Topoisomerase II (TOP2) poisons interfere with the breakage/reunion reaction of TOP2 resulting in DNA cleavage. In the current studies, we show that two different classes (ATP-sensitive and -insensitive) of TOP2 poisons can be identified based on their differential sensitivity to the ATP-bound conformation of TOP2. First, in the presence of 1 mM ATP or the nonhydrolyzable analog adenosine 5′-(β,γ-imino)triphosphate, TOP2-mediated DNA cleavage induced by ATP-sensitive TOP2 poisons (e.g. doxorubicin, etoposide, mitoxantrone, and 4′-(9-acridinylamino)methanesulfon-m-anisidide) was 30–100-fold stimulated, whereas DNA cleavage induced by ATP-insensitive TOP2 poisons (e.g. amonafide, batracylin, and menadione) was only slightly (less than 3-fold) affected. In addition, ADP was shown to strongly antagonize TOP2-mediated DNA cleavage induced by ATP-sensitive but not ATP-insensitive TOP2 poisons. Second, C427A mutant human TOP2α, which exhibits reduced ATPase activity, was shown to exhibit cross-resistance to all ATP-sensitive but not ATP-insensitive TOP2 poisons. Third, using ciprofloxacin competition assay, TOP2-mediated DNA cleavage induced by ATP-sensitive but not ATP-insensitive poisons was shown to be antagonized by ciprofloxacin. These results suggest that ATP-bound TOP2 may be the specific target of ATP-sensitive TOP2 poisons. Using Lac repressor-operator complexes as roadblocks, we show that ATP-bound TOP2 acts as a circular clamp capable of entering DNA ends and sliding on unstructured duplex DNA.

EXPERIMENTAL PROCEDURES

Chemicals and Drugs—VM-26 was a gift from Bristol-Myers Squibb Co. m-AMS A, mitoxantrone, and amonafide were obtained from the Drug Synthesis and Chemistry Branch, Division of Cancer Treatment, National Cancer Institute. Batracylin was a gift from Dr. C. C. Cheng (University of Kansas). 5-Hydroxy-1,4-naphthoquinone was obtained from Aldrich. All drugs were dissolved in Me2SO (10 mM) and kept frozen in aliquots at −20 °C. Ciprofloxacin was obtained from Bayer. ATP, AMPPNP, and ADP were purchased from Sigma. Except for fetal bovine serum, which was obtained from Gemini Biotech, media and other agents for tissue culture were purchased from Life Technologies, Inc. [32P]dATP (3000 Ci/mmol) was obtained from DuPont.

Construction of Mutant Topoisomerase II Overexpression Plasmid—The mutation C427A was generated by PCR-based site-directed mutagenesis. Three rounds of PCR were carried out to introduce the C427A mutation.
into human TOP2α cDNA in YEpWob6. The resulting plasmid is named Yhtop2αC427A. The following four primers were used (the mutations are marked in bold, and the restriction sites are underlined): primer A, 5'-AGGGCTCGAGCGAAATCTCAGGTTAC-3' SacI; primer B, 5'-ACAAGAAGGCTCGAGCTGTA-3'; primer C, 5'-TACAGCTGAGGCCCTTCTCTGT-3'; and primer D, 5'-GGCTGTTACGAAAACGAGC-3' KpnI.

Primers B and C contain the alanine codon instead of the wild-type cysteine codon. Primers A and D contain the recognition sites for SacI and KpnI, respectively. Two fragments, AC and BD, which have the alanine codon, were generated during the first round PCR in the presence of YEpWob8 DNA. After denaturation and renaturation of fragments AC and BD, two cycles of a second round of PCR without any primer were carried out to generate a small amount of the fragment containing C427A as the template for the third round PCR. The third round of PCR amplified the fragment containing C427A using primers A and D. SacI and KpnI were used to digest both the fragment-containing C427A and YEpWob6 (partially digested with SacI), and ligation was carried out at 14 °C overnight. The mutated site was confirmed by sequence analysis.

Enzymes and Nucleic Acids—TOP2 was purified to homogeneity from calf thymus glands according to the published procedure (21). Full-length human TOP2β cDNA (hTOP2β CDNA) was isolated by reverse transcription-PCR using mRNA isolated from human U937 cells and primers with sequences according to the published sequence of the human TOP2β cDNA in YEpWob6 (23). The resulting plasmid, YEphTOP2α, was constructed by inserting the same 42-bp oligomer into the XbaI site in pYtop2α (26).

**FIG. 1.** ATP stimulation of TOP2-mediated DNA cleavage induced by TOP2 poisons. TOP2 cleavage assays were performed as described under “Experimental Procedures.” The presence or absence of ATP (1.0 mM) is indicated on top of each lane. All reactions contained 1% Me2SO. The concentrations of VM-26 (A) and amonafide (AM) (B) are as indicated.

Enzymes and Nucleic Acids—TOP2 was purified to homogeneity from calf thymus glands according to the published procedure (21). Full-length human TOP2β cDNA (hTOP2β CDNA) was isolated by reverse transcription-PCR using mRNA isolated from human U937 cells and primers with sequences according to the published sequence of the human TOP2β cDNA in YEpWob6 (23). The resulting plasmid, YEphTOP2α, was constructed by inserting the same 42-bp oligomer into the XbaI site in pYtop2α (26).

**Preparation of End-labeled DNA Fragments—**3'-end-labeling of plasmid DNA was performed as described previously (21). Briefly, 10 μg of DNA was digested with a proper restriction enzyme followed by labeling at its 3' ends with the large fragment of *Escherichia coli* DNA polymerase I and [α-32P]dATP. Unincorporated triphosphates were removed by two cycles of ethanol precipitation in the presence of 2.5 M ammonium acetate.

**TOP2 Cleavage Assay—**The TOP2 cleavage assay was performed as described previously (27). The reaction mixtures (20 μl each) containing 40 mM Tris-HCl, pH 7.5, 100 mM KCl, 10 mM MgCl2, 1.0 mM ATP, 0.5 mM dithiothreitol, 0.5 mM EDTA, 30 μg/ml bovine serum albumin, calf thymus TOP2 (titrated prior to the experiment), and various amounts of ADP and/or ATP as indicated were incubated at 37 °C for 30 min. The reactions were terminated by the addition of 5 μl of a solution containing 20% Ficoll, 5% Sarkosyl, 50 mM EDTA, and 0.05 mg/ml bromphenol blue. Reaction products were analyzed by electrophoresis in 1% agarose gel containing TPE buffer.

**ATPase Assay—**The ATPase assay was performed as described (29) except that an 8.6-kilobase plasmid DNA, pCaSpeRhs83 (30), was used. Radioactivities were quantified by a PhosphorImager (Molecular Dynamics, Sunnyvale, CA).

**RESULTS**

Differential ATP Stimulation of TOP2-mediated DNA Cleavage Induced by TOP2 Poisons—The possible effect of ATP on TOP2-mediated DNA cleavage was studied using purified TOP2 and various TOP2 poisons. As shown in Fig. 1A, 1 mM ATP stimulated calf thymus TOP2-mediated DNA cleavage induced by VM-26 by about 60-fold (Fig. 1A) (ATP stimulation is estimated as the-fold of increased drug concentration in the absence of ATP for achieving the same extent of cleavage in the presence of ATP). By contrast, TOP2-mediated DNA cleavage induced by amonafide was affected only slightly (less than 3-fold) by 1 mM ATP (Fig. 1B). The nonhydrolyzable ATP analog, AMPPNP, gave similar results as ATP (data not shown). Similar results were obtained with recombinant human TOP2α and TOP2β (data not shown). TOP2 poisons that are highly (about 30–100-fold) stimulated by ATP in the TOP2-mediated
DNA cleavage assay include VM-26, VP-16, m-AMSA, doxorubicin, and mitoxantrone (referred to as ATP-sensitive TOP2 poisons). TOP2 poisons that are affected only slightly by ATP (less than 3-fold) include amonafide, batracyclin, and menadione (referred to as ATP-insensitive TOP2 poisons).

ADP Antagonizes ATP-stimulated DNA Cleavage Activity and ATP-dependent Strand-passing Activity of TOP2—Although ATP strongly stimulated TOP2-mediated DNA cleavage induced by VM-26, ADP alone had no such effect (Fig. 2). However, in the presence of ATP, ADP effectively antagonized the ATP stimulatory effect on TOP2-mediated DNA cleavage induced by VM-26 (Fig. 2). The antagonistic effect of ADP on VM-26-induced DNA cleavage was observed also with other ATP-sensitive TOP2 poisons (data not shown). By contrast, ADP had a minimum effect on TOP2-mediated DNA cleavage in the presence of amonafide, an ATP-insensitive TOP2 poison. In this case, ADP had a minimal effect on TOP2-mediated DNA cleavage induced by amonafide in the presence of ATP (Fig. 2). These results suggest that ADP specifically antagonizes the ATP-stimulatory effect on TOP2-mediated DNA cleavage induced by ATP-sensitive TOP2 poisons. We also had tested the effect of ADP on the catalytic activity of TOP2 using a P4 unknotting assay. As shown in Fig. 3, ADP also effectively antagonized the P4 unknotting activity of TOP2.

C427A Mutant TOP2α is Cross-resistant to ATP-sensitive but Not ATP-insensitive TOP2 Poisons—To characterize the role of ATP in the action of TOP2 poisons further, we generated C427A mutant TOP2α. The cysteine 427 is located in the ATPase domain of TOP2α (31). In the absence of ATP, C427A mutant TOP2α exhibited almost identical sensitivity to both VM-26 and amonafide compared with wild-type TOP2α in a standard DNA cleavage assay (Fig. 4). Strikingly, in the presence of 1 mM ATP, C427A mutant TOP2α was at least 10-fold more resistant to VM-26 as compared with the wild-type enzyme. The resistance of C427A mutant TOP2α to VM-26 is apparently caused by a reduced ATP-stimulatory effect on DNA cleavage as compared with the wild-type enzyme (Fig. 4). By contrast, both mutant and wild-type TOP2α were equally sensitive to amonafide (Fig. 4). We also tested other ATP-sensitive drugs such as doxorubicin, m-AMSA, mitoxantrone, and CP115,953. Similar results to VM-26 were observed (data not shown). These results suggest that C427A mutant TOP2α can distinguish between ATP-sensitive and -insensitive TOP2 poisons, possibly because of its altered interaction with ATP.

C427A Mutant Enzyme Exhibits Reduced ATPase Activity and Increased ATP Requirement for Its Catalytic Activity—Previous studies on another multidrug-resistant mutant TOP2α mutant have shown that the mutant enzyme exhibits an increased ATP requirement for catalysis (16). To test whether C427A behaves similarly, the catalytic activity of the C427A mutant TOP2α was measured by a P4 unknotting assay in the presence of two different concentrations of ATP. As shown in Fig. 5, C427A mutant TOP2α was about 5-fold less active than the wild-type enzyme in the presence of 1 mM ATP. However, in the presence of 50 μM ATP, C427A was at least 25-fold less active than the wild-type enzyme. This result is similar to the result from the experiment performed on another mutant TOP2α enzyme, R450Q TOP2α, which is cross-resistant to ATP-sensitive TOP2 poisons and exhibits an increased ATP requirement for enzyme catalysis (17).

The DNA-stimulated ATPase activity of C427A mutant TOP2α also was measured and shown to be much reduced relative to the wild-type enzyme. The Vmax was reduced from 60 to 11 μmol min⁻¹, and Km was increased from 0.78 to 3.2 μM.

Ciprofloxacin Antagonizes TOP2-mediated DNA Cleavage Induced by ATP-sensitive but Not ATP-insensitive TOP2 Poisons—Ciprofloxacin is known to interact with TOP2 but does not induce significant TOP2-mediated DNA cleavage (32). Consequently, ciprofloxacin has been used to compete with other TOP2 poisons in a standard DNA cleavage assay to assess possible overlap of interaction domains on TOP2 (32). Based on this kind of ciprofloxacin competition assay, it has been suggested that various TOP2 poisons including etoposide, m-AMSA, genistein, and the antineoplastic quinolone, CP-115,953, share a common interaction domain with ciprofloxacin on TOP2 (32). To test whether ATP-sensitive and -insensitive TOP2 poisons may interact with different domains on TOP2, we performed the ciprofloxacin competition assay (32). As shown in Fig. 6, ciprofloxacin reduced TOP2-mediated DNA cleavage induced by VM-26 as evidenced by the gradual increase in band intensity of the uncleaved DNA bands (see the
FIG. 4. C427A mutant TOP2α is resistant to VM-26 but not amonafide.
TOP2 cleavage assays were performed as described under "Experimental Procedures." The concentrations of VM-26 and amonafide (AM) are as indicated on top of each lane. 1 mM ATP was used in the +ATP lanes.

arrow) with increasing ciprofloxacin concentrations (see lanes labeled 0.1 μM VM). By contrast, ciprofloxacin had little effect on TOP2-mediated DNA cleavage induced by amonafide (see the intensity of the uncleaved DNA bands in lanes labeled 1.0 μM AM). Similar ciprofloxacin competition assays were performed with other TOP2 poisons. All ATP-sensitive but not ATP-insensitive TOP2 poisons were antagonized by ciprofloxacin in this DNA cleavage assay (data not shown).

FIG. 5. The P4 unknotting activity of C427A mutant TOP2α exhibits an increased requirement for ATP. The P4 unknotting assay for the catalytic activity of C427A mutant TOP2α and wild-type TOP2α were performed as described under "Experimental Procedures." The concentrations of TOP2 and ATP were as indicated on top of the figure.

ATP-bound TOP2 Is a Sliding Protein Clamp—Previous studies have suggested that yeast TOP2 when bound to AMPPNP can undergo a conformational change into a circular protein clamp (19, 20), which is consistent with results from x-ray crystallographic studies (18). To test whether calf thymus TOP2 also can form a circular protein clamp in its ATP-bound form, we have designed a more stringent assay requiring the TOP2 protein clamp to slide on unobstructed DNA under physiological conditions. As shown in Fig. 7, a linear DNA (8310-bp, 32P end-labeled) with two internally bound Lac repressor molecules at their respective Lac operator sites was used to demonstrate entry and sliding of AMPPNP-bound TOP2. Calf thymus TOP2 was reacted first with AMPPNP to form a circular protein clamp and then incubated with the linear DNA bound by Lac repressors. VM-26 or amonafide was used subsequently to locate the TOP2 sliding clamps on DNA by inducing TOP2-mediated DNA cleavage. As shown in Fig. 7, in the presence of ATP, TOP2-mediated DNA cleavage sites induced by VM-26 (lane 3) scattered all over the linear DNA (a similar result was obtained in the absence of ATP; data not shown). However, in the presence of AMPPNP, TOP2-mediated DNA cleavage induced by VM-26 (lane 5) occurred primarily near the two ends of the linear DNA and extended up to the Lac repressor binding site.

FIG. 6. Ciprofloxacin antagonizes TOP2-mediated DNA cleavage induced by VM-26. TOP2 cleavage assays were performed as described under "Experimental Procedures." 0.1 μM VM-26 (lanes labeled 0.1 μM VM) and 1.0 μM amonafide (lanes labeled 1.0 μM AM) were used in the cleavage assays with increasing concentrations of ciprofloxacin (0, 125, and 250 μM). The control experiment in the presence of 1% Me2SO (solvent control for VM-26 and amonafide) and increasing concentrations of ciprofloxacin is shown in lanes labeled 1% DMSO. All drugs were present in the reaction mixture prior to the addition of TOP2. The arrow points to the uncleaved DNA bands.
**DISCUSSION**

Our results have demonstrated that different TOP2-mediated DNA cleavage induced by various TOP2 poisons exhibits a different degree of ATP dependence. The differences in ATP dependence among various TOP2 poisons may reflect differences in their interaction with TOP2 and/or TOP2-DNA complexes. Based on our current results, there seems to be two distinct classes of TOP2 poisons, ATP-sensitive and ATP-insensitive.

These two classes of TOP2 poisons show quite different responses to ATP stimulation in the standard DNA cleavage assay. The specific antagonistic effect of ADP against ATP-sensitive but not -insensitive TOP2 poisons has demonstrated further the differences between these two classes of TOP2 poisons. The fact that ADP also strongly inhibits ATP-dependent catalytic activity of TOP2 suggests that ADP may compete with ATP both in enzyme catalysis and cleavable complex formation by the same mechanism. Studies in bacteria have established that the ATP/ADP ratio is a critical determinant for the supercoiling state in cells probably because of the sensitivity of DNA gyrase to the ATP/ADP ratio (14, 15). More recent studies have demonstrated also that quinolone-induced DNA cleavage depends strongly on the ATP/ADP ratio, both in cells and using purified gyrase (13). These results suggest that the ATP/ADP ratio may be a common determinant for sensitivity/resistance to both antibiotics and antitumor drugs directed against TOP2. Although ATP-sensitive TOP2 poisons used in this work have very disparate structures, their interaction domains with TOP2 have been suggested to overlap (32).

Previous studies have demonstrated that a multidrug-resistant mutant TOP2α is cross-resistant to all ATP-sensitive TOP2 poisons (17). This multidrug-resistant mutant TOP2α was shown to exhibit an increased requirement of ATP for catalysis and cleavage. It has been suggested that the R450Q mutation on this mutant TOP2α is responsible for altered ATP utilization and cross-resistance to ATP-sensitive TOP2 poisons (17). This mutation is located in a Walker consensus motif (17). In the current study, we have created another mutation C427A on TOP2α. Like the R450Q mutant TOP2α, C427A mutant TOP2α also exhibits multidrug resistance to all ATP-sensitive poisons. Interestingly, C427A mutant TOP2α retains the same sensitivity to ATP-insensitive TOP2 poisons as compared with the wild-type enzyme. C427A mutant TOP2α exhibits reduced ATPase activity and an increased requirement of ATP for catalysis. Taken together, these results suggest that ATP-sensitive and -insensitive TOP2 poisons interfere with the breakage/reunion reaction of TOP2 by distinct mechanisms and that ATP-sensitive TOP2 poisons may interfere specifically with a step in TOP2 catalysis requiring ATP utilization.

Results from the ciprofloxacin competition experiment have suggested that the ATP-insensitive TOP2 poisons do not share the same interaction domain on TOP2 with ATP-sensitive TOP2 poisons. This result suggests that ATP-sensitive TOP2 poisons may target TOP2 with a distinct conformation compared with ATP-insensitive poisons.

Based on our results, it seems plausible that ATP-sensitive TOP2 poisons may specifically target an ATP-bound conformation of TOP2. Our current studies have suggested that AMP-PNP-bound TOP2 is capable of entering duplex DNA only from its ends, consistent with the closed circular clamp conformation of ATP-bound TOP2 proposed previously on the basis of studies of yeast TOP2 (19). Our results also indicate that upon entry, AMP-PNP-bound TOP2 can slide on unobstructed duplex DNA under physiological conditions. Previous studies on *Drosophila* TOP2 and yeast TOP2 have implicated linear diffusion in high salt conditions that presumably weaken protein-DNA interactions to allow mobility of the protein circular clamp (19, 33). Our results, however, show that AMP-PNP-bound mammalian TOP2 is able to linearly diffuse under physiological conditions. The ability of TOP2 to slide on DNA under physiological conditions may imply a role of limited linear diffusion, dictated by ATP binding and hydrolysis, in its strand-passing reaction. Our limited understanding of the role of ATP in TOP2 catalysis precludes us from any meaningful speculation on the mechanistic and/or functional implications of the sliding action of ATP-bound TOP2. The resistance of TOP2 poisons has been studied in cells under stress conditions (e.g., hypoxia and glucose deprivation) that are associated often with solid tumors (9–12, 34–38). Reduced TOP2α levels in stressed cells have been found and suggested to be responsible in part for the
observed resistance (38–40). Our results raise the possibility that alteration in ATP/ADP ratios, which is known to occur in hypoxic and nutrient-depleted cells (41), may contribute to the overall resistance mechanisms through its modulation on TOP2-mediated DNA cleavage. Thus, it seems plausible that ATP-insensitive TOP2 poisons may be useful particularly for treating hypoxic tumors that have compromised ATP/ADP ratios.

Acknowledgment—We thank Dr. Kathleen S. Matthews for supplying us with purified Lac repressor.

REFERENCES
1. Uemura, T., Ohkura, H., Adachi, Y., Morino, K., Shiozaki, K., and Yanagida, M. (1987) Cell 50, 917–925
2. Helm, C., Stearns, T., and Botstein, D. (1989) Mol. Cell. Biol. 9, 159–168
3. Sumner, A. T. (1991) Chromosoma (Berl.) 100, 410–418
4. Brill, S. J., DiNardo, S., Voelkel-Meiman, K., and Sternglanz, R. (1987) Nature 326, 414–416
5. Wu, H. Y., Shyy, S. H., Wang, J. C., and Liu, L. F. (1988) Cell 53, 433–440
6. Tsao, Y. P., Wu, H. Y., and Liu, L. F. (1989) Cell 56, 111–116
7. Yang, L., Wold, M. S., Li, J. J., Kelly, T. J., and Liu, L. F. (1987) Proc. Natl. Acad. Sci. U. S. A. 84, 950–954
8. Liu, L. F. (1989) Annu. Rev. Biochem. 58, 351–375
9. Coloffiore, J. R., Ara, G., Berry, D., and Belli, J. A. (1982) Cancer Res. 42, 3934–3940
10. Kupfer, G., Bodeley, A. L., and Liu, L. F. (1987) NCI Monogr. 4, 37–40
11. Utsumi, H., Shibuya, M. L., Kosaka, T., Buddenbaum, W. E., and Elkind, M. M. (1990) Cancer Res. 50, 2577–2581
12. Suzuki, H., Ikeda, T., Yamagishi, T., Nakaize, S., Nakane, S., and Ohsawa, M. (1995) Mutat. Res. 328, 151–161
13. Li, T. K., and Liu, L. F. (1998) Antimicrob. Agents Chemother. 42, 1022–1027
14. Hsieh, L. S., Burger, R. M., and Drlica, K. (1991) J. Mol. Biol. 219, 443–450
15. Hsieh, L. S., Rouviere-Yaniv, J., and Drlica, K. (1991) J. Bacteriol. 173, 3914–3917
16. Danks, M. K., Schmidt, C. A., Deneka, D. A., and Beck, W. T. (1989) Cancer Commun. 1, 101–109
17. Mao, Y., Yu, C., Hsieh, T. S., Nittis, J. L., Liu, A. A., Wang, H., and Liu, L. F. (1999) Biochemistry 38, 10800–10809
18. Berger, J. M., Gamblin, S. J., Harrison, S. C., and Wang, J. C. (1996) Nature 379, 235–232
19. Boca, J., and Wang, J. C. (1992) Cell 71, 833–840
20. Lindley, J. E., and Wang, J. C. (1991) Proc. Natl. Acad. Sci. U. S. A. 88, 10485–10489
21. Halligan, B. D., Edwards, K. A., and Liu, L. F. (1985) J. Biol. Chem. 260, 2475–2482
22. Jenkins, J. R., Ayton, P., Jones, T., Davies, S. L., Simmons, D. L., Harris, A. L., Sheer, D., and Hickson, I. D. (1992) Nucleic Acids Res. 20, 5587–5592
23. Wasserman, R. A., Austin, C. A., Fisher, L. M., and Wang, J. C. (1993) Cancer Res. 53, 3591–3596
24. Wyckoff, E., and Hsieh, T. S. (1988) Proc. Natl. Acad. Sci. U. S. A. 85, 6272–6276
25. Wu, H. Y., and Liu, L. F. (1991) J. Mol. Biol. 219, 615–622
26. Bi, X., and Liu, L. F. (1994) J. Mol. Biol. 235, 414–423
27. Tewey, K. M., Rowe, T. C., Yang, L., Halligan, B. D., and Liu, L. F. (1984) Science 226, 466–468
28. Liu, L. F., Davis, J. L., and Calendar, R. (1981) Nucleic Acids Res. 9, 3979–3989
29. Osheroff, N., Shelton, E. R., and Brutlag, D. L. (1983) J. Biol. Chem. 258, 9536–9543
30. Horabin, J. I., and Schlegel, P. (1993) Mol. Cell. Biol. 13, 1408–1414
31. Beck, W. T., Banks, M. K., Wolverton, J. S., Chen, M., Granzen, B., Kim, R., and Sittel, D. P. (1994) in DNA Topoisomerases: Topoisomerase-targeting Drugs (Liu, L. F., ed), pp. 145–169, Academic Press, New York
32. Elsea, S. H., Westergaard, M., Burden, D. A., Lomenick, J. P., and Osheroff, N. (1997) Biochemistry 36, 2919–2924
33. Osheroff, N. (1998) J. Biol. Chem. 261, 9944–9950
34. Yamahachi, T., Raffin, T. A., Yang, P., and Sikic, B. I. (1987) Cancer Chemosother. Pharmacol. 19, 282–286
35. Shen, J., Hughes, C., Chao, C., Cai, J., Bartels, C., Gessner, T., and Subjeck, J. (1987) Proc. Natl. Acad. Sci. U. S. A. 84, 3278–3282
36. Hughes, C. S., Shen, J. W., and Subjeck, J. R. (1989) Cancer Res. 49, 4452–4454
37. Yang, P., Raffin, T. A., and Sikic, B. I. (1987) Cancer Res. 47, 5798–5803
38. Chatterjee, S., Cheng, M. F., Berger, S. J., and Berger, N. A. (1994) Cancer Res. 54, 4405–4411
39. Yang, P., Raffin, T. A., and Sikic, B. I. (1987) Cancer Chemosother. Pharmacol. 19, 282–286
40. Shen, J. W., Subjeck, J. R., Lock, R. B., and Ross, W. E. (1989) Mol. Cell. Biol. 9, 3284–3291
41. Kennedy, K. A. (1987) Anticancer Drug Des. 2, 181–194
