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Perspective

Anticancer drug FL118 is more than a survivin inhibitor: where is the Achilles' heel of cancer?

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Abstract: Can a solution be found that overcomes all chemotherapy and/or radiation resistance resulting from different genetic and epigenetic alternations in various cancer types? The answer is likely NO. However, there are two ways that may be followed to approach this goal. One way is through the use of poly-therapies that target multiple mechanisms to kill cancer cells, which is the current state of the art. This approach raises issues of high costs and/or toxic limitations, since the toxicities of each agent are often additive. This poly-pharmacy approach has not proven to be a major success, although it has proven to be superior to most current mono-pharmacy approaches. The other way to approach the goal is to find a single anticancer drug that targets multiple different treatment resistant mechanisms. In this regard, a small chemical molecule (FL118) was recently discovered by serendipity during targeted discovery of anticancer drugs using the survivin gene as a target and biomarker. FL118 was found to not only inhibit multiple antiapoptotic proteins (survivin, XIAP, cIAP2) in the inhibitor of apoptosis (IAP) family, but to also inhibit the antiapoptotic protein Mcl-1 in the Bcl-2 family, while inducing the pro-apoptotic proteins Bax and Bim expression. Importantly, inhibition of these target genes and of tumor growth by FL118 is independent of p53 status (wild type, mutant or null), although mechanisms of action may be distinct among cells with different p53 status. Therefore, FL118 may effectively control cancer that loses functional p53, in which most DNA damage drugs (if not all) show a marked lack of efficiency. Recent studies further revealed that the superior anticancer activity of FL118 is highly dependent on its primary structure and steric configuration, suggesting that FL118 may be a promising drug platform for generating novel derivatives based on its core structure. Intriguingly, although FL118 has structural similarity to irinotecan and topotecan, two FDA-approved topoisomerase 1 (Top1) inhibitors for cancer treatment, cancer cells with Top1 mutations shows little contributions of treatment resistance to FL118 antitumor activity, while strikingly increasing irinotecan and topotecan resistance. Furthermore, both irinotecan and topotecan are the efflux pump ABCG2 substrates; cancer cells with high expression of ABCG2 showed strong irinotecan and topotecan resistance. In contrast, FL118 is not an ABCG2 substrate; ABCG2 overexpression in cancer cells does not show resistance to FL118 treatment. Current evidence suggests that future studies may unravel more unexpected mechanisms of action for this unique small molecule FL118.

Keywords: Anticancer, drug, FL118, survivin inhibitor, the inhibitor of apoptosis, topoisomerase 1

Introduction

Eradication of cancer is an ultimate mission in the cancer research field and clinical practice. One unsolved challenge for realizing the mission is cancer treatment (chemotherapy, radiation) resistance, which is a major cause of a high rate of cancer recurrence after treatment. Treatment resistance and cancer recurrence are responsible for the majority (if not all) of cancer patient deaths. Such resistance therefore continues to challenge the entire field.

The question is where is the Achilles' heel of cancer and can we overcome these challenges. Accumulated knowledge from cancer research and clinical trials reveals that cancer treatment resistance results from multiple different mechanisms, and the resistance to traditional cytotoxic drugs and molecularly targeted agents shares similar characteristics including genetic and/or epigenetic alternations, induced and/or constitutive activation of pro-survival pathways to evade cell death, and increased drug efflux via ATP-binding cassette (ABC) transporters, to name some of the more commonly encountered mechanisms of resistance [1]. Cancer is a highly heterogeneous disease [2]; new studies indicate that gene-expression signatures of

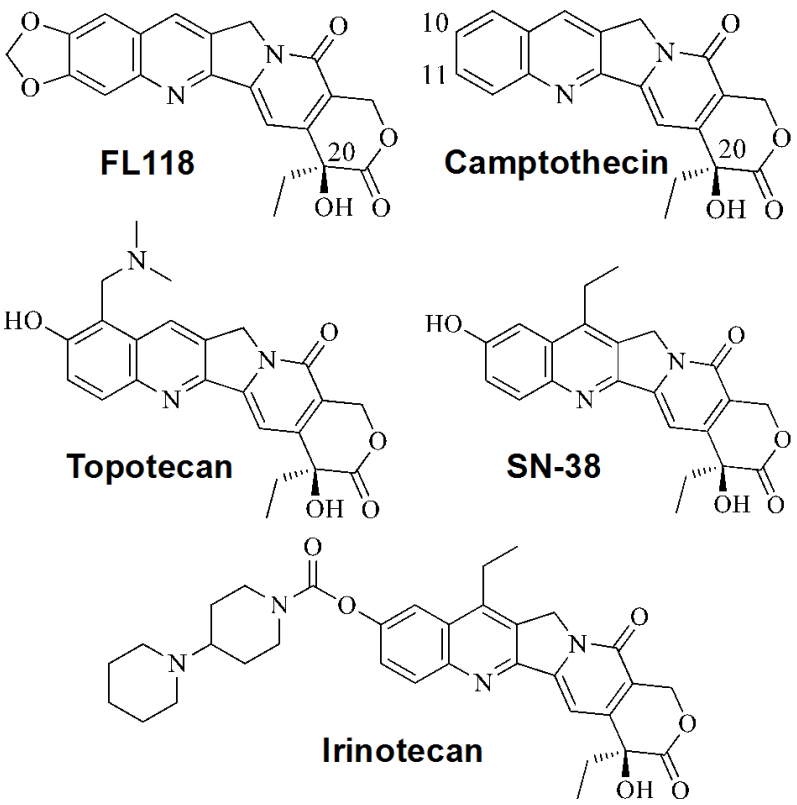

Figure 1. Chemical structure of FL118, Camptothecin (CPT), topotecan, SN-38 (active metabolite of irinotecan) and irinotecan (CPT11).

favorable versus unfavorable prognosis can be detected in different regions of the same tumor, and a significant percentage of somatic mutations may not be detected across every tumor region [3]. It is clear that such extensive intratumor heterogeneity presents a new challenge for the current concept of personalized cancer treatment (personalized medicine) and biomarker development. Since the new findings provide a rich seeding soil for positive selection of resistant cancer cells during treatment with current medicines, the current medicine and approaches would not well resolve the issue of cancer treatment resistance. New approaches are needed.

To face up to the continuing challenge in treatment resistance, we must consider the fact that treatment resistance results from diverse molecular mechanisms. Based on the nature of various anticancer agents that are currently available for cancer treatment, we can use a defined treatment regimen that contains multiple molecularly targeted agents to target multiple different resistant mechanisms. While this approach may help to control some cancers without inducing high toxicity to normal tissue, this approach will be too costly for cancer patients or insurance coverage. So clinically, it is rare to employ this approach for cancer treatment. Alternatively, we can use a defined treatment regimen that applies multiple traditional cytotoxic agents. This approach would maintain affordable costs for patients, while enjoying maximal control of cancer with traditional cytotoxic drugs. The challenge of this approach is the high toxicity to patients and thus limited its application. To balance the above two approaches, the trend in the current clinical practice is to use one molecularly targeted agent plus one or two traditional cytotoxic drugs as a combination regimen to balance the issue of toxicity, efficacy and cost. However, this approach is also unable to avoid eventual escapes by the treated cancer in many situations, as resistance usually develops during treatment. Furthermore, current medicines and approaches still only extend life by months in comparison with best supportive care shown in clinical trials. For example, regorafenib (Trade name: Stivarga) was approved in the United States on Sept 27, 2012 for treatment of metastatic colorectal cancer. However, the clinical trial showed that although regorafenib extended overall survival for metastatic colorectal cancer patients after failure from all approved standard therapies, median overall survival was only 6.4 months with regorafenib versus 5.0 months with best supportive care [4].

In this perspective, the author proposes an additional strategy to face up to the challenge of treatment resistance. While a drug that overcomes all types of treatment resistance may not be created or discovered, it is highly possible that one anticancer agent that targets mul-

Table 1. Comparison of the relative potency (RP) of FL118 with topotecan, SN-38 (active form of irinotecan) and camptothecin (CPT): RP was calculated by dividing the IC50 of topotecan with the IC50 of CPT, SN-38 and FL118 in each line*

	DU-145		RC0.1		RC1	
	IC50 (nM)	IP	IC50 (nM)	IP	IC50 (nM)	IP
CPT	60	3.17	63300	0.97	21700	2.69
SN-38	40	4.75	11670	5.24	4430	13.2
Topotecan	190	1	61200	1	58300	1
FL118	4.56	41.7	78.7	778	102	572

*The IC50 data for CPT, SN-38, topotecan is adopted from Urasaki Y et al., Characterization of a novel Topoisomerase I mutation from a camptothecin-resistant human prostate cancer cell line. Cancer Res 2001; 61: 1964-1969.

tiple treatment resistant mechanisms can be created or discovered, thus greatly improving outcomes while lowering costs to more sustainable levels. Here, the author will take FL118 (a novel camptothecin analog in terms of the compound structure) as a "proof of concept" example to show that one molecule can target or bypass multiple different treatment resistant mechanisms and thus FL118 shows high effective to eliminate human colon and head-&-neck cancer in animal models with favorable toxicity profiles [5-7].

Is FL118 a topoisomerase 1 (Top1) inhibitor?

This question is raised at the beginning, because FL118 structurally has similarity with irinotecan, SN-38 (active metabolite of irinotecan), and topotecan, which are classified as camptothecin (CPT) derivatives (**Figure 1**). It is known that the CPT analogs, irinotecan, SN-38 and topotecan are Top1 inhibitors. We demonstrated that the antitumor efficacy of FL118 is much superior to the antitumor efficacy of irinotecan in animal model of both human colon and head-&-neck tumors [5]. Therefore, it is possible that FL118 may be a better Top1 inhibitor than irinotecan. Irinotecan is a pro-drug and shows very low activity in the *in vitro* experiment, we therefore used its active metabolite SN-38 to compare their relative ability to inhibit Top1 activity for an answer. Our studies indicated that even at a 1 μM level, which is the highest SN-38 dose that can be reached by irinotecan *in vivo*, FL118 shows poor ability to inhibit Top1 activity (at most, half of those that SN-38 shows) [5]. However, FL118 can effectively inhibit cancer cell growth at far below a nM level [5]. These observations suggest that inhibition of Top1 activity by FL118 unlikely plays a major role in FL118-mediated inhibition of cancer cell growth and induction of tumor regression. This notion was further supported by the observation that the Du145 prostate cancer cell line-derived two sub-cell lines with Top1 mutations (RC0.1, RC1) strikingly increase resistance to CPT, SN-38 and topotecan in comparison with their parental Du145 cell line (**Table 1**). In other words, in the parental Du145 cell line, FL118 is only about 10-40 folds more effective than CPT, SN-38 and topotecan to inhibit cancer cell growth. However, after Top1 is mutated in Du145-derived RC0.1 and RC1 cell lines, FL118 is up to 800 folds more effective than CPT, SN-38 and topotecan (**Table 1**). Specifically, RC0.1 and RC1 are 778 and 572 times more resistant to topotecan, respectively, in comparison with FL118 (**Table 1**). Altogether, these observations indicate that although FL118 structurally has similarity to topotecan, SN-38 and CTP (**Figure 1**), FL118's anticancer activity is unlikely through the inhibition of Top1 activity as its major mechanism of action. FL118 should have its unique mechanisms of action that are different from the Top1 inhibitors, irinotecan, SN-38 and topotecan.

What is the selectivity of FL118 to inhibit IAP and Bcl-2 family antiapoptotic proteins?

As reported, FL118 has been discovered by serendipity when researchers used genetically engineered cancer cell models in which the survivin gene was used as a target and biomarker, to find survivin inhibitors through high throughput screening (HTS), followed by *in vitro* and *in vivo* characterization [5]. FL118 selectively inhibits the survivin gene promoter activity and endogenous survivin expression. Specifically, FL118 at a concentration of 1-10 nM can effectively inhibit survivin promoter activity, while FL118 at 10 nM shows no inhibitory effects on promoter activity of the cell cycle regulator p21 gene, the dihydrofolate reductase (DHFR) gene, the human thrombin receptor (HTR) gene and the thymidine kinase (TK) gene [5], indicating high selectivity compared to those non-cancer related genes. However, in addition to survivin, FL118 selectively inhibits the expression of XIAP and cIAP2 (IAP family), and Mcl-1 (Bcl-2 family), while inducing the expression of pro-

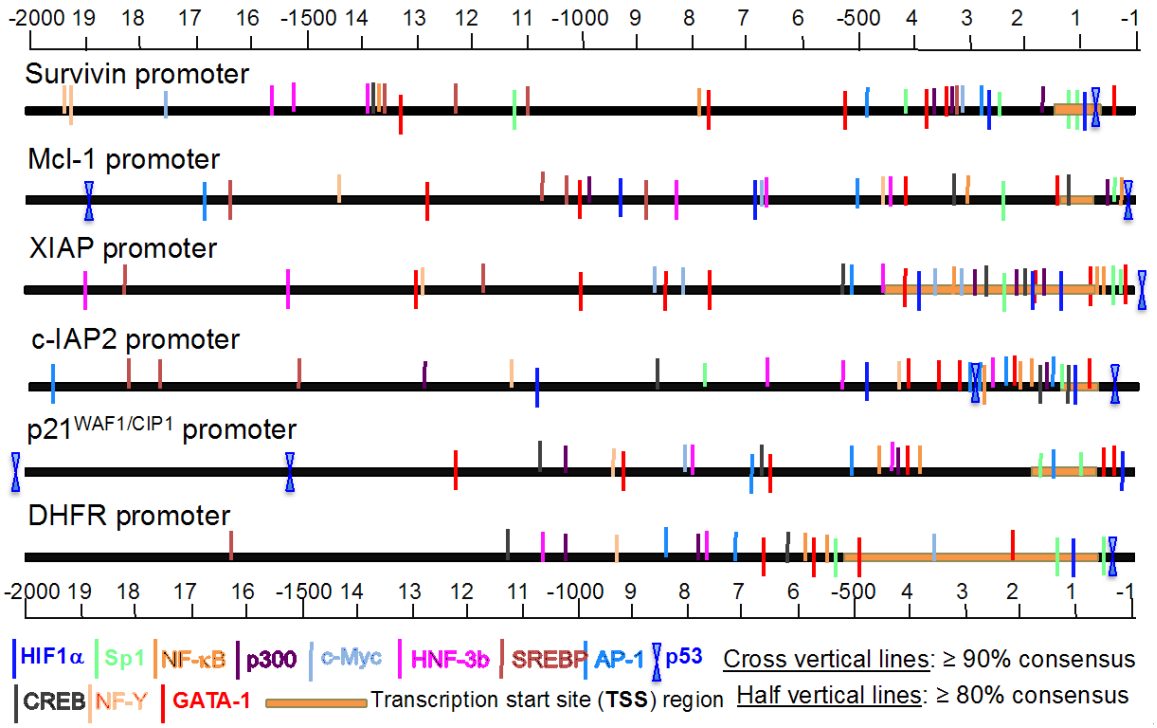

Figure 2. Major transcription factor (TF) binding sites on FL118 target gene promoters: Using the UCSC Human Genome Bioinformatics website, individual gene sequences were isolated. A 2 kb promoter for individual genes was arbitrarily selected based on their transcription start site (TSS) region identified using the NCBI EST Database. The 3'-end for each promoter is the location including an additional 60 bp downstream of the TSS region (the defined 3'-end is designated as -1 bp). If the 60 bp overlaps with translation start site (ATG), we selected the sequence available upstream of ATG (only survivin is the case, 49 bp left). Of note: 1) the upstream p53 site in the Mcl-1 promoter is a p53 DNA binding sit, while the downstream one is a p53 binding region (likely via p53 interacting with general TF). 2) The XIAP promoter does not have typical p53 binding sites; p53 was reported to bind on the XIAP gene promoter, which is likely via binding to other TF but not directly on DNA. 3) Interestingly, while the individual promoters for *survivin, Mcl-1, XIAP* and *cIAP2* contain more than 50% repeat DNA sequences, the *DHFR* and *p21* promoters contain less than 15% repeat sequences.

apoptotic proteins Bax and Bim in various cancer cell types [5]. The inhibition of survivin, Mcl-1, XIAP, and cIAP2 by FL118 can be partially explained by the similarity of the promoter region of the survivin, Mcl-1, XIAP, and cIAP2 genes for the transcription factor (TF) binding, which are distinct from the promoter region of p21 and DHFR genes (**Figure 2**). Of course, this is not the entire story, since modulation of the expression of these genes by FL118 may only partially go through transcriptional regulation. Importantly, inhibition of survivin, Mcl-1, XIAP, and cIAP2 by FL118 is independent events, since genetic knockdown of survivin shows no inhibitory effects on the expression of Mcl-1, XIAP and cIAP2 [5]. The selectivity of FL118 on the expression of its downstream targets was further validated using the Affymetrix GeneChip® Human Gene 1.0 ST Array. The DNA microarray was hybridized with FL118-treated and untreated PC3 cells-derived biotinylated cRNA probes. The results showed that IAP and Bcl-2 family genes are the major targets. Specifically, in the IAP family, FL118 decreases (2 fold cutoff) NAIP, cIAP2, XIAP and Bruce, and shows no effects on cIAP1, Livin and hILP2. In the Bcl-2 family, FL118 slightly decreases Mcl-1 and Bcl-XL, and shows no effect on Bcl-2, Bcl2A1, Bcl-w, Bcl-B, Bcl2L12, Bcl2L13, Bcl-G and Bcl2L15. In contrast, FL118 increases proapoptotic proteins Bax, Bad, Bim, Hrk, and Bmf without affecting the expression of Bid, Bik, Bak and Bok. Taken these observations together, FL118 selectively modulates the expression of multiple antiapoptotic and proapoptotic proteins in the IAP and Bcl-2 families. In this regard, we were curiosity for the effect of SN-38 and topotecan on the expression of these genes. Our studies revealed that SN-38 and topotecan are at least 10 times less effec-

tive to inhibit the expression of survivin [5], Mcl-1, XIAP, and cIAP2 (Liu and Li, unpublished observation). We should point out that inhibition of the expression of survivin, Mcl-1, XIAP, and cIAP2 by FL118 does not mean that FL118 is able to always inhibit all of these genes in all types of cancer cells. Instead, inhibition of one or all of these genes by FL118 can vary among different cancer cell types. However, induction of cancer cell death usually does require inhibition of two or more of these genes, since cancer cells usually express multiple antiapoptotic gene products at the same time. It is important to cover as many of these genes as possible because a given tumor contains pre-clonal heterogeneity, each of which may express a different combination of such gene products.

Does FL118-mediated inhibition of survivin, Mcl-1, XIAP, and cIAP2 play a role in FL118 efficacy?

This is an important question. Without demonstration of a role of these genes in FL118 function, we cannot consider these genes as the downstream targets of FL118. Our studies showed that genetic knockdown of survivin increases FL118-mediated inhibition of cancer cell growth and induction of apoptosis (Annexin V positive cells) [5]; in contrast, Tet-on induced survivin expression decreases FL118's ability to inhibit cancer cell growth and induce DNA fragmentation (a hallmark of apoptosis) [7]. Similarly, genetic knockdown of Mcl-1 increases the cleavage of PARP, another hallmark of apoptosis [5]; vice versa, forced expression of Mcl-1 in cancer cells shows resistance to FL118-mediated inhibition of cancer cell growth [7]. Our studies also revealed similar results about XIAP and cIAP2. Forced expression of XIAP decreases FL118 mediated PARP cleavage and resists FL118-induced apoptosis (Annexin V positive cells) [5]. Forced expression of cIAP2 decreases caspase-3 activation (a hallmark of apoptosis) [5]. Together, these studies implicate the four FL118 downstream targets (survivin, Mcl-1, XIAP, cIAP2) as downstream targets of FL118.

What is the effect of p53 status on FL118 mediated inhibition of its downstream targets and tumor growth?

p53 is a pivotal tumor suppressor that can be activated by various stress signals, such as DNA damage. Activated p53 participates many important cellular processes, including arrest of cell cycle and induction of apoptosis or senescence. This is mainly through control of p53 downstream target genes in the p53 transcriptional networks [8]. Therefore, cancer cells with wild type p53 is essential for efficacy of many anticancer drugs that work through eventual induction of apoptosis and/or senescence, especially for those that interfere DNA synthesis, repair and cell cycle. In other words, loss of functional p53 (p53 mutated or null) would make cancer cells acquire treatment resistance to many chemotherapeutic drugs that are currently used in clinical practice. In addition, the efficacy of targeted drugs can also be affected by loss of p53. For example, loss of wild type p53 or mutation of p53 induces Gleevec (imatinib) resistance without affecting Gleevec-mediated inhibition of BCR-ABL kinase activity [9]. In this regard, FL118 has been demonstrated to effectively inhibit cancer cell growth and induce apoptosis regardless of p53 status (wild type, mutant or null) [5]. Similarly, the *in vivo* studies revealed that FL118 effectively eliminates human colon and head-&-neck tumor xenografts in animal models, regardless of whether the tumor contains wild type p53 or mutant p53 [5-7]. This is consistent with the observation that inhibition of survivin, Mcl-1, XIAP, and cIAP2 by FL118 is p53 status-independent [5].

Interestingly, our recent studies indicate that cancer cells with null p53 are even more sensitive to FL118 treatment than cancer cells with wild type p53 (Ling and Li, unpublished observation). This raises the critical question as to what role is played by the wild type p53 in FL118-mediated cancer cell growth inhibition and tumor elimination, and why cancer cells with null p53 can be more sensitive to FL118 treatment? While these questions are actively under investigation in our research team, one possibility is that both p53 dependent and p53 independent mechanisms of action play a role in FL118 function. In this regard, we found that FL118 rapidly activate p53 signaling pathway in cancer cells with wild type p53 (Ling, Xu, Wang and LI, manuscript in preparation). However, in the situation of cancer cells with null or mutant p53, FL118-involved p53-independent pathway will fully release its power to contribute FL118 efficacy in control of cancer, which may slightly over weigh the total power in

the case of cancer cells with wild type p53 upon FL118 treatment. If this hypothesis is correct, it will well explain why FL118 shows high efficacy in controlling tumors with wild type, mutant or null p53, and why FL118 shows more effective to control cancer cells with null p53. Additional studies will be needed to tease out the precise reasons for this finding.

Is FL118 a substrate of the major ABC efflux transporter ABCG2?

The drug efflux pump ABCG2 (also called BCRP) is an important member of the ATP-binding cassette (ABC) transporter family. ABCG2 is considered as a major cancer stem cell marker, functional molecule and drug resistant factor [10]. Previous studies revealed that ABCG2 is a SN-38 and topotecan resistant factor. Cancer cells with high ABCG2 expression significantly increase SN-38 and topotecan resistance. Clinically, development of resistance to these agents usually occurs during treatment, often through upregulation of ABCG2. If FL118 is not an ABCG2 substrate or is even an ABCG2 inhibitor, FL118 will bypass or inhibit the ABCG2-mediated drug resistance and thus, FL118 may overcome irinotecan and topotecan resistance due to ABCG2 overexpression. In this regard, using several HCT116-derived irinotecan-resistant colon cancer cell lines, we observed a decrease in the potency of SN-38 in irinotecan-resistant cells that overexpressed ABCG2 compared to cells that did not overexpress ABCG2; in contrast, this loss of potency was not observed for FL118 [11]. To confirm the decrease in potency was ABCG2-dependent, HCT116-A2, an ABCG2 overexpressing cell line, was treated with SN-38 or FL118 in the presence or absence of Ko143, an ABCG2 inhibitor. We observed that Ko143 could restore potency to SN-38 in HCT116-A2 cells [11], confirming that irinotecan resistance in HCT116-A2 cells is dependent on ABCG2 expression. However, Ko143 could not modulate the potency of FL118, further suggesting that FL118 is not affected by ABCG2 activity modulation and is not an ABCG2 substrate. Similar results were observed by knockdown of ABCG2 expression with anti-ABCG2 shRNA [11]. Based on these observations, we propose that FL118 is not a substrate of ABCG2 and can bypass ABCG2-mediated drug resistance. Currently, we are carrying out *in vitro* studies to evaluate the potential of using FL118 for patients with irinotecan-resistant colorectal cancer.

What is the toxicology profile of FL118 in animal models?

This is another critical issue that needs to be addressed before FL118 is moved into clinical trials. While a complete profile of FL118 toxicology data is under investigation, there is a basis for FL118 to have a favorable toxicology profile. Several aspects support this notion. Firstly, FL118 selectively inhibits cancer-associated antiapoptotic proteins (survivin, Mcl-1, XIAP, cIAP2). These proteins are well known to be good therapeutic targets to avoid toxicity to normal tissues, since these proteins, especially survivin, are expressed at a very low or undetectable level in normal tissue. Secondly, cancer cells usually require the overexpression of these proteins for survival; interference of two or more of these proteins would effectively disrupt the survival balance and inhibit tumor cell growth and induce apoptosis. However, normal tissues are relatively less sensitive to the modulation of these proteins. For example, studies revealed that FL118 is highly effective at inhibiting cancer cell growth; but is much less effective at inhibiting normal cell growth [5]. This is, at least in part, because normal cells either do not have or show a low expression of the targeted proteins, as in the case of survivin [5]. Thirdly, all normal cells have wild type p53; our studies indicated that cancer cells with null p53 are more sensitive to FL118 treatment than cancer cells with wild type p53 (Ling and Li, unpublished observation). This provides a possibility that both p53-dependent and p53-independent pathways may be involved in FL118 function to kill cancer cells. Given this possibility, the activated p53 can either induce cancer cell death, senescence or arrest cell cycle, which will depend on p53 downstream target activation. For example, p53 activation of cell cycle regulator p21 may result in cell cycle arrest without cell killing, while p53 activation of proapoptotic proteins Bax and/or Puma may result in cell killing. Therefore, it is possible that FL118 may exhibit a differential pathway usage between cancer cells and normal cells and thus, while FL118 can effectively kill cancer cells, FL118 may show relative nontoxic to normal cells due to p53 protection. Fourthly, although FL118 structurally has simi-

larity to irinotecan, SN-38 and topotecan (**Figure 1**), in contrast to these antitumor agents, FL118 is a poor Top1 inhibitor. While Top1 mutation significantly increases resistance to SN-38 and topotecan, FL118 sensitivity is largely unaffected in comparison with topotecan (**Table 1**). Additionally, different from SN-38 and topotecan, FL118 is not an ABCG2 substrate. These and other (yet to be explored) characteristics may make FL118 stand out to be a unique antitumor agent with less toxicity to normal tissues in comparison with irinotecan, SN-38 and topotecan. Finally, it appears that good formulation of FL118 could further decrease FL118 toxicity and increase its efficacy [6]. Our recent studies revealed that FL118 intravenous injection is rapidly accumulated in tumor and cleared from blood stream; while FL118 can be maintained in tumor over 48 hours, FL118 was cleared from blood within 12 hours (Ling and Li, unpublished data). This may also contribute FL118 low toxicity to normal tissue and high efficacy to tumor.

Is FL118's core structure a good platform for generation of safe and efficacious FL118 derivatives?

The exceptional antitumor efficacy of FL118 triggers our enthusiasm to explore the possibility that the core structure of FL118 may represent a promising platform for the generation of novel FL118 analogs. The FL118-derived analogs may exhibit differential selectivity preferences for cancers with different genetic and/or epigenetic alternations. In this regard, we have demonstrated that the exceptional anti-cancer activity of FL118 is highly dependent on its primary structure and steric configuration [7]. In contrast to previous studies on prototype camptothecin compounds, we found that maintenance of a free hydroxyl group in the lactone ring of FL118 is critical for FL118 maintenance of its exceptional antitumor efficacy [7]. Thus, we confirmed FL118's high potential for further development toward clinical trials; meanwhile, the studies provided the first evidence pointing to a possibility that FL118 is a promising platform for the generation of novel FL118 analogs.

We have synthesized a series of FL118 structure-based analogues. The *in vivo* animal model of human tumor studies indicated that these FL118 derivatives exhibit distinct antitumor sensitivity in different cancer types or in the same cancer type with distinct genetic alterations. In other words, one compound may be very effective to certain human cancer, but failed to effectively control another type of cancer or the same type of cancer with different genetic alterations. For example, FL714 and FL75 only have a small steric configuration difference in their side chain, but exhibit different profiles of antitumor activity, toxicity and solubility. Similar situations are founded for other FL118 analogs, such as FL715 versus FL78, and FL717 versus FL76 (Jiang and Li labs unpublished observation). Altogether, while the studies showed that FL118 itself is highly promising for further development toward clinical applications, the FL118 core structure platform may open new doors for generating novel anticancer agents on the basis of FL118 core structure. The new FL118-derived analogs may be used for overcoming treatment resistance resulted from different genetic and epigenetic alternations (personalized cancer treatment).

Concluding remarks

Overcoming treatment resistance is challenging because cancer cells develop multiple treatment resistance mechanisms. Currently, researchers have mainly developed targeted drugs that attack a single mechanism of resistance. Therefore, combination of one molecularly targeted agent with one or two classical cytotoxic agents is the current trend in modern clinical practice for treatment of cancer. While this approach has certain advantages among balanced toxicity, efficacy, and cost with up-to-date technologies, this approach may not ultimately resolve the challenge due to the efficacy and toxicity limitation of this approach. In this perspective, the author employs FL118 as an example to demonstrate the feasibility of developing a single molecule that can target and/or bypass multiple treatment resistant mechanisms. The author propose that a versatile anticancer molecule can better resolve the newly discovered challenging issue of cancer treatment resistance for personalized medicine and biomarker development [2, 3], while keeping the treatment at a relative low toxicity, low cost, and high efficacy. FL118 and/or its core structure-derived analogs are expected to make great contributions to the current cancer treatment resistance.

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Disclosure of conflict of interest

FL118 and FL118 core structure-based analogs will be further developed in Canget BioTekpharma (www.canget-biotek.com), a Roswell Park Cancer Institute (RPCI)-spinoff company. The author is the founder and has made significant investment in the company for development of the FL118 relevant anticancer agents.

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