was implanted intraperitoneally. Live images were collected immediately. Next day curcumin (200 ug/ mouse) was injected ip. Images were collected after 2nd and 4th days with fluorescent stereomicroscope. Upon necropsy peritoneal wash was collected for culture and further examination to assess the cell death relative to the imaging data.
Results: In vitro results showed all treated cancer cells displayed green fluorescence. Viability test showed 100% cells were dead that were GFP-positive. In vivo images showed curcumin incorporation into the implanted cancer cells that were was imaged with GFP filter. On day 2 more GFP signal was detected than 4, since cells were killed by curcumin.
Conclusions: Therapeutic effect of curcumin was detected by fluorescent stereomicroscopy in a non-invasive way. This natural product can be used as a preventive medicine against cancer.

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A new antitumor compound, ECO-04601: preclinical evaluation and in vivo efficacy in glioma

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ECO-04601 is a structurally novel farnesylated diazepinone (MW 462) discovered using Ecopia's genomic platform through analysis of actinomycete loci encoding bioactive compounds. ECO-04601 is being developed as an antitumor agent as it shows suitable pharmaceutical properties, including in vivo efficacy, low toxicity, rapid absorption and bioavailability in target tissues. We have recently shown that ECO-04601 strongly inhibits proliferation of several human cancer cell lines in vitro, including low and high-grade human glioma cells (IC50 = 1 to 8 microM). To demonstrate in vivo efficacy, nude mice were inoculated with rat C6 glioma cells (5 millions/ml) either subcutaneously (6/group), or orthotopically in the caudate putamen (10/group). Daily treatment (10 to 30 mg/kg, i.p.) was initiated 24 hrs following glioma cell inoculation. When tumors cells were implanted subcutaneously, treatment with ECO-04601 resulted in a significant decrease of the tumor volume by 60%. In the orthotopic model, mice were treated daily with ECO-04601 until spontaneous death. Initial results indicate efficacy of ECO-04601 in this model as we observed a seven-day increase in the median survival of treated mice as compared to the vehicle-treated group. No significant loss of body weight was observed during the chronic treatment regimen of tumor-bearing mice suggesting a favorable toxicity profile of the compound that has been further confirmed by acute and subchronic administration of ECO-04601 in healthy animals. Female CD-1 mice tolerated single intravenous doses of 100 mg/kg of ECO-04601 and repeated subcutaneous or oral doses of 225 mg/kg. Preliminary pharmacokinetic experiments suggest rapid absorption and tissue distribution of the compound following administration by various routes of administration. These data highlight the promising therapeutic potential of ECO-04601 in aggressive tumors like gliomas.

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In vitro and in vivo characterizations of naturally occurring BBIs in reversal of p-gp mediated multidrug resistance

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Background: Multidrug resistance (MDR) is one of the major obstacles limiting the efficacy of cancer chemotherapy. The overexpression of the membrane associated P-glycoprotein (P-gp), which acts as an energy-dependent drug efflux pump, is believed to play a critical role in MDR. A promising strategy to conquer drug resistance is to develop functional MDR modulators that can specifically inhibit the P-gp activity. Through screening a series of natural products, we have recently identified six bisbenzylisoquinoline alkaloids (BBIs) that possess potent activity to reverse P-gp-mediated drug resistance. In this study, we characterized and evaluated the ability of these newly identified MDR Modifiers in reversal of P-gp-mediated drug resistance caused by different antineoplastic agents.
Materials and Methods: T wo human MDR cells (MCF-7/adr and KBv200) and their drug-sensitive parental cells were used for *in vitro* evaluation and characterization. The *in vivo* activity of these promising BBIs was evaluated through establishment of xenograft tumor models.
Results: In vitro assays indicated that these natural BBIs showed potent activities to restore sensitivity of resistant tumor cells, such as MCF-7/adr and KBv200 cells, to many antitumor drugs including doxorubicin, vincristine and paclitaxel. Further analyses by measurement of radioactive [^{3}H]-vincristine and [^{3}H]-paclitaxel indicated that these BBIs increased intracellular drug accumulation in MDR cells, but had little effect on drug-sensitive cells. Through establishment of xenograft models bearing the intrinsically resistant KBv200 tumors, we also tested one of these compounds (FF0019) and demonstrated that this class of naturally occurring MDR modifiers could also significantly potentiate the antitumor activity of VCR and paclitaxel *in vivo*.

Table 1. Effect of BBIs on reversing MDR[a]

		Fold shift of Dox IC_{50}^b		Fold shift of VCR IC_{50}^c	
		MCF-7/ADR	MCF-7	KBv200	KB
FF0011	5 μM	22.1±6.6	1.2±0.7	12.8±1.5	1.3±0.8
	2.5 μM	19.7±1.9	1.1±0.2	9.5±1.9	1.0±0.2
	1.25 μM	7.6±2.2	0.9±0.3	4.1±1.1	1.0±0.3
	0.625 μM	2.3±1.7	0.9±0.2	1.8±0.2	0.9±0.4
FF0012	5 μM	24.5±3.8	1.1±0.4	17.1±3.5	1.2±0.2
	2.5 μM	17.1±2.3	1.0±0.2	9.4±1.7	1.0±0.1
	1.25 μM	7.5±1.9	1.0±0.4	6.1±2.5	1.0±0.2
	0.625 μM	3.0±0.5	1.4±0.4	3.4±2.9	1.1±0.5
FF0014	5 μM	35.0±7.7	1.9±0.3	18.0±6.4	1.4±0.6
	2.5 μM	13.3±4.8	1.4±0.4	9.4±3.6	1.3±0.4
	1.25 μM	6.9±1.6	1.3±0.1	6.1±2.2	1.0±0.1
	0.625 μM	3.2±0.9	O.9±0.3	27±0.5	0.8±0.4
FF0015	5 μM	43.9±15.0	1.1±0.2	21.9±3.5	1.8±0.6
	2.5 μM	32.0±7.2	0.9±0.4	12.9±5.0	1.3±0.5
	1.25 μM	10.3±7.3	1.0±0.3	7.2±4.0	1.3±0.3
	0.625 μM	5.3±2.0	1.1±0.4	3.9±1.6	1.1±0.2
FF0018	5 μM	42.7±6.8	1.3±0.6	20.1±4.6	1.6±0.5
	2.5 μM	22.9±5.4	1.3±0.4	12.9±3.8	1.1±0.3
	1.25 μM	7.7±2.2	1.0±0.3	5.8±2.3	1.1±0.4
	0.625 μM	3.6±1.1	1.0±0.3	2.8±1.1	1.0±0.4
FF0019	5 μM	49.0±7.9	1.4±0.4	23.0±5.6	1.5±0.6
	2.5 μM	29.4±5.8	1.0±0.3	15.6±6.6	1.3±0.4
	1.25 μM	12.3±3.9	1.0±0.2	8.9±2.5	1.1±0.5
	0.625 μM	3.4±0.7	0.9±0.2	3.2±0.9	0.9±0.2
VRP	5 μM	7.6±3.4	1.0±0.3	6.4±1.4	1.1±0.4

[a]This table is based on three separate experiments and presented as mean±SEM.
[b]The IC_{50} of Dox for MCF-7/adr and MCF-7 cells in the absence of BBIs are 16.712 μM and 0.1718 μM, respectively.
[c]The IC_{50} of VCR on KBv200 and KB cells in the absence of BBIs are 0.054 μM and 4.437 μM, respectively.

Conclusions: These results suggested that the mechanism of these compounds to reverse MDR was associated with the increase in the intracellular drug accumulation through inhibiting the activity of P-gp. These compounds may possess great promising in being developed into novel anticancer drugs as modifiers of MDR (Supported by NIH Grants CA82440 and CA92280).

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Bioavailability and pharmacokinetic study of the novel oral C-Seco taxane derivative IDN 5390 in mice

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Background. IDN5390 is the prototype of C-Seco taxanes, a new class of semi-synthetic taxoids. C-seco taxanes are characterized by an opening of C-ring by cleavage of C7-C8 bond. It was selected from a screening of new molecules with antiangiogenic and antimetastatic properties. It has shown high antitumor activity and good tolerability against a variety of human tumor xenografts including ovarian, colon ca and glioblastoma either sensitive or resistant to paclitaxel. The therapeutic advantages of IDN 5390 over paclitaxel were evident when the drug was administered by protracted oral-treatment schedules.
Aims: To characterize the pharmacokinetic of IDN 5390 after single and repeated administration in mice, we have determined the bioavailability, tissue distribution, faecal and urinary excretion and the *in vitro* (hepatic microsomes) and *in vivo* metabolism.
Materials and Methods. The study was carried out in CDF1 female mice treated with single intravenous and oral doses of 60, 90 and 120 mg/Kg or, for one week with protracted oral daily exposure of 90 mg/Kg. Blood, urine, faeces and tissue samples were taken at different time points. IDN 5390 were determined by HPLC with UV detection in plasma and tissues and by HPLC/MS/MS in urine, faeces and microsomes.