Circumvention of Vincristine and Adriamycin Resistance in Vitro and in Vivo by Calcium Influx Blockers

Takashi Tsuruo, Harumi Iida, Makiko Nojiri, Shigeru Tsukagoshi, and Yoshio Sakurai

Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Toshima-ku, Tokyo 170, Japan

ABSTRACT

Calcium influx blockers, diltiazem, nicardipine, nifedipine, niludipine, and nimodipine, which possess coronary vasodilator activity, greatly enhanced the cytotoxicity of vincristine (VCR) in tumor cells and especially in VCR-resistant sublines of P388 leukemia (P388/VCR) and human K562 myelogenous leukemia. The extent of enhancement was different among the drugs, and up to a 50- to 70-fold increase in VCR cytotoxicity occurred in P388/VCR cells with nontoxic or marginally toxic concentrations of diltiazem and nicardipine. A 50- to 100-fold enhancement occurred in VCR-resistant human K562 myelogenous leukemia cells with diltiazem, nicardipine, niludipine, and nimodipine. VCR resistance of these cell lines was circumvented completely by these blockers. Calcium influx blockers also enhanced the cytotoxicity of Adriamycin in P388 leukemia cells and especially in its Adriamycin-resistant subline. The extent of enhancement, however, was lower than that which occurred in VCR-resistant tumor lines with VCR. An approximately 10- to 30-fold increase in Adriamycin cytotoxicity occurred in P388 Adriamycin-resistant subline cells with diltiazem, nicardipine, niludipine, and nimodipine. Although VCR alone at 100 μg/kg did not confer a significant therapeutic effect in P388/VCR-bearing mice, calcium influx blockers in doses of 30 to 125 mg/kg administered daily for 10 days with VCR enhanced the chemotherapeutic effect of VCR in P388/VCR-bearing mice. A maximum of approximately a 40 to 50% increase in life span occurred with diltiazem, nicardipine, niludipine, and nimodipine. The calcium influx blockers also enhanced the therapeutic effect of Adriamycin in P388 Adriamycin-resistant subline-bearing mice, although the extent of enhancement was smaller than that observed with VCR in P388/VCR-bearing mice.

INTRODUCTION

In the chemotherapy of cancer of humans and animals, it has been observed widely that, although tumors respond well initially to certain drugs, they become progressively resistant to these drugs, which finally leads to therapeutic failure. Similarly, in experimental tumors, one of the major reasons for treatment failure is the appearance and proliferation of drug-resistant tumor cells during the course of treatment (12, 13, 15). Because the only approach to circumventing drug resistance in tumor cells at the present time is a combination therapy with other anticancer drugs having different modes of action, the development of a new modality to circumvent the drug resistance in tumor cells could be beneficial in the chemotherapy of cancer.

In various experimental tumor systems, one of the most important mechanisms of drug resistance, especially to Vinca alkaloid and anthracycline classes of antitumor agents, has been attributed to the enhanced drug efflux function of the resistant tumor cells (3, 6, 10, 16, 17, 24). These observations suggest that if we could control the drug efflux function of tumor cells appropriately, then we could expect anticancer agents to be effective against resistant cells (14). We found that the cellular calcium may be involved in the drug efflux mechanisms of the cells (25). Some calcium influx blockers and calmodulin inhibitors efficiently inhibit the VCR and ADM efflux function of tumor cells and especially of resistant tumor cells (24–26). VCR and ADM accumulate in resistant cells, and the drug resistance is circumvented efficiently through a marked enhancement of drug cytotoxicity (24–26).

To explore the possible clinical application of this approach, we have tried to determine the effectiveness of drug transport modifiers from various calcium influx blockers and calmodulin inhibitors. We found that calcium influx blockers are generally more effective than are calmodulin inhibitors. In this paper, we describe the effects of several calcium influx blockers now used clinically or preclinically to circumvent VCR and ADM resistance in vivo and in vitro.

MATERIALS AND METHODS

Drugs. VCR and ADM, formulated for clinical use, were obtained from Shionogi & Co., Ltd., Osaka, Japan, and Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan. The following calcium influx blockers were used: diltiazem (9, 11), obtained from Tanabe Seiyaku Co., Ltd., Osaka, Japan; nicardipine (19, 21), obtained from Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan; and nifedipine (4, 27), niludipine (4, 18), and nimodipine (20, 22), obtained from Bayer AG, Wuppertal-Elberfeld, Germany.

Animals and Tumor Cells. Adult female BALB/c × DBA/2JR F1 (hereafter called CD2F1) mice weighing 20 to 23 g were obtained from Charles River Japan, Inc., Tokyo, Japan. P388 and P388/VCR cell lines were supplied by the National Cancer Institute, NIH, Bethesda, Md. (24). The P388/ADM cell line, established at the National Cancer Institute, NIH, was provided by Dr. Inaba (6). The human myelogenous leukemia K562 cell line (8) was provided by Dr. Ezaki, and the K562/VCR cell line was established in this laboratory.4

Cell Culture and Drug Treatment. Tumor cells were maintained in suspension in plastic dishes (Coming Glass Works, Coming, N. Y.) in Roswell Park Memorial Institute Medium 1640 supplemented with 10% fetal bovine serum (Flow Laboratories, Stanmore, New South Wales, Australia) and kanamycin (100 μg/ml) (growth medium) (24). The culture media contained in a working solution of Vinca alkaloid and anthracycline classes of antitumor agents, has been attributed to the enhanced drug efflux function of the resistant tumor cells (3, 6, 10, 16, 17, 24). These observations suggest that if we could control the drug efflux function of tumor cells appropriately, then we could expect anticancer agents to be effective against resistant cells (14). We found that the cellular calcium may be involved in the drug efflux mechanisms of the cells (25). Some calcium influx blockers and calmodulin inhibitors efficiently inhibit the VCR and ADM efflux function of tumor cells and especially of resistant tumor cells (24–26). VCR and ADM accumulate in resistant cells, and the drug resistance is circumvented efficiently through a marked enhancement of drug cytotoxicity (24–26).
was incubated at 37°C in a humidified atmosphere of 5% CO₂. For the drug treatment experiments, tumor cells (2 x 10⁶ for P388, P388/VCR, and P388/ADM cells and 4 x 10⁴ for K562 and K562/VCR cells) were cultured at 37°C for 5 hr in Falcon No. 2054 culture tubes containing 2 ml of growth medium in a humidified atmosphere of 5% CO₂. Then the cells were treated with graded drug concentrations (0.1 to 100 nM for VCR and 10 to 10⁴ nM for ADM) in the absence or presence of the calcium influx blockers (3.5 to 100 μM depending on the drugs), re-incubated for 72 hr in the presence of drugs, and counted with a Model ZBI Coulter Counter (24). Three tubes were used for each drug concentration. In the control experiment, tumor cells grew exponentially during the incubation period, and the final cell numbers were described in each chart and table. Calcium influx blockers were dissolved in dimethyl sulfoxide at a final concentration of 100 mM and diluted with phosphate-buffered saline (0.2 M sodium phosphate:0.15 M NaCl, pH 7.4). The final concentration of dimethyl sulfoxide in the culture was less than 0.1% (v/v), and no effect from dimethyl sulfoxide on cell growth or cell differentiation was observed.

IC₅₀ in the presence or absence of calcium influx blockers was determined by plotting the logarithm of the drug concentration versus the growth rate (percentage of control) of the treated cells (23). Evaluation of Antitumor Activity. One-tenth ml of diluted ascites fluid containing 10⁶ P388 and P388/VCR cells or 10⁵ P388/ADM cells was transplanted i.p. into CD2F₁ mice. Calcium influx blocker and VCR or ADM were dissolved in 0.9% NaCl solution [if necessary, calcium influx blockers were suspended in a small volume of 2% (w/v) methyl cellulose No. 25 (Nakarai Chemicals, Ltd., Kyoto, Japan) and diluted in 0.9% NaCl solution]. The final concentration of methyl cellulose was less than 0.1%. This vehicle has no effect on the antitumor activity of VCR. Both drugs were mixed, and the mixture was administered at a constant rate of 0.02 ml/g body weight i.p. daily for 10 days starting from the day after tumor inoculation. Doses of calcium influx blockers, VCR, and ADM were 30 to 125 mg/kg, 10 to 400 μg/kg, and 0.5 to 1.0 mg/kg, respectively. Five mice were used for each experimental group (24). Antitumor activity was evaluated by the mean survival time of a group of mice and also expressed by the T/C (%) value (24).

RESULTS

Potentiation of VCR Cytotoxicity by Calcium Influx Blockers. Calcium influx blockers showed different growth-inhibitory activity against various tumor cells used in this experiment. At the concentration studied, only niludipine at 35 μM significantly inhibited the growth of any of the cell lines derived from mice, while diltiazem and nifedipine appeared to inhibit the growth of a human-derived cell line at concentrations of 100 μM. We used nontoxic or slightly toxic (growth inhibition did not exceed 10%) concentrations of calcium influx blockers in this experiment.

The sensitivities of P388 and P388/VCR cells to VCR and the effect of diltiazem and nicardipine on these sensitivities are illustrated in Chart 1. P388/VCR cells were resistant to VCR, and the index of resistance was approximately 15 when compared with the IC₅₀ values of both cells (Chart 1). Diltiazem and nicardipine enhanced the cytotoxicity of VCR in P388 cells. An increase in cytotoxicity of 7.6- and 4.3-fold was produced by 10 μM nicardipine and 100 μM diltiazem, respectively, as compared to the IC₅₀ values. These calcium influx blockers greatly potentiated the cytotoxicity of VCR against P388/VCR cells. Increases in VCR cytotoxicity were 70- and 54-fold at the maximum concentrations of nicardipine and diltiazem, respectively. As the IC₅₀ values of VCR for P388/VCR cells shifted to smaller values than those (2.10 nM) of P388 cells by diltiazem and nicardipine, perfect circumvention of VCR resistance was attained by these blockers.

The effect of other calcium influx blockers on the sensitivities of P388 and P388/VCR cells to VCR was also estimated by the same manner as illustrated in Chart 1. The IC₅₀ values of VCR in the absence or presence of calcium influx blockers were summarized in Table 1. Niludipine and nilomodipine also enhanced the cytotoxicity of VCR against P388 and especially against P388/VCR cells. An increase in cytotoxicity of 26-fold was produced in P388/VCR cells at the maximum concentrations of niludipine and nilomodipine. Perfect circumvention of VCR resistance was also attained by these blockers.

These calcium influx blockers also enhanced VCR cytotoxicity against human K562 cells and especially that of VCR-resistant...
cells, differing from the effect observed for mouse cells; the most
2- to 3-fold increase in VCR cytotoxicity occurred in K562 cells
with diltiazem, nicardipine, and nimodipine as compared to the
IC50 values. Niludipine at 35 μM was marginally toxic to human
cells lines (Table 2). Diltiazem at 100 μM was toxic to human
cell lines (Table 2). Diltiazem at 100 μM was toxic to human

Table 1

<table>
<thead>
<tr>
<th>Calcium influx blocker and concentration (μM)</th>
<th>P388</th>
<th>P388/VCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2.10 ± 0.10a</td>
<td>32.4 ± 2.30</td>
</tr>
<tr>
<td>Nifedipine 35</td>
<td>1.08 ± 0.06b</td>
<td>7.37 ± 0.15c</td>
</tr>
<tr>
<td>100</td>
<td>1.14 ± 0.01b</td>
<td>2.60 ± 0.31c</td>
</tr>
<tr>
<td>Niludipine 3.5</td>
<td>1.03 ± 0.02b</td>
<td>2.93 ± 0.02c</td>
</tr>
<tr>
<td>10</td>
<td>0.65 ± 0.07b</td>
<td>1.25 ± 0.03c</td>
</tr>
<tr>
<td>Nimodipine 10</td>
<td>0.98 ± 0.06b</td>
<td>1.63 ± 0.01c</td>
</tr>
<tr>
<td>35</td>
<td>0.65 ± 0.04b</td>
<td>1.25 ± 0.01c</td>
</tr>
</tbody>
</table>

a Significant (p < 0.05) by Student’s t test as compared to the value without calcium influx blocker (2.10 ± 0.10).
b Significant (p < 0.05) by Student’s t test as compared to the value without calcium influx blocker (32.4 ± 2.30).

Effects of calcium influx blockers upon growth-inhibitory actions of VCR on P388 and K562/VCR cells

Tumor cells were treated with graded VCR concentrations with or without calcium influx blockers 5 hr after seeding the cells at 2 × 10^6 per 2 ml of the medium. Cell number was counted 72 hr after the continuous drug exposure, and the IC50 was determined as is shown in Chart 1 (24). In the absence of the drugs, cells grew exponentially, and the final cell numbers were (4.0 ± 0.2) × 10^6 and (2.2 ± 0.1) × 10^6 per 2 ml of the medium for P388 and K562/VCR cells, respectively.

Calcium influx blocker and concentration (μM) | IC50 (nM) of VCR against | K562 | K562/VCR |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2.68 ± 0.25a</td>
<td>56.3 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>Diltiazem 10</td>
<td>1.65 ± 0.09b</td>
<td>6.49 ± 0.57c</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>1.08 ± 0.19b</td>
<td>1.14 ± 0.10c</td>
<td></td>
</tr>
<tr>
<td>Nicardipine 3.5</td>
<td>1.57 ± 0.09b</td>
<td>2.28 ± 0.18c</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1.14 ± 0.03b</td>
<td>1.08 ± 0.04c</td>
<td></td>
</tr>
<tr>
<td>Nifedipine 10</td>
<td>2.49 ± 0.01b</td>
<td>28.2 ± 0.31c</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>1.95 ± 0.05b</td>
<td>5.85 ± 0.07c</td>
<td></td>
</tr>
<tr>
<td>Niludipine 10</td>
<td>1.52 ± 0.03b</td>
<td>1.17 ± 0.03c</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>0.48 ± 0.01b</td>
<td>0.46 ± 0.06c</td>
<td></td>
</tr>
<tr>
<td>Nimodipine 10</td>
<td>1.68 ± 0.05b</td>
<td>3.79 ± 0.16c</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>0.98 ± 0.01b</td>
<td>1.04 ± 0.01c</td>
<td></td>
</tr>
</tbody>
</table>

Table 2

Effects of calcium influx blockers upon growth-inhibitory actions of VCR on K562 and K562/VCR cells

Calcium influx blocker and concentration (μM) | IC50 (nM) of ADM against P388 | P388/ADM |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>17.3 ± 3.0a</td>
<td>849 ± 97</td>
</tr>
<tr>
<td>Diltiazem 35</td>
<td>11.9 ± 1.2c</td>
<td>92.7 ± 5.2c</td>
</tr>
<tr>
<td>100</td>
<td>10.4 ± 0.7c</td>
<td>53.0 ± 7.0c</td>
</tr>
<tr>
<td>Nicardipine 3.5</td>
<td>7.3 ± 0.4c</td>
<td>216 ± 56c</td>
</tr>
<tr>
<td>10</td>
<td>4.7 ± 0.1c</td>
<td>31.1 ± 1.7c</td>
</tr>
<tr>
<td>Nifedipine 35</td>
<td>20.8 ± 1.6c</td>
<td>260 ± 1.8c</td>
</tr>
<tr>
<td>100</td>
<td>17.3 ± 1.3c</td>
<td>208 ± 8.3c</td>
</tr>
<tr>
<td>Niludipine 3.5</td>
<td>9.0 ± 0.5c</td>
<td>145 ± 2.1c</td>
</tr>
<tr>
<td>10</td>
<td>7.3 ± 0.3c</td>
<td>86.5 ± 3.5c</td>
</tr>
<tr>
<td>Nimodipine 10</td>
<td>10.0 ± 0.1c</td>
<td>100 ± 1.6c</td>
</tr>
<tr>
<td>35</td>
<td>5.7 ± 0.6c</td>
<td>55.8 ± 3.3c</td>
</tr>
</tbody>
</table>

a Significant (p < 0.05) by Student’s t test as compared to the value without calcium influx blocker (17.3 ± 3.0).

potentiation of ADM Cytotoxicity by Calcium Influx Blockers. These calcium influx blockers also enhanced the cytotoxicity of ADM against P388 cells and especially against P388/ADM cells. The enhancement, however, was not as prominent as that observed for VCR in P388/VCR cells. An approximately 50-fold increase in cytotoxicity was observed for diltiazem, nicardipine, and niludipine at maximum concentrations used. Perfect circumvention of VCR resistance was attained by these blockers.

The effect of niludipine was not impressive throughout these experiments.

Circumvention of Drug Resistance by Calcium Antagonists

Effects of calcium influx blockers upon growth-inhibitory action of ADM on P388 and P388/ADM cells

Tumor cells were treated with graded ADM concentrations with or without calcium influx blockers 5 hr after seeding the cells at 2 × 10^6 per 2 ml of the medium. Cell number was counted 72 hr after the continuous drug exposure, and the IC50 was determined as is shown in Chart 1 (24). In the absence of the drugs, cells grew exponentially, and the final cell numbers were (4.1 ± 0.2) × 10^6 and (3.3 ± 0.2) × 10^6 per 2 ml of the medium for P388 and P388/ADM cells, respectively.
apeutic effect in P388/VCR-bearing mice except at dosages of 200 and 400 μg/kg, where a slightly longer survival time was obtained (Charts 2 and 3). Each calcium influx blocker alone also did not confer a significant therapeutic effect against P388/VCR-bearing mice (data not shown).

However, calcium influx blockers given 10 times with VCR significantly increased the life span of the P388/VCR-bearing mice (Charts 2 and 3). Especially notable was a 4- to 6-day increase in life span which was observed when diltiazem (100 to 125 mg/kg) was administered with VCR (200 μg/kg), nicardipine (45 to 75 mg/kg) was combined with VCR (100 to 200 μg/kg), niludipine (60 to 75 mg/kg) was combined with VCR (100 μg/kg), and nimodipine (75 to 125 mg/kg) was combined with VCR (100 μg/kg). The combination of 2 drugs at other doses also increased the life span of the mice significantly.

At a VCR dose of 30 μg/kg in P388/VCR-bearing mice, a T/C value of approximately 140% was obtained with nicardipine (75 mg/kg), niludipine (75 mg/kg), and nimodipine (150 mg/kg). At a VCR dose of 100 μg/kg, a T/C value of approximately 150% was obtained with nicardipine (75 mg/kg), niludipine (60 to 75 mg/kg), and nimodipine (100 mg/kg). These T/C values were less than those obtained in P388-bearing mice treated with VCR alone at 30 μg/kg (T/C = 150%) and at 100 μg/kg (T/C = 173%), respectively. These results indicate that the circumvention of VCR resistance in vivo was not perfect at the same VCR dosages; however, VCR resistance could be almost completely overcome in the P388/VCR bearer when approximately triple amounts of VCR were given with appropriate calcium influx blockers, because the T/C value of the P388/VCR bearer treated with VCR (100 μg/kg) and calcium influx blockers was almost equal to that obtained in the P388 bearer that was treated with VCR alone at 30 μg/kg.

Combined Effect of ADM and Calcium Influx Blockers on P388/ADM-bearing Mice. The effect of calcium influx blockers on the circumvention of ADM resistance in vivo was examined. In this case, the ADM resistance [index of resistance was 49 (Table 3)] was stronger than the VCR resistance in P388/VCR cells (index of resistance was 15), and the effect of calcium influx blocker in P388/ADM cells was not as prominent as that seen in P388/VCR cells. We inoculated 10^6 P388/ADM cells into mice, and drugs were administered in a way similar to that for the P388/VCR bearer.

ADM administered daily for 10 days increased the life span of the P388-bearing mice. T/C values of 183 and 189% were obtained at ADM dosages of 0.5 and 1.0 mg/kg, respectively (data not shown). ADM at 1 mg/kg conferred a marginal therapeutic effect (T/C values were 117 and 109% in repeated experiments). Calcium influx blockers alone showed no therapeutic activity. However, calcium influx blockers given along with ADM increased the life span of P388/ADM bearers significantly (Table 4), although the extent of increase was smaller than that observed with VCR for P388/VCR bearers. A maximum increase
in life span by calcium influx blockers was approximately 3 days. Similar enhancement of chemotherapeutic effect also occurred with ADM at 0.5 mg/kg along with the calcium influx blockers (data not shown). Although this value is less than that obtained in the experiment with VCR in P388/VCR bearers, these results indicate that calcium influx blockers can render the ADM-resistant tumor cells partly susceptible to ADM in vivo.

**DISCUSSION**

We have reported previously that verapamil, a calcium influx blocker, enhanced the cytotoxicity of VCR and vinblastine in P388 and P388/ADM cells and that VCR resistance of P388/VCR cells could be overcome in vivo and in vitro (24). In a variety of tumor cells, Vinca alkaloid-resistant cells are also resistant to anthracyclines (1–3, 7, 17, 28). Both classes of antitumor agents are actively transported outside the tumor cells and especially those that are drug resistant (3, 6, 10, 16, 17, 24). Subsequent studies revealed that verapamil enhances the cytotoxicity of VCR in P388/ADM cells and also enhances the cytotoxicity of ADM in P388/VCR and P388/ADM cells in vitro (26). Calmodulin inhibitors also effectively enhance VCR and ADM cytotoxicity in P388/VCR and P388/ADM (25). We found that verapamil and calmodulin inhibitors efficiently inhibit the VCR- and ADM efflux function of tumor cells and especially of resistant cells (25). VCR and ADM accumulated greatly in resistant tumor cells and resulted in the marked enhancement of drug cytotoxicity in drug-resistant tumor cells (24–26).

These results suggest the possibility of using this approach to overcome the drug resistance clinically. In order to find out which drugs are potentially effective clinically, we examined various calcium influx blockers and calmodulin inhibitors. Among those drugs examined, calcium influx blockers generally were more effective than calmodulin inhibitors, especially in vivo experiments. Among calcium influx blockers, diltiazem, nicardipine, niludipine, and nimodipine showed an impressive effect in vitro and in vivo which was almost comparable to that obtained by verapamil (24).

The precise mechanism and the involvement of cellular calcium in the enhancement of VCR and ADM cytotoxicity are under investigation. Nifedipine possesses a very strong calcium influx-blocking action in vascular smooth muscle (5); however, the effect of nifedipine in the present study was not impressive. This could indicate that the calcium influx-blocking action in smooth muscle might be different from that in tumor cells. Actually, different calcium influx blockers possess different specificity for organs or cells, and also one calcium influx blocker showed different response in organs and cells (5). In this study, we found that calcium influx blockers also possessed different growth-inhibiting activity against various tumor lines used. Diltiazem and nifedipine were more cytotoxic to human cells than to mouse tumor cells, while niludipine showed a stronger cytotoxicity to mouse tumor cells. We have not clarified the action of calcium influx blockers in tumor cells. However, it might be possible to speculate that the calcium influx-blocking action of the drugs is involved in the enhancement of the antitumor activity in tumor cells, since all calcium influx blockers examined possessed an impressive effect. We have speculated that the efflux of VCR and ADM from tumor cells, especially from drug-resistant cells, is possibly controlled by the calcium-calmodulin complex (25); however, the real mechanism remains to be discerned. We are presently investigating more closely the action of cellular calcium in the drug transport mechanisms of tumor cells in order to determine the validity of our speculation.

The present approach using calcium influx blockers in cancer chemotherapy has at least the 4 following advantages: (a) circumvention of drug resistance in tumor cells; (b) circumvention of heterogeneity of tumor cells in drug response; (c) effectiveness against various antitumor agents which are transported outside the cells by the same efflux mechanism; and (d) dose deescalation of antitumor agents. We are currently undertaking a preclinical toxico logic study of these calcium influx blockers, including verapamil, to explore the possibility of applying the present approach clinically for the circumvention of drug resistance.

**ACKNOWLEDGMENTS**

We thank Tanabe Seiyaku, Co., Ltd., Yamanouchi Pharmaceutical Co., Ltd., Bayer AG, Germany, for their gifts of calcium influx blockers. We are indebted to E. Sass for editing and to M. Shimizu for typing the manuscript.

**REFERENCES**


Circumvention of Vincristine and Adriamycin Resistance \textit{in Vitro} and \textit{in Vivo} by Calcium Influx Blockers

Takashi Tsuruo, Harumi Iida, Makiko Nojiri, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/43/6/2905

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.