

# Supplementary Material

**Differential Sensitivity Analysis for Resistant Malignancies (DISARM v1.0)**  
[DISARM user guide](#)

Data Set:   
GDSC  
NCI-SCLC

Select data set for query from drop down menu.

Tip: Click "DISARM user guide" link or hover over question mark icon for help.

**Differential Sensitivity Analysis for Resistant Malignancies (DISARM v1.0)**  
[DISARM user guide](#)

Data Set:

Disease:   
SCLC  
STAD  
PAAD  
OV  
LUAD  
HNSC  
ESCA  
COAD  
BLCA

Select disease histology of interest from drop down menu.

**Differential Sensitivity Analysis for Resistant Malignancies (DISARM v1.0)**  
[DISARM user guide](#)

Data Set:

Disease:

Drug X (Reference):   
Cisplatin

Manually enter reference drug of entrance which will query data set and trigger auto-complete (if present).

**Differential Sensitivity Analysis for Resistant Malignancies (DISARM v1.0)**  
[DISARM user guide](#)

Data Set:

Disease:

Drug X (Reference):

X Resistance Cut-Off:

Y Sensitivity Cut-Off:

Search Reset

Finally, click search tab.

Select drug X (reference drug) resistance cut-off. In this example, 0.25 will define the highest 25% of IC50 values as resistant.

Select drug Y (candidate drug) sensitivity cut-off. In this example, 0.75 will define the lowest 75% of IC50 values as sensitive.

**Supplementary Figure S1. Step-by-step user guide for DISARM application – Part 1.** The above panels outline the steps required by the user to perform a query in DISARM web application or, similarly, DISARM software package, using the example of cisplatin as reference drug to query GDSC database for DISARM candidate drugs.

Copy CSV Search:

Disease	DrugName	Score	nSample	p	Bonferroni adjusted p	mu1	mu2	d
SCLC	VX.702	5.2463	28	<0.00001	0.00001	1.314	0.731	0.54
SCLC	Elesclomol	5.2463	28	<0.00001	0.00001	1.222	-0.663	0.54
SCLC	AICAR	4.9529	27	<0.00001	0.00005	1.247	2.285	0.52
SCLC	Methotrexate	4.9529	27	<0.00001	0.00005	1.293	-0.352	0.56
SCLC	GDC.0449	4.9529	27	<0.00001	0.00005	1.253	1.635	0.48
SCLC	SB.216763	4.9529	27	<0.00001	0.00005	1.222	1.511	0.48
SCLC	PLX4720	4.6567	26	<0.00001	0.00022	1.378	1.267	0.50
SCLC	BIRE.0796	4.6567	26	<0.00001	0.00022	1.407	1.677	0.46
SCLC	NVR.BE2235	4.6567	26	<0.00001	0.00022	1.369	-0.700	0.50
SCLC	AZ08055	4.6567	26	<0.00001	0.00022	1.342	-0.057	0.50

Resulting table lists candidate drugs ranked by p-value. Clicking on column headings ranks by specified quantity, which include DISARM score ("score"), p-value ("p"),  $\mu_1$  (or average reference drug IC50 value for cell lines in quadrant D, "mu1"),  $\mu_2$  (or average candidate drug IC50 value for cell lines in quadrant D, "mu2"), and prop D (proportion of total cell lines that fall within quadrant D, "d").

Tip: Click "CSV" tab to export data table as CSV. This allows user to subject data to additional selection and filters, as in our GDSC example where top hits were selected by requiring DISARM score >2.0 and prop D >0.2 before filtering for  $\mu_1$  in upper 45% for all candidates and  $\mu_2$  in lower 40% for all candidates.

Copy CSV Search:

Manually entering candidate drug of interest (as in obatclax, at right) searches data set.

Disease	DrugName	Score	nSample	p	Bonferroni adjusted p	mu1	mu2	d
SCLC	Obatoclax.Mesyate	4.6501	25	<0.00001	0.00023	1.393	-0.147	0.56

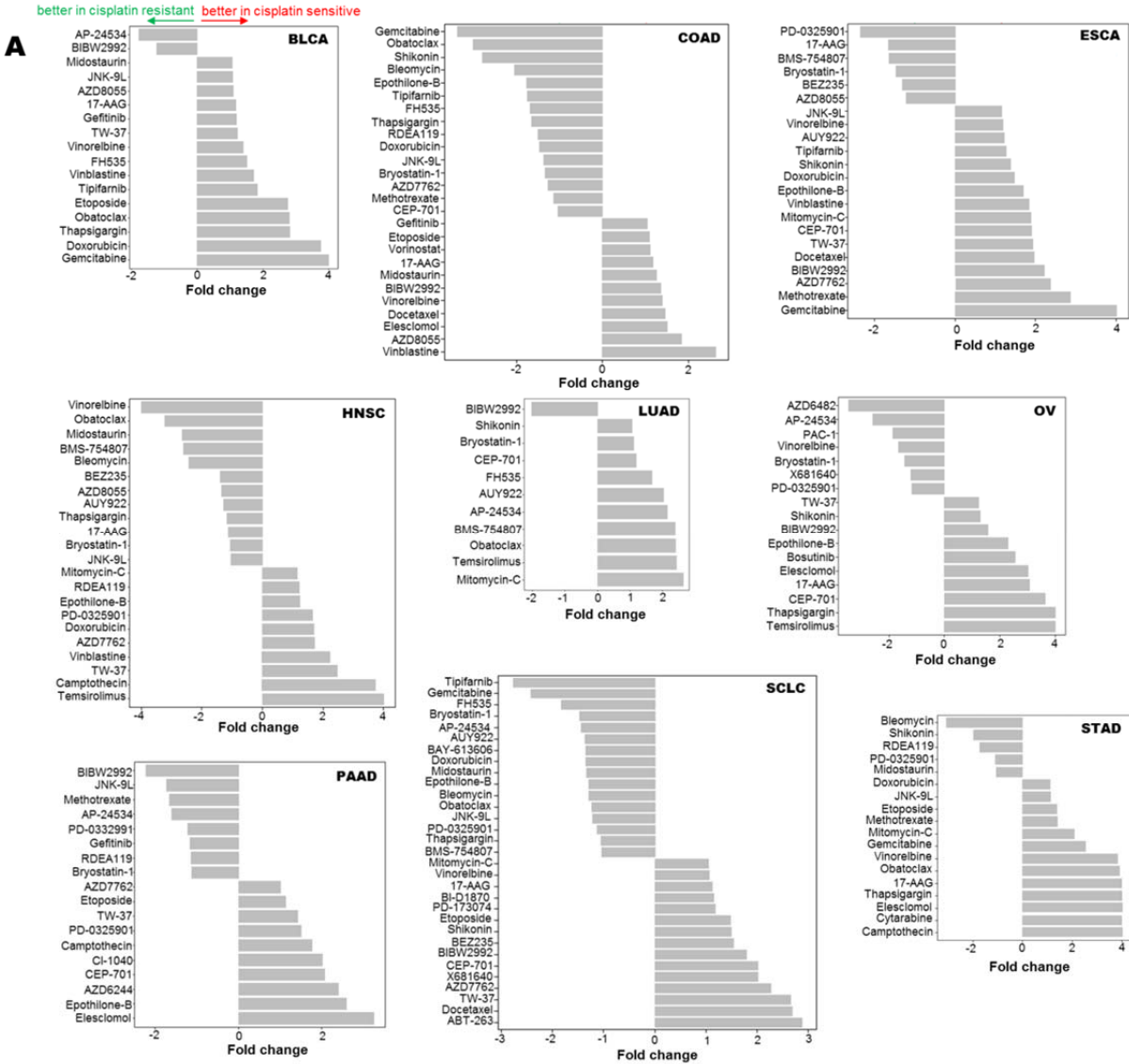
Clicking within row of candidate drug of interest generates DISARM 2x2 cell line plot along with associated score and statistics. User may drag red circle at nexus of dashed lines in plot to adjust sensitivity/resistance cut-offs with auto-updating score and statistics. For example, in plot on right, cut-off for obatoclax was adjusted to  $\log_{10}$  IC50 of 0.0 (1  $\mu$ M). This reduces DISARM score for obatoclax to 1.62 (below 2.0 threshold) and renders p-value insignificant.

Tip: Click "PDF" tab to generate PDF of selected 2x2 DISARM plot or click "Show Cell Line" to automatically add cell line labels to each data point on plot.

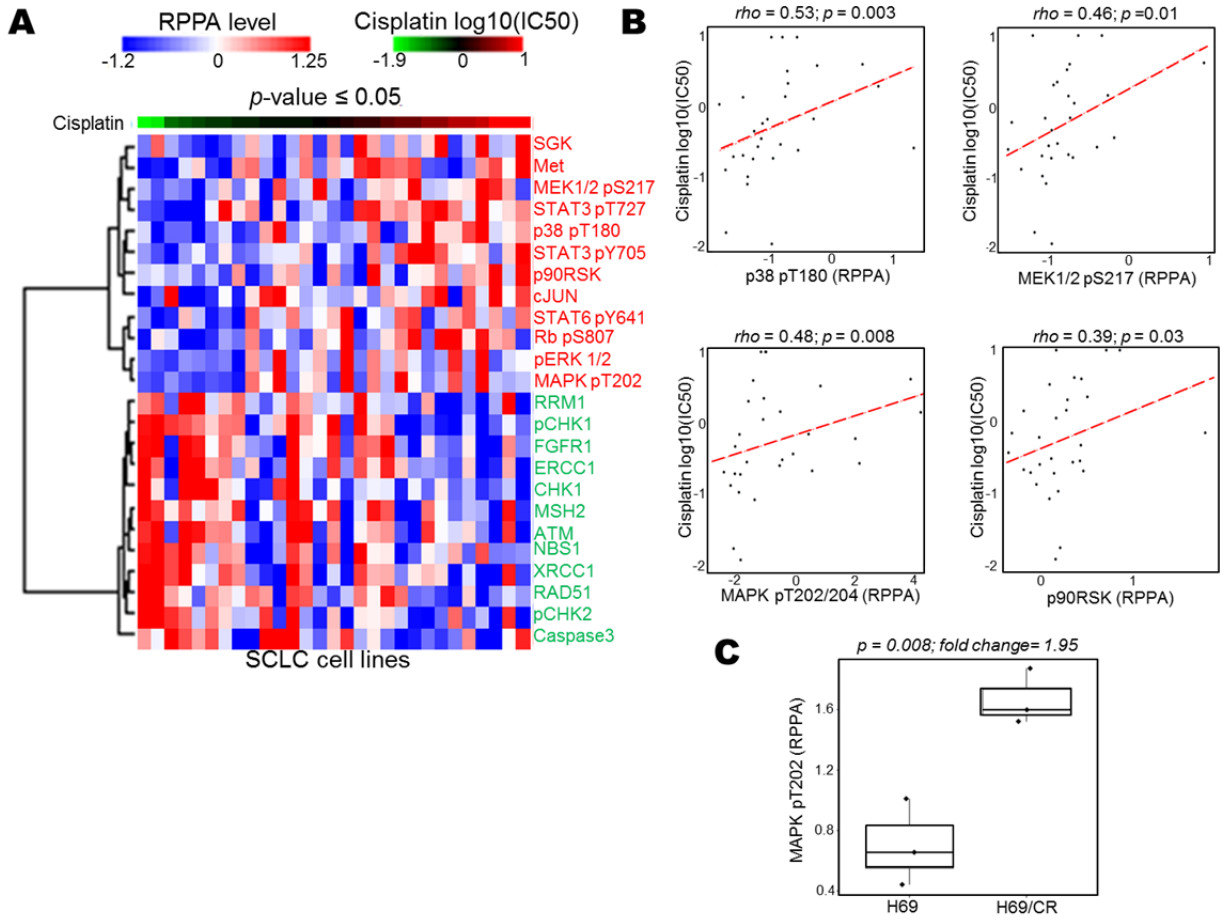
Obatoclax.Mesyate vs Cisplatin  
Score: 4.6501 p: <0.00001 x cutoff: 0.25 y cutoff: 0.75

Obatoclax.Mesyate vs Cisplatin  
Score: 1.6213 p: 0.05248 x cutoff: 0.23 y cutoff: 0.35

**Supplementary Figure S2. Step-by-step user guide for DISARM web application – Part 2.** The above panels highlight features of DISARM application following initial query, including sortable characteristics, searchable candidate drug list, and interactive DISARM 2x2 plots. The application also allows users to export data as comma-separated value (.csv) file in order to perform additional sorting and filtering as described.

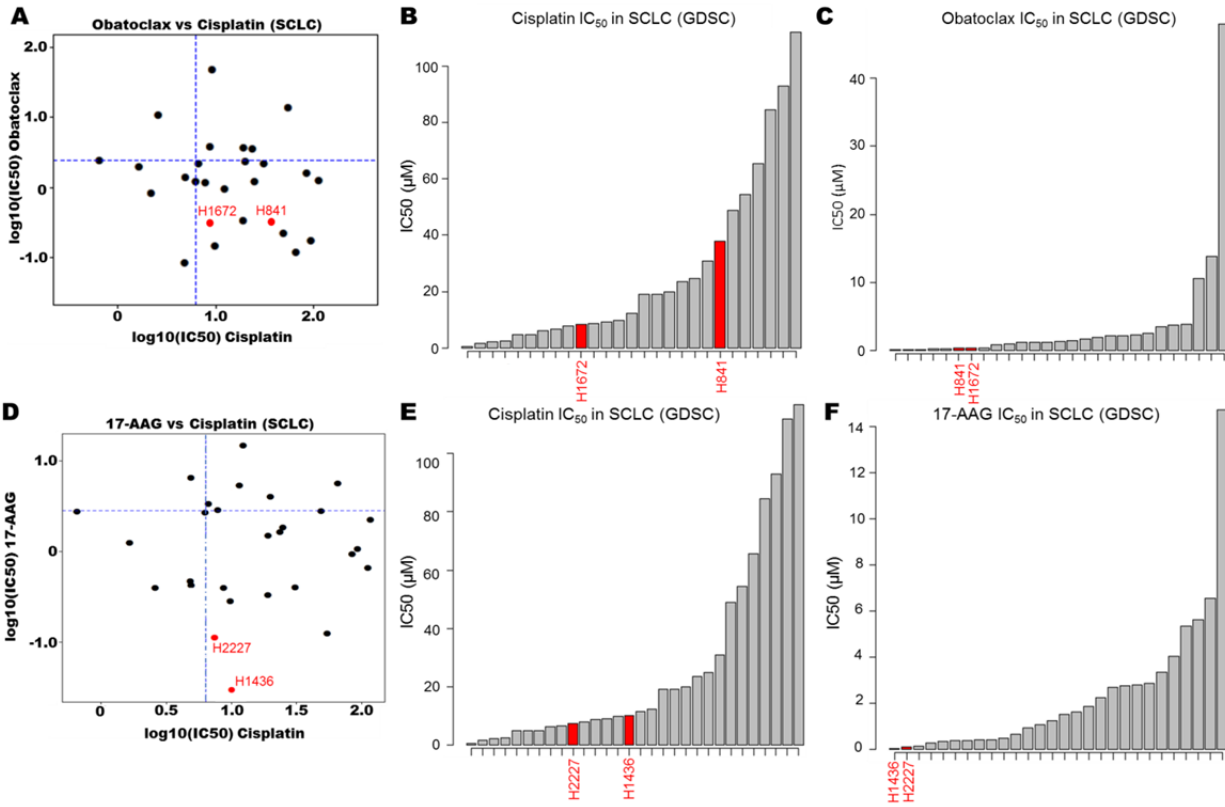


**Supplementary Figure S3. Comparison of DISARM-selected candidates from GDSC in cisplatin-sensitive and -resistant models identifies numerous drugs that are more effective in cisplatin-resistant models (A)** Bar charts illustrating fold change comparing mean  $IC_{50}$  values for specified drugs from GDSC data base in models that are cisplatin-sensitive or cisplatin-resistant on the basis of DISARM categorization. As indicated at top left, those to left of zero trend toward improved  $IC_{50}$  values in cisplatin-resistant models.



**Supplementary Figure S4. Cisplatin-resistance in SCLC, both *de novo* and acquired, is associated with increased expression of RAF-MEK-ERK (MAPK) pathway, a target predicted by DISARM**

(A) Heatmap illustrating proteins whose expression, as quantified by RPPA, is correlated significantly with *de novo* cisplatin response in SCLC cell lines. (B) Correlation plots for selected proteins from (A) highlighting the abundance of components of the MAPK signaling pathway. (C) Box plot showing significant increase in phospho-MAPK expression by RPPA following acquired cisplatin-resistance by prolonged exposure to cisplatin in SCLC cell lines.



**Supplementary Figure S5. Cisplatin-resistant SCLC models not previously analyzed by DISARM are sensitive to DISARM candidates. (A,D)** Updated DISARM 2x2 plots for cisplatin/obatoclox (**A**) and cisplatin/17-AAG (**D**) illustrating placement of experimentally observed SCLC IC<sub>50</sub> values in context of GDSC data. (**B-C, E-F**) Bar graphs highlighting our own experimentally calculated IC<sub>50</sub> values for for cisplatin (**A, D**), obatoclox (**B**), and 17-AAG (**E**) in cell lines not previously included in the respective GDSC analyses. All IC<sub>50</sub> values are expressed as µM