. W. Tolcher, A. Mita, L. D. Lewis, C. R. Garrett, E. Till, A. I. Daud, A. Patnaik, K. Papadopoulos, C. Takimoto, P. Bartels, A. Keating and S. Antonia: Phase I and pharmacokinetic study of YM155, a small-molecule inhibitor of survivin. *J Clin Oncol*, 26(32), 5198-203 (2008)

77. T. Iwasa, I. Okamoto, M. Suzuki, T. Nakahara, K. Yamanaka, E. Hatashita, Y. Yamada, M. Fukuoka, K. Ono and K. Nakagawa: Radiosensitizing effect of YM155, a novel small-molecule survivin suppressant, in non-small cell lung cancer cell lines. *Clin Cancer Res*, 14(20), 6496-504 (2008)

78. T. Nakahara, M. Takeuchi, I. Kinoyama, T. Minematsu, K. Shirasuna, A. Matsuhisa, A. Kita, F. Tominaga, K. Yamanaka, M. Kudoh and M. Sasamata: YM155, a novel small-molecule survivin suppressant, induces regression of established human hormone-refractory prostate tumor xenografts. *Cancer Res*, 67(17), 8014-21 (2007)

79. T. Iwasa, I. Okamoto, K. Takezawa, K. Yamanaka, T. Nakahara, A. Kita, H. Koutoku, M. Sasamata, E. Hatashita, Y. Yamada, K. Kuwata, M. Fukuoka and K. Nakagawa: Marked anti-tumour activity of the combination of YM155, a novel survivin suppressant, and platinum-based drugs. *Br J Cancer* (2010)

80. K. D. Lewis, W. Samlowski, J. Ward, J. Catlett, L. Cranmer, J. Kirkwood, D. Lawson, E. Whitman and R. Gonzalez: A multi-center phase II evaluation of the small molecule survivin suppressor YM155 in patients with unresectable stage III or IV melanoma. *Invest New Drugs* (2009)

81. M. D. Siegelin, A. Habel and T. Gaiser: 17-AAG sensitized malignant glioma cells to death-receptor mediated apoptosis. *Neurobiol Dis*, 33(2), 243-9 (2009)

82. J. Okamoto, I. Mikami, Y. Tominaga, K. M. Kuchenbecker, Y. C. Lin, D. T. Bravo, G. Clement, A. Yagui-Beltran, M. R. Ray, K. Koizumi, B. He and D. M. Jablons: Inhibition of Hsp90 leads to cell cycle arrest and apoptosis in human malignant pleural mesothelioma. *J Thorac Oncol*, 3(10), 1089-95 (2008)

83. J. Plescia, W. Salz, F. Xia, M. Pennati, N. Zaffaroni, M. G. Daidone, M. Meli, T. Dohi, P. Fortugno, Y. Nefedova, D. I. Gabrilovich, G. Colombo and D. C. Altieri: Rational design of shepherdin, a novel anticancer agent. *Cancer Cell*, 7(5), 457-68 (2005)

84. P. Fortugno, E. Beltrami, J. Plescia, J. Fontana, D. Pradhan, P. C. Marchisio, W. C. Sessa and D. C. Altieri: Regulation of survivin function by Hsp90. *Proc Natl Acad Sci U S A*, 100(24), 13791-6 (2003)

85. C. H. Cheung, H. H. Chen, L. T. Cheng, K. W. Lyu, J. R. Kanwar and J. Y. Chang: Targeting Hsp90 with small molecule inhibitors induces the over-expression of the anti-apoptotic molecule, survivin, in human A549, HONE-1 and HT-29 cancer cells. *Mol Cancer*, 9, 77 (2010)

86. S.-a. Wang and J.-J. Hung: Hsp90 localized with Sp1 in mitosis involves in Sp1 stability. *FASEB J.*, 22(1_MeetingAbstracts), 838.2- (2008)

87. J. Imai, M. Maruya, H. Yashiroda, I. Yahara and K. Tanaka: The molecular chaperone Hsp90 plays a role in the assembly and maintenance of the 26S proteasome. *EMBO J*, 22(14), 3557-67 (2003)

88. L. Stingl, T. Stuhmer, M. Chatterjee, M. R. Jensen, M. Flentje and C. S. Djuzenova: Novel HSP90 inhibitors, NVP-AUY922 and NVP-BEP800, radiosensitise tumour cells through cell-cycle impairment, increased DNA

damage and repair protraction. *Br J Cancer*, 102(11), 1578-91 (2010)

89. R. A. Lopez, A. B. Goodman, M. Rhodes, J. A. Blomberg and J. Heller: The anticancer activity of the transcription inhibitor terameprocol (meso-tetra-O-methyl nordihydroguaiaretic acid) formulated for systemic administration. *Anticancer Drugs*, 18(8), 933-9 (2007)

90. N. Khanna, R. Dalby, M. Tan, S. Arnold, J. Stern and N. Frazer: Phase I/II clinical safety studies of terameprocol vaginal ointment. *Gynecol Oncol*, 107(3), 554-62 (2007)

91. P. Karna, S. M. Sharp, C. Yates, S. Prakash and R. Aneja: EM011 activates a survivin-dependent apoptotic program in human non-small cell lung cancer cells. *Mol Cancer*, 8, 93 (2009)

92. M. A. Jordan and L. Wilson: Microtubules as a target for anticancer drugs. *Nat Rev Cancer*, 4(4), 253-265 (2004)

Abbreviations: AE (adverse effect), IAP (inhibitor-of-apoptosis), INCENP (inner centromere protein), TRAIL (tumor necrosis factor–related apoptosis-inducing ligand), YM155 (1-(2-Methoxyethyl)-2-methyl-4,9-dioxo-3-(pyrazin-2-ylmethyl)-4,9-dihydro -1H-naphtho[2,3-d]imidazolium bromide)

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