Supplement to 'Membrane Transporters and Channels: Role of the Transportome in Cancer Chemosensitivity and –resistance'.

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This supplement provides additional data testing the validity of the 70-mer oligonucleotide array results (cell clustering and comparison to other analytical methods) and a complete list of all significant drug-transportome correlations.

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Hierachical clustering of the NCI-60 cell panel using transportome gene expression

We used hierarchical clustering by gene expression to determine whether cells with similar tissue origin cluster together, as shown previously with other array results (1). This is an important validation step. When using results from all probes of the 70-mer array, cell clusters differed in some detail from those obtained with select genes from other arrays (cDNA and Affymetrix). Any differences probably resulted from the inclusion of all genes, even where mRNA levels were below or close to the detection limit. However, use of 170 select probes from the 70-mer arrays showing concordant results with other array datasets on the NCI-60 yielded cell clusters comparable to those previously published. (1) Generally, cells of similar tissue origin tended to cluster together (supplementary Fig. 1), with a few differences from cell

clusters obtained with expression data of 1,376 genes reported by Scherf et al. (1). MDA-MB-435 and its Erb/B2 transfectant MDA-N clustered immediately next to each other, demonstrating reproducibility of the array results. Moreover, both cell lines clustered with melanomas since they express genes characteristic of melanoma-derived cells (1). These cell lines express high levels of *ABCB5*, a novel putative resistance gene proposed in this study. Overall, cell clustering supports the validity of the 70-mer array results. Failure of some cell lines to cluster with their tissue of origin is probably due to the different gene panel used. Genes relevant to chemosensitivity may not reflect fully the physiology of the cell(1, 2).

Cell line NCI/ADR-RES, tested in duplicate using independent labeling and hybridizations, clustered together in the same branch, supporting reproducibility of the analysis. However, comparison of the expression of single genes measured by different arrays shows that only a subset of gene probes yields results that can be interpreted with confidence. Confounding factors include possible cross-hybridization between closely related genes (although the 70-mer probes were designed to discriminate between closely related homologues, a possible advantage over cDNA arrays), insufficient levels of mRNA, and low signal to noise ratios. Therefore, criteria for selecting significant gene-drug correlations were set at a sufficiently stringent level to minimize false discovery while still capturing a fair portion of valid correlations. Moreover, each significant gene-drug correlation must be validated by other means.

Comparing gene expression data obtained with the 70-mer oligo array to expression datasets using other arrays or methods

To validate the microarray results, mRNA expression data obtained with the 70-mer arrays were compared to those obtained with cDNA (1), and Affymetrix HG-6800 (3) arrays.

137 and 235 genes were commonly represented between the 70-mer and the cDNA and HG-6800 arrays, respectively. The mean Pearson Correlation coefficients between the 70-mer oligo and cDNA arrays for all 60 cell lines was 0.43 ± 0.14 ($p<0.05$). This indicates that for a majority of common genes, these two arrays yielded similar results. Correlation between the 70-mer and the Affymetrix array on the other hand were poor. However, discrepancy may result from differences in normalization procedures necessitated by the different platforms (the Affymetrix arrays yield absolute values rather than ratios), and differences in sensitivity between probes. In a comprehensive comparison between mRNA expression in Caco-2 cells, measured with the 70-mer array and the Affymetrix U95A array, correlations improved with increasing gene expression level (4). It should be noted that robust gene-drug correlations depend on strong gene expression in a portion of the cell lines of the NCI-60; this provides another filter against spurious result.

To validate the array data further, we determined *ATP1B1* expression by real-time RT-PCR and compared the result with those from our 70-mer oligo and cDNA arrays. The RT-PCR experiment agreed well the array results (Supplementary Fig. 2). In a previous study on mRNA expression in Caco-2 cells and human intestines, we had already performed a serious of additional comparisons between results from the 70-mer array and RT-PCR, showing comparable results in most cases (5)**.**

Complete representation of all significant gene-drug correlations

We compiled all gene-drug correlations reaching a bootstrap p value of <0.001. Where prior knowledge supports a substrate-transporter relationship, for example, if a substrate-transporter interaction had already been published, or if a correlated substrate has obvious

structural similarity to the known natural substrate or drug, we used <0.05 as the cutoff value. This minimizes the risk of false-positive relationships, and yet, significant gene-drug pairs will be missed. False negative results are particularly likely because significant correlations require not only that a cytotoxic drug be a substrate, but that this interaction also play a significant role in variability across the NCI-60. In the case of ion exchangers and ATPases, and channels (which commonly are not thought to serve as transporters *per se*, $p<0.001$ was used, unless a substantial number of drugs correlated at $p<0.05$, suggesting a general trend as either a resistance or sensitivity factor. Spurious significant correlations can also occur if genes are coordinately expressed, or the oligo probes lack specificity.

Results for solute transporters, ABC transporters, and ion pumps and channels are listed in supplemental Tables 1 to 3. Genes are highlighted if they show concordance (Pearson correlation coefficient $r> 0.3$) in at least one comparison with other expression studies, using different arrays or methods, or RT-PCR data. In using these data, users are advised to use strict selection criteria before pursuing any gene drug correlations. The database is also useful for selecting cell lines strongly expressing any genes of interest.

Methods

Clustering of cell lines by gene expression profiles. Hierarchical clustering can be used to group cell lines in terms of their patterns of gene expression (1, 6). To obtain cell clusters based on tissue of origin, cluster trees were constructed using 170 genes found to be common with other data sets. We used the programs “Cluster” and “TreeView” (7) with average linkage clustering and a correlation metric.

Comparison between the 70-mer oligo, cDNA, and Affymetrix array studies. Gene expression profiles for the NCI-60 had also been measured using cDNA arrays and Affymetrix oligonucleotide chips (HG-6800). Both sets are available at http://discover.nci.nih.gov. For the cDNA arrays, each cell type was hybridized against a reference pool of mRNA from 12 highly diverse cell lines (1). The cDNA data were normalized using Gaussian-windowed moving-average fits without background subtraction (8) and log2 transformed (1). Average differences from the Affymetrix data were calculated using the Affymetrix GeneChip software, with spot intensity floored at 30 (i.e., all values lower than 30 were set to 30), then log2 transformed. To begin the comparison analysis, we used UniGene clustering and Genbank sequence information to identify genes common to the different types of arrays. For that purpose, we used parseUniGene, an early version of the program MatchMiner (9) (http://discover.nci.nih.gov), with UniGene build 132 (February 2001). 137 genes were common to the 70-mer arrays and cDNA arrays, 235 genes were common to the 70-mer arrays and Affymetrix arrays, and 102 genes were common to all three array types. Pearson correlation coefficients served as an index of the concordance between expression levels of common genes for each cell line, and across the 60 cell lines for each gene. Correlation coefficients (r) of 0.3 were taken to indicate that the two arrays yield concordant results. This recognizes a substantial degree of variability; however, gene-drug correlation results are predicated on strong gene expression in a few cell lines, which is measured with a high degree of confidence by all platforms. Therefore, even a low overall correlation between array results can result in similar gene-drug correlations.

Supplementary Table 1. SLC transporters showing significant correlations with drugs.

Gene	Number of drug				Substrate	Representative drug
	P <0.001		*P* <0.05			
	r>0	r<0	r>0	r<0		
SLC1A1	1	0	24	1	amino acid	[L-Asparaginase][L-Alanosine]
SLC1A4	3	1	11	12	amino acid	[Asaley][Taxol analog][Acivicin][L-Alanosine]
SLC1A5	0	2	0	15	amino acid	[Carboplatin][Mechlorethamine]
SLC2A1	1	0	5	0	glucose	[Taxol analog]
SLC2A3	1	0	10	1	glucose	[Geldanamycin]
SLC2A4	2	0	10	0	glucose	[Asaley][Spiromustine]
SLC2A5	0	2	0	12	glucose	[Aminopterin][Aminopterin]
SLC2A11	2	0	38	0	glucose	[Anthrapyrazole][Oxanthrazole]
SLC2A12	2	0	12	0	glucose	[Taxol analog]
SLC3A1	0	0	4	0	amino acid	[L-Asparaginase]
SLC3A2	0	3	1	30	amino acid	[Asaley][Cisplatin][beta-2'-Deoxythioguanosine][Melphalan]
SLC4A7	18	0	56	0	sodium bicarbonate	[Mitomycin][Spiromustine][CPT,10-OH][Mitoxantrone]
SLC5A6	7	0	18	0	vitamin	[CCNU][Baker's-soluble-antifolate][Paclitaxel]
SLC6A10	0	7	1	29	creatin	[Deoxydoxorubicin][Menogaril][Teniposide]
SLC6A14	9	0	58	0	amino acid	[CPT,7-Cl][Methotrexate][Taxol analog][Melphalan]
SLC6A2	1	0	5	1	norepinephrine	[beta-2'-Deoxythioguanosine]
SLC7A1	1	0	8	0	amino acid	[Colchicine][Vinblastine][Taxol analog][Geldanamycin]
SLC7A2	0	0	13	0	amino acid	[L-Alanosine]
SLC7A3	0	0	12	0	amino acid	[L-Asparaginase]
SLC7A8	0	0	0	14	amino acid	[N-phosphonoacetyl-L-aspartic-acid]
SLC7A9	0	0	3	1	amino acid	[Acivicin]
SLC7A10	3	0	39	0	amino acid	[Clomesone][Oxanthrazole (piroxantrone)][Teniposide]
SLC7A11	2	0	12	5	amino acid	[Anthrapyrazole][Colchicine][L-Alanosine]
SLC8A1	1	0	3	1	sodium/calcium	[Carboplatin]
SLC9A3R2	2	0	21	0	sodium/hydrogen	[CPT,9-MeO][L-Asparaginase]
SLC11A1	7	0	57	0	metal ion	[Asaley][Iproplatin][CPT,9-MeO][Ftorafur]
SLC15A1*	0	0	0	7	peptide	[Asaley][Fluorodopan][CPT,11-HOMe (RS)]
SLC15A1	0	0	5	0	peptide	[Fluorodopan][Teroxirone][Etoposide][L-Asparaginase]
SLC16A2	0	1	2	9	monocarboxylic acid	[Clomesone][Azacytidine]
SLC16A3	5	0	40	2	monocarboxylic acid	[CPT,20-ester (S)][Mitoxantrone][L-Asparaginase]
SLC17A1	1	0	35	5	sodium phosphate	[Asaley]
SLC17A7	1	0	2	0	sodium phosphate	[Carboplatin]
SLC19A1	0	0	19	0	folate	[6MP][Gemcitabine]
SLC19A2	2	0	24	1	folate	[Tetraplatin][Iproplatin][an-antifol][Trimetrexate]
SLC19A3	0	0	4	0	folate	[an-antifol]
SLC20A2	0	1	0	20	phosphate	[CCNU]
SLC21A12	2	0	14	15	organic anion	[Aminopterin]
SLC21A8	0	3	1	41	organic anion	[Asaley][Fluorodopan][Spiromustine]
SLC22A1L	0	2	0	36	organic cation	[CPT,11-HOMe (RS)]
SLC23A2	1	0	8	0	nucleobase	[5FU]
SLC25A12	4	0	29	0	aspartate glutamate	[Thioguanine][N-phosphonoacetyl-L-aspartic-acid]
SLC25A13	0	0	0	41	aspartate glutamate	[L-Asparaginase][CPT][Hepsulfam]
SLC25A14	1	0	7	0	proton	[Colchicine]
SLC25A15	1	0	13	0	ornithine	[Inosine-glycodialdehyde][Taxol analog]
SLC25A17	0	2	7	44	ATP	[Clomesone][Cyanomorpholinodoxorubicin]
SLC25A3	2	0	12	0	phosphate	[Aminopterin][Methotrexate]
SLC25A5	5	0	20	0	ADP ATP	[Colchicine][Vinblastine][Taxol analog][Geldanamycin]
SLC27A5	0	1	0	12	fatty acid	[Aminopterin][5FU]
SLC28A1	0	0	7	0	nucleoside	[Aminopterin][6MP]
SLC28A3	2	0	38	0	nucleoside	[Thioguanine][Cytarabine (araC)][Gemcitabine]
SLC29A1	2	0	21	0	nucleoside	[CCNU][Azacytidine][Thioguanine]
SLC29A2	0	0	2	1	nucleoside	[alpha-2'-Deoxythioguanosine][Inosine-glycodialdehyde]
SLC30A3	0	1	0	23	zinc	[Colchicine][Trityl-cysteine][Vinblastine]
SLC31A1	0	5	0	44	copper	[Diaminocyclohexyl-Pt-II][Tetraplatin][Iproplatin][Cisplatin]
SLC34A2	0	3	1	22	sodium phosphate	[5FU][Taxol analog]
SLC38A2	1	0	14	0	amino acid	[Maytansine][Acivicin][L-Alanosine]
SLC38A5	2	0	25	0	amino acid	[Clomesone][Colchicine][L-Asparaginase]
KIAA1939	1	0	12	0	unknown	[L-Asparaginase]
LOC133308	7	0	51	0	sodium/hydrogen	[CCNU][6MP][Doxorubicin][Taxol analog]

Activities of the underlined drugs have negative correlations with expression of the corresponding genes. Shadowed genes have concordant expression patterns in at least one comparison between results obtained with 70-mer arrays, cDNA arrays, and Affymetrix arrays. For each gene, the number of drugs with positive or negative correlation values (r) is shown, with $P< 0.05$ and $P<0.001$. *: The pH-sensing regulatory splice variant of *SLC15A1*.

Supplementary Table 2. ABC transporters that show significant correlations with drugs.

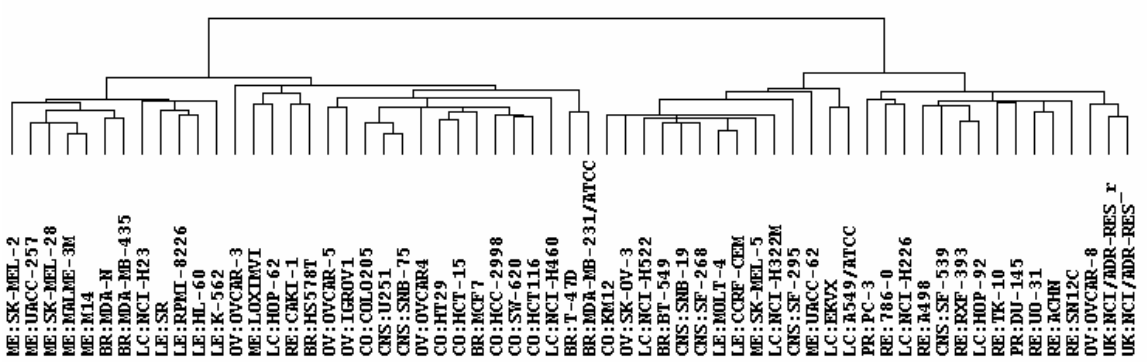
Gene	Alias	Number of drug				Representative drugs
		P <0.001		*P* <0.05		
		r>0	r<0	r>0	r<0	
ABCA1	ABC1	1	0	10	0	[Asaley]
ABCA2	ABC2	0	0	1	1	[Taxol analog][CPT,9-MeO]
ABCB1	MDR	0	3	2	32	[Bisantrene][Taxol analog]
ABCB2	TAP1	0	0	2	1	[Aminopterin-derivative]
ABCB3	TAP2	1	0	55	0	[Lomustine (CCNU)]
ABCB5		0	1	1	25	[CPT,7-Cl]
ABCB11	SPGP	1	0	3	4	[Dolastatin-10][Spiromustine]
ABCC1	MRP1	0	4	0	20	[Semustine (MeCCNU)][Vinblastine][Taxol analog]
ABCC2	MRP2	0	0	0	1	[Pyrazoloacridine]
ABCC3	MRP3	0	2	0	18	[Vincristine][Methotrexate-derivative]
ABCC4	MRP4	0	0	2	2	[L-Asparaginase][Bisantrene]
ABCC5	MRP5	0	0	0	14	[Bisantrene][Mitoxantrone]
ABCC10	MRP7	1	0	5	5	[Geldanamycin][CPT,9-MeO]
ABCF2		2	0	15	0	[Aminopterin]
ABCG1	ABC8	3	0	22	0	[Doxorubicin][CPT,9-MeO]
ABCG8		1	0	15	0	[Cyanomorpholinodoxorubicin]

Underlined genes are those previously reported to be involved in chemo-resistance. Underlined drugs are those showing negative correlation with the corresponding genes. Shadowed genes are those showing concordant expression patterns in at least one comparisons between results obtained with 70-mer arrays, cDNA arrays, and Affymetrix arrays. For each gene, the number of drugs with positive or negative correlation values (r) is shown, with $P< 0.05$ and $P<0.001$.

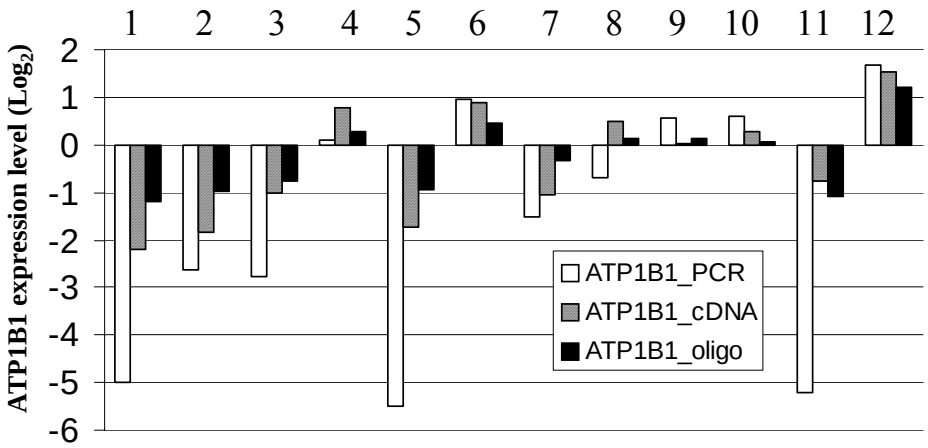
Supplementary Table 3. Ion pumps and channels showing significant drug correlations.

Gene	Function	Number of drug				Representative drug
		P <0.001		*P* <0.05		
		r>0	r<0	r>0	r<0	
Ion pump						
ATP1A1	sodium/potassium	0	5	6	43	[Uracil mustard][CPT,11-formyl (RS)][N-N-Dibenzyl-daunomycin]
ATP1A3	sodium/potassium	0	3	0	24	[CCNU][Daunorubicin][5-6-Dihydro-5-azacytidine]
ATP1B1	sodium/potassium	0	10	0	34	[CCNU][Tetraplatin][5-6-Dihydro-5-azacytidine][Taxol analog]
ATP1B3	sodium/potassium	0	0	2	20	[Daunorubicin][5FU]
ATP1G1	sodium/potassium	0	0	4	14	[Tetraplatin][Taxol analog]
ATP2A1	calcium	1	0	12	0	[Morpholino-adriamycin][Doxorubicin][5FU]
ATP2A3	calcium	0	0	37	0	[BCNU][Gemcitabine]
ATP2B3	calcium	0	0	0	8	[Colchicine-derivative][Taxol analog]
ATP2B4	calcium	0	11	0	44	[Tetraplatin][Methotrexate][5FU][Taxol analog]
ATP2C1A	calcium	0	3	0	31	[Iproplatin][Mechlorethamine][Deoxydoxorubicin]
ATP6V1D	proton	0	0	0	25	[Daunorubicin][Methotrexate][Taxol analog]
ATP8A2	aminophospholipid	3	0	15	0	[Aminopterin][Methotrexate]
ATP8B1	aminophospholipid	0	8	0	34	[MeCCNU]][Tetraplatin][Taxol analog][Doxorubicin]
ATP11B	unknown	1	0	14	2	[Taxol analog]
Ion channel						
AQP1	water	0	4	0	20	[Aminopterin][an-antifol][Methotrexate]
AQP4	water	0	1	0	10	[L-Alanosine]
AQP9	water, urea, arsenite	1	0	11	1	[Taxol analog]
MIP	water	2	0	46	0	[Pipobroman][Halichondrin B]
CACNA1D	calcium	0	4	0	37	[Mitozolamide][Cyclodisone][Deoxydoxorubicin]
KIAA1169	sodium/calcium	0	2	0	35	[Aminopterin][5FU]
SCN3A	sodium	0	1	0	8	[Ftorafur]
CLCA1	chloride	0	2	0	29	[Anthrapyrazole][Oxanthrazole]
CLCN6	chloride	0	3	0	15	[Iproplatin][Dolastatin-10][Inosine-glycodialdehyde]
CLCNKA	chloride	0	1	0	6	[Pyrazofurin]
KCNA2	potassium	1	0	17	1	[Colchicine]
KCNA5	potassium	0	1	0	26	[an-antifol]
KCNH2	potassium	1	0	2	8	[Maytansine]
KCNH3	potassium	0	1	1	4	[Aminopterin]
KCNK15	potassium	0	1			[Aminopterin]
KCNMA1	potassium	0	1	10	17	[CPT][Mitoxantrone][Inosine-glycodialdehyde][Taxol analog]
KCNS3	potassium	2	2	12	37	[Taxol analog][Cyanomorpholinodoxorubicin][Daunorubicin]
HCN2	potassium	7	0	54	0	[CPT] [Cyanomorpholinodoxorubicin][Gemcitabine]
TRPC5	cation	0	1	0	16	[Bisantrene]
TRPC7	cation	1	0	3	0	[CCNU]
TRPM1	cation	1	0	4	1	[Asaley]
TRPM4	cation	0	1	0	8	[Aminopterin]
TRPV2	cation	3	0	7	4	[Asaley][Taxol analog][Geldanamycin]
P2RX4	cation	0	1	1	17	[Pyrazoloacridine]
CNGB3	cation	1	0	9	0	[Spiromustine]
GJA1	connexin 43	2	0	11	5	[CPT,10-OH][Mitoxantrone]
T1A-2	unknown	0	6	0	46	[Thioguanine][Aminopterin][Trimetrexate]
PKDREJ	unknown	0	3	0	14	[Diaminocyclohexyl-Pt-II][Hycanthone][Pyrazoloacridine]

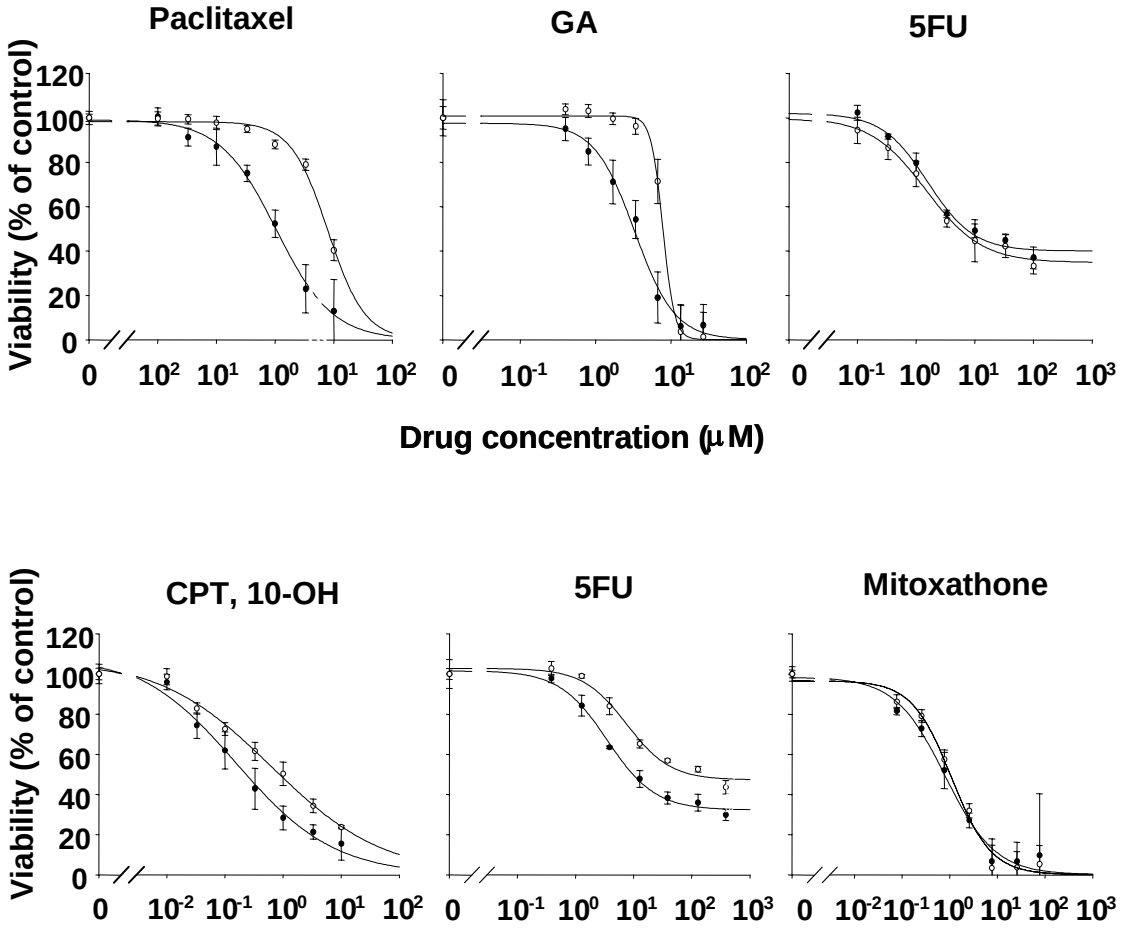
Underlined drugs correlate negatively with the corresponding genes. Shadowed genes have concordant expression patterns in at least one comparison between results obtained with 70-mer arrays, cDNA arrays, and Affymetrix arrays. For each gene, the number of drugs with significantly positive or negative gene-drug correlation coefficients, *r*, ($P< 0.05$ and $P<0.001$) is shown.



Supplementary Figure 1. Hierarchical cluster analysis of the NCI-60 cell lines. The clustering was based on expression profiles of 170 genes that showed concordant gene expression across various array datasets (correlation coefficient ≥ 0.3). Data from 61 hybridizations were used, one for each cell line, plus duplicate analysis of NCI/ADR-RES. BR: breast cancer; CNS: CNS cancer; CO: colon cancer; LC: lung cancer; LE: leukemia; ME: melanoma; OV: ovarian cancer; PR: prostate cancer; RE: renal cancer; UK: unknown origin.



Supplementary Figure 2. Comparison of *ATP1B1* mRNA levels by real-time quantitative RT-PCR, cDNA microarray, and 70-mer microarray. The expression levels were plotted as abundance (log2) of the *ATP1B1* transcript relative to its abundance in the reference pool of 12 cell lines. The RT-PCR data are normalized to β-actin. Cell lines tested are: 1, SR; 2, SK-MEL-28; 3, SW-620; 4, ACHN; 5, HL-60; 6, SN12C; 7,T-47D; 8, SF-295; 9, COLO205; 10, 786-0; 11, K562; 12, OVCAR-5.



Supplementary Figure 3. Validation of gene-drug relationships by suppressing the level of expressed mRNA with specific siRNA. Cells were transfected with siRNA targeted against *ABCB1* or *ABCB-5* (●), or with mock-siRNA (○). After 24 hours, cells were exposed to drugs for 4 days, and cell growth was measured with the SRB assay. Results are expressed as percentage of control cells with no drug treatment (means ± SD from 3-6 replicates). *Panel a.* Effect of *ABCB1*-targeted siRNA on chemosensitivity of NCI/ADR-RES cells to paclitaxel and geldanamycin (GA) and 5FU. *Panel b.* Effect of *ABCB5*-targeted siRNA on chemosensitivity of SK-MEL-28 cells to CPT, 10-OH, and mitoxantrone.

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