The NCI Transcriptional Pharmacodynamics Workbench (NCI TPW)

User Guide

Updated in November 2018

For NCI TPW questions or assistance, please contact ncitpwsupport@mail.nih.gov at the Biometric Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute.

General description of the NCI TP Workbench

The NCI Transcriptional Pharmacodynamics workbench (NCI TPW) is a powerful webtool that uses advanced computational and visualization tools to empower developmental therapeutics investigators worldwide by providing access to the genome-wide characterization of NCI-60 cell lines and the enormous time-course databases on genome-wide response to treatment with drugs.

For more information about the data and the findings for this project, please refer to the following publication:
Monks, A, et al. "The NCI Transcriptional Pharmacodynamics Workbench: a tool to examine dynamic expression profiling of therapeutic response in the NCI-60 cell line panel." Cancer Research (2018): canres-0989. https://www.ncbi.nlm.nih.gov/pubmed/30355619

Table 1: Dosage used at high and low concentrations for each drug

Drug	High Concentration (nM)	Low Concentration (nM)
azacytidine	5000	1000
bortezomib	100	10
cisplatin	15000	3000
dasatinib	2000	100
doxorubicin	1000	100
erlotinib	10000	1000
geldanamycin	1000	100
gemcitabine	2000	200
lapatinib	10000	1000
paclitaxel	100	10
sirolimus	100	10
sorafenib	10000	5000
sunitinib	2000	200
topotecan	1000	10
vorinostat	5000	1000

Access NCI TP Workbench

The NCI TPW website is available at https://tpwb.nci.nih.gov/
When the URL is entered, the user get access to the main NCI TPW page, which contains multiple tabs with numerous analysis and features. Each of the tab is described in a separate section below.

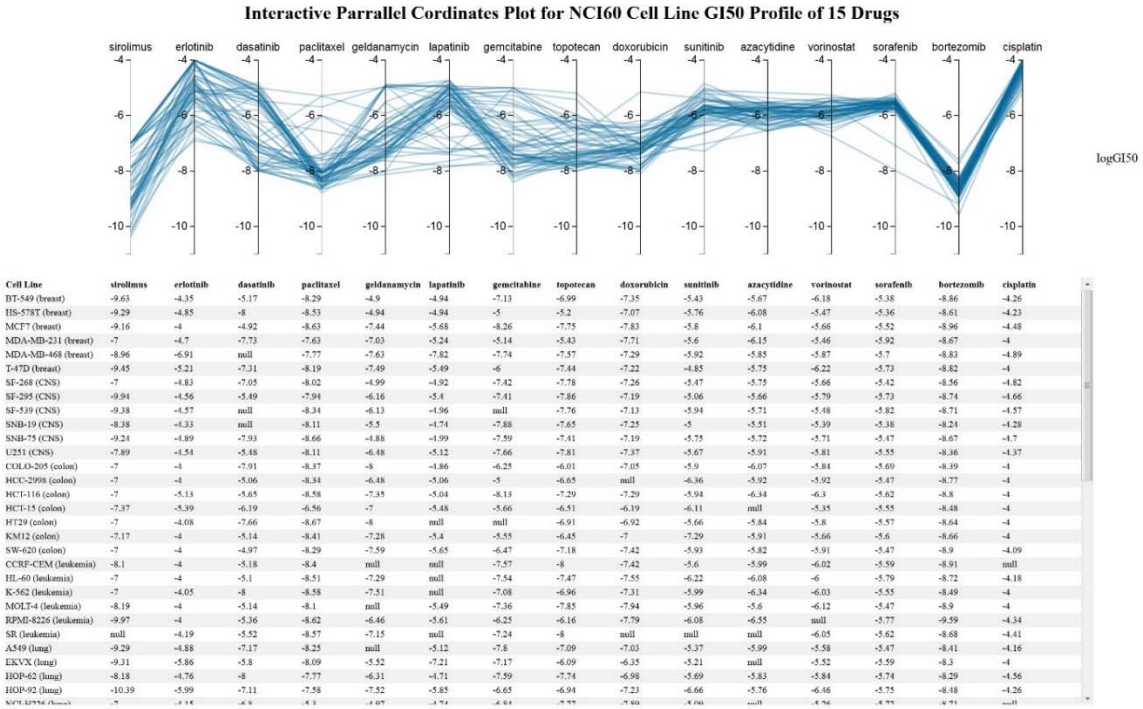
"About" tab

This section collects general information about the data. The table lists the drugs used in the experiments, as well as the number of points available of each data type.

Figure 1: the NCI TPW About tab. General information about the data.

A page containing an interactive plot of the available GI50 measurements can also be accessed through the link in the "About" tab (https://tpwb.nci.nih.gov/GeneExpressionNCI60/GI50.html).

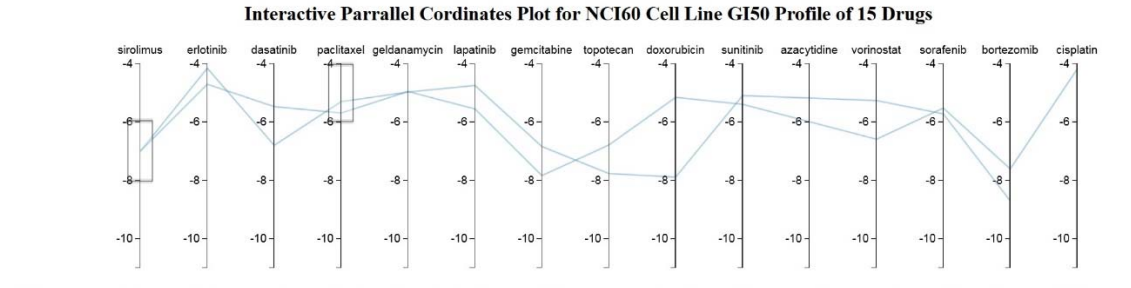
This page contains sensitivity data ($\log_{10}[GI_{50}]$) for each cell line and each drug (Figure 2). Changes in gene expression were measured using Affymetrix GeneChip HT Human Genome U133A microarrays, and drug-induced gene expression was compared to basal expression (measured in untreated control cultures) at the same time points to generate positive and negative log2 fold expression change values for each gene in the context of each cell line, drug, and time point.



Cell Line	sirolimus	erlotinib	dasatinib	paclitaxel	geldanamycin	lapatinib	gemcitabine	topotecan	doxorubicin	sunitinib	azacytidine	vorinostat	sorafenib	bortezomib	cisplatin
BT-549 (breast)	-9.63	-4.35	-5.17	-8.29	-4.9	-4.94	-7.13	-6.99	-7.35	-5.43	-5.67	-6.18	-5.38	-8.86	-4.26
HS-578T (breast)	-9.29	-4.85	-8	-8.53	-4.94	-4.94	-5	-5.2	-7.07	-5.76	-6.08	-5.47	-5.36	-8.61	-4.23
MCF7 (breast)	-9.16	-4	-4.92	-8.63	-7.44	-5.68	-8.26	-7.75	-7.83	-5.8	-6.1	-5.66	-5.52	-8.96	-4.48
MDA-MB-231 (breast)	-7	-4.7	-7.73	-7.63	-7.03	-5.24	-5.14	-5.43	-7.71	-5.6	-6.15	-5.46	-5.92	-8.67	-4
MDA-MB-468 (breast)	-8.96	-6.91	null	-7.77	-7.63	-7.82	-7.74	-7.57	-7.29	-5.92	-5.85	-5.87	-5.7	-8.83	-4.89
T-47D (breast)	-9.45	-5.21	-7.31	-8.19	-7.49	-5.49	-6	-7.44	-7.22	-4.85	-5.75	-6.22	-5.73	-8.82	-4
SF-268 (CNS)	-7	-4.83	-7.05	-8.02	-4.99	-4.92	-7.42	-7.78	-7.26	-5.47	-5.75	-5.66	-5.42	-8.56	-4.82
SF-295 (CNS)	-9.94	-4.56	-5.49	-7.94	-6.16	-5.4	-7.41	-7.86	-7.19	-5.06	-5.66	-5.79	-5.73	-8.74	-4.66
SF-539 (CNS)	-9.38	-4.57	null	-8.34	-6.13	-4.96	null	-7.76	-7.13	-5.94	-5.71	-5.48	-5.82	-8.71	-4.57
SNB-19 (CNS)	-8.38	-4.33	null	-8.11	-5.5	-4.74	-7.88	-7.65	-7.25	-5	-5.51	-5.39	-5.38	-8.24	-4.28
SNB-75 (CNS)	-9.24	-4.89	-7.93	-8.66	-4.88	-4.99	-7.59	-7.41	-7.19	-5.75	-5.72	-5.71	-5.47	-8.67	-4.7
U251 (CNS)	-7.89	-4.54	-5.48	-8.11	-6.48	-5.12	-7.66	-7.81	-7.37	-5.67	-5.91	-5.81	-5.55	-8.36	-4.37
COLO-205 (colon)	-7	-4	-7.91	-8.37	-8	-4.86	-6.25	-6.01	-7.05	-5.9	-6.07	-5.84	-5.69	-8.39	-4
HCC-2998 (colon)	-7	-4	-5.06	-8.34	-6.48	-5.06	-5	-6.65	null	-6.36	-5.92	-5.92	-5.47	-8.77	-4
HCT-116 (colon)	-7	-5.13	-5.65	-8.58	-7.35	-5.04	-8.13	-7.29	-7.29	-5.94	-6.34	-6.3	-5.62	-8.8	-4
HCT-15 (colon)	-7.37	-5.39	-6.19	-6.56	-7	-5.48	-5.66	-6.51	-6.19	-6.11	null	-5.35	-5.55	-8.48	-4
HT29 (colon)	-7	-4.08	-7.66	-8.67	-8	null	null	-6.91	-6.92	-5.66	-5.84	-5.8	-5.57	-8.64	-4
KM12 (colon)	-7.17	-4	-5.14	-8.41	-7.28	-5.4	-5.55	-6.45	-7	-7.29	-5.91	-5.66	-5.6	-8.66	-4
SW-620 (colon)	-7	-4	-4.97	-8.29	-7.59	-5.65	-6.47	-7.18	-7.42	-5.93	-5.82	-5.91	-5.47	-8.9	-4.09
CCRF-CEM (leukemia)	-8.1	-4	-5.18	-8.4	null	null	-7.57	-8	-7.42	-5.6	-5.99	-6.02	-5.59	-8.91	null
HL-60 (leukemia)	-7	-4	-5.1	-8.51	-7.29	null	-7.54	-7.47	-7.55	-6.22	-6.08	-6	-5.79	-8.72	-4.18
K-562 (leukemia)	-7	-4.05	-8	-8.58	-7.51	null	-7.08	-6.96	-7.31	-5.99	-6.34	-6.03	-5.55	-8.49	-4
MOLT-4 (leukemia)	-8.19	-4	-5.14	-8.1	null	-5.49	-7.36	-7.85	-7.94	-5.96	-5.6	-6.12	-5.47	-8.9	-4
RPMI-8226 (leukemia)	-9.97	-4	-5.36	-8.62	-6.46	-5.61	-6.25	-6.16	-7.79	-6.08	-6.55	null	-5.77	-9.59	-4.34
SR (leukemia)	null	-4.19	-5.52	-8.57	-7.15	null	-7.24	-8	null	null	null	-6.05	-5.62	-8.68	-4.41
A549 (lung)	-9.29	-4.88	-7.17	-8.25	null	-5.12	-7.8	-7.09	-7.03	-5.37	-5.99	-5.58	-5.47	-8.41	-4.16
EKVX (lung)	-9.31	-5.86	-5.8	-8.09	-5.52	-7.21	-7.17	-6.09	-6.35	-5.21	null	-5.52	-5.59	-8.3	-4
HOP-62 (lung)	-8.18	-4.76	-8	-7.77	-6.31	-4.71	-7.59	-7.74	-6.98	-5.69	-5.83	-5.84	-5.74	-8.29	-4.56
HOP-92 (lung)	-10.39	-5.99	-7.11	-7.58	-7.52	-5.85	-6.65	-6.94	-7.23	-6.66	-5.76	-6.46	-5.75	-8.48	-4.26

Figure 2: the NCI TPW GI50 measurements. Please refer to the text for the interactive capabilities of this page.

- In the upper section, 15 columns represent the drugs used in the project.
- Columns can be rearranged by dragging left/right the name of the drug at the top of a column;
- Positioning the mouse on one of the $\log_{10}$GI50 bars, the cursor will change to a plus (+), allowing the user to select a subset of values for display. For example, by selecting the range of values between -6 and -4 for sirolimus and the range of values between -4 and -6 for paclitaxel, we can visualize only the cell lines that meet those criteria. The table below is updated according to the selection of the upper graph.



Cell Line	sirolimus	erlotinib	dasatinib	paclitaxel	geldanamycin	lapatinib	gemcitabine	topotecan	doxorubicin	sunitinib	azacytidine	vorinostat	sorafenib	bortezomib	cisplatin
NCI-H226 (lung)	-7	-4.15	-6.8	-5.3	-4.97	-4.74	-6.84	-7.77	-7.89	-5.09	null	-5.26	-5.72	-8.71	null
NCI-ADR-RES (ovarian)	-7	-4.7	-5.47	-5.69	-4.95	-5.55	-7.84	-6.79	-5.15	-5.39	null	-6.59	-5.52	-7.61	-4.18

- Hovering the mouse on one of the cell line rows in the table below will highlight the corresponding line in the upper graph, allowing users to see trends across the 15 drugs.

“Query for a Single Gene” tab

The first thing a user may want to know is a general picture of how the expressions of a specific gene of interest change when treated by a specific drug. To access this information, the user can explore the options in the “Query for a Single Gene” tab (Figure 3).

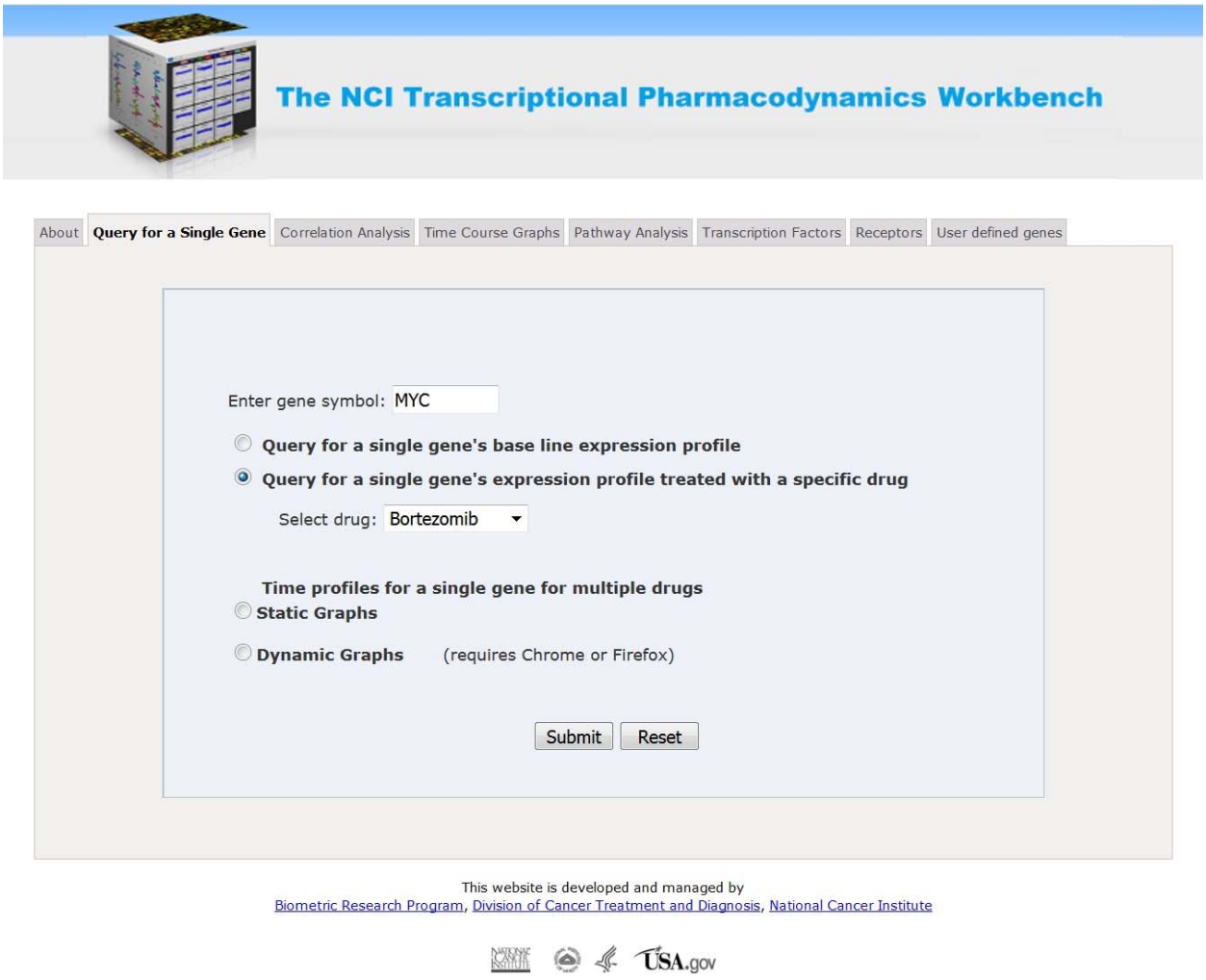


Figure 3: the NCI TPW “Query for a Single Gene” tab. The gene of interest (MYC) and one of the treatment drugs (bortezomib) have been selected in the interface.

By entering a gene symbol, (e.g., MYC), and selecting a drug from the drop-down menu (e.g., bortezomib), the query function will return a series of graphs that show the expression of gene MYC in cell lines treated (Figure 3).

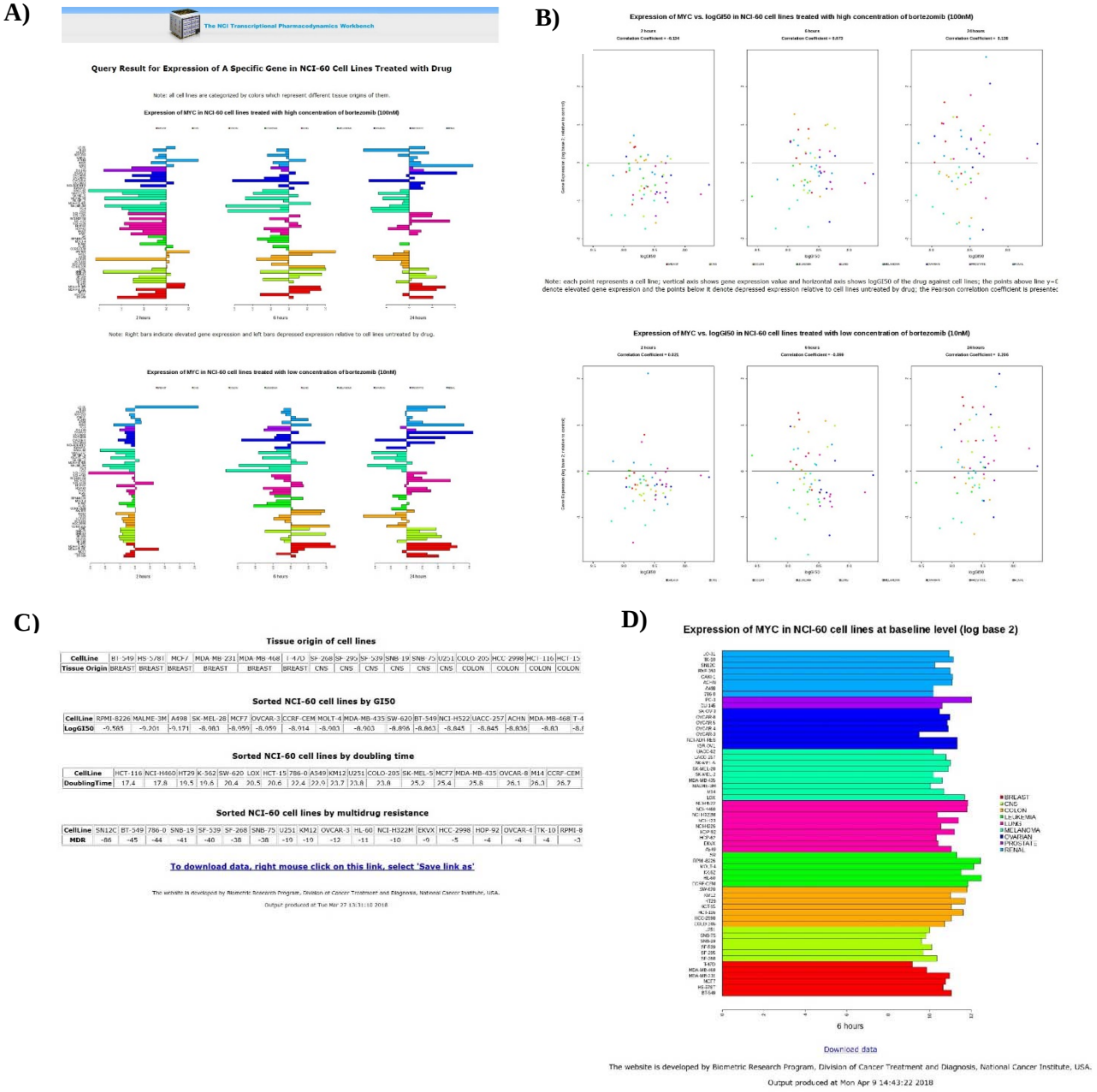


Figure 4: the NCI TPW results of query gene MYC and treatment drug Bortezomib (panels A, B and C). Panel D shows the baseline MYC gene expression at 6 hours.
Refer to the text for details on the different plots.

The graphs displayed as a result of the single gene query include:

- two groups of bar graphs that show the relative expression of the gene in cell lines treated by high and low concentrations of drug, respectively (Figure 4A). Each group contains graphs of different time points (2 hours, 6 hours and 24 hours). In the bar plots, bars

extending to the right indicate elevated gene expression, and bars extending to the left depressed expression relative to cell lines untreated by drug. Each bar represents a cell line, and cell lines are grouped and color coded by tissue type (Refer to Table 2 for details on the cell lines).

- two groups of scatter plots that show the relative expression of the gene vs. $\log_{10}$GI50 in cell lines treated by high and low concentrations of drug, respectively (Figure 4B). Each group contains plots of different time points (2 hours, 6 hours and 24 hours). In the scatter plots, each point represents a cell line; vertical axis shows the gene expression value and horizontal axis shows $\log_{10}$GI50 of the drug against cell lines; the points above line y=0 denote elevated gene expression and the points below the zero line denote depressed expression relative to cell lines untreated by drug. Pearson correlation coefficients are calculated and shown above each scatter plot.
- two groups of scatter plots that show the relative expression of the gene vs. doubling time or multidrug resistance in cell lines treated by high and low dose of drug, respectively. Each group contains plots of different time points (2 hours, 6 hours and 24 hours).
- at the bottom of the page, the raw data used to create these plots is displayed. A link is provided so that users can save the data into a CSV format file, that can be opened in any spreadsheet software (e.g., MS Excel).

Table 2: NCI 60 cell lines stratified in nine tissue types

Tissue Type	Cell line
Breast	BT-549, HS-578T, MCF7, MDA-MB-231, MDA-MB-468, T-47D
CNS	SF-268, SF-295, SF-539, SNB-19, SNB-75, U251
Colon	COLO-205, HCC-2998, HCT-116, HCT-15, HT29, KM12, SW-620
Leukemia	CCRF-CEM, HL-60, K-562, MOLT-4, RPMI-8226, SR
Lung	A549, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, NCI-H460, NCI-H522
Melanoma	LOX, M14, MALME-3M, MDA-MB-435, SK-MEL-2, SK-MEL-28, SK-MEL-5, UACC-257, UACC-62
Ovarian	IGR-OV1, NCI-ADR-RES, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, SK-OV-3
Prostate	DU-145, PC-3
Renal	786-0, A498, ACHN, CAKI-1, RXF-393, SN12C, TK-10, UO-31

Another way to get a whole picture of gene expression changes is to query the time course line plots for a gene of interest. The user can get up to 60 line plots for each of the 15 drugs at once, so that differences of gene expression patterns can be visually examined across all 15 drugs. The NCI TPW offers both static and dynamic types of graphs.

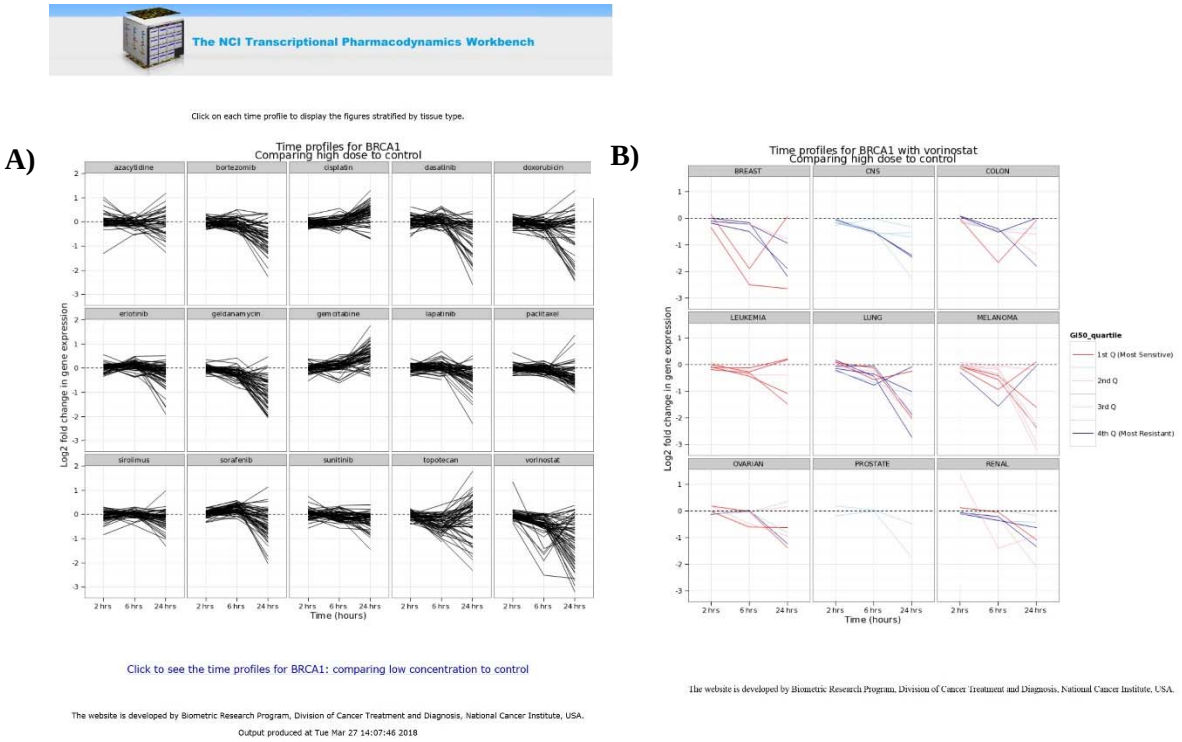


Figure 5: the NCI TPW results of query gene BRCA1 time courses.
Refer to the text for details on the different plots.

Figure 5A shows a static output of 15 time course line plots for BRCA1 when treated by each of the 15 drugs at high concentration. In each line plot, each line stands for the log2 fold change in gene expression for a specific cell line across three time points (i.e., 2hr, 6hr, and 24 hr). Time profiles under high concentration are shown by default. The user can also click the link at the bottom on the page to see the time profiles under low concentration.

The user can click on each graph in the output page to get the time profiles grouped by tissue type. Figure 5B shows the 9 plots stratified by tissue for the vorinostat drug. The lines are colored according to their drug sensitivity measured by GI50. The dark red lines indicate the most sensitive cell lines whose growth inhibition for this drug is in the top 25 percentile of NCI-60 cell lines when ordered by $\log_{10}$GI50, while the dark blue lines indicate the most resistant cell lines whose growth inhibition for this drug is in the bottom 25 percentile of NCI-60 cell lines when ordered by $\log_{10}$GI50.

In addition to static plots, the NCI TPW provides a dynamic way to generate time course line plots. After the user enters the gene name of interest in the "Query for a Single Gene" tab, the system uses the powerful Javascript library D3 (https://d3js.org/) to load the data in the browser on the client side: this allows the creation of dynamic and interactive line plots (Figure 6). The D3 library works in modern browsers like Google Chrome or Firefox.

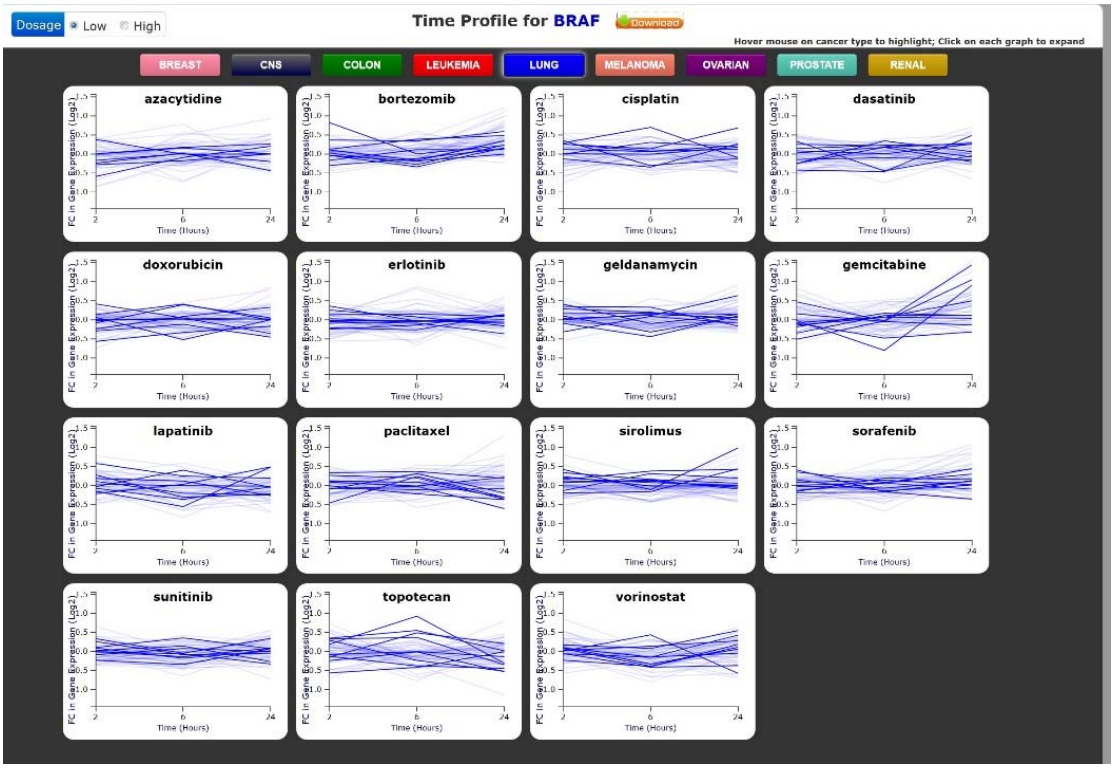


Figure 6: the NCI TPW results of query gene BRAF time courses using dynamic plots. By hovering the mouse over the "Lung" button at the top, the lines related to this tissue type are highlighted in each plot, leaving the other lines of a light blue. A list of the cell lines grouped under each tissue type can be found in Table 2.
Refer to the text for additional details.

Figure 6 displays 15 time course line plots for BRAF, each line corresponds to cell lines treated by one of the 15 drugs. When moving the mouse cursor on each of the 9 tissue types colored buttons at the top of the page, the cell lines for that specified tissue type are highlighted. The highlighted lines can be fixed by clicking the tissue type button. On the top left of the display, the dosage level is set at low concentration by default. The user can switch between high and low concentration plots by clicking the desired concentration level radio button. The user can also click on any of the 15 drug time course line plots: this will open a pop-up window which shows an enlarged version of the selected plot. Figure 7 shows an example of time course line plots for cisplatin on high concentration.

A) B)

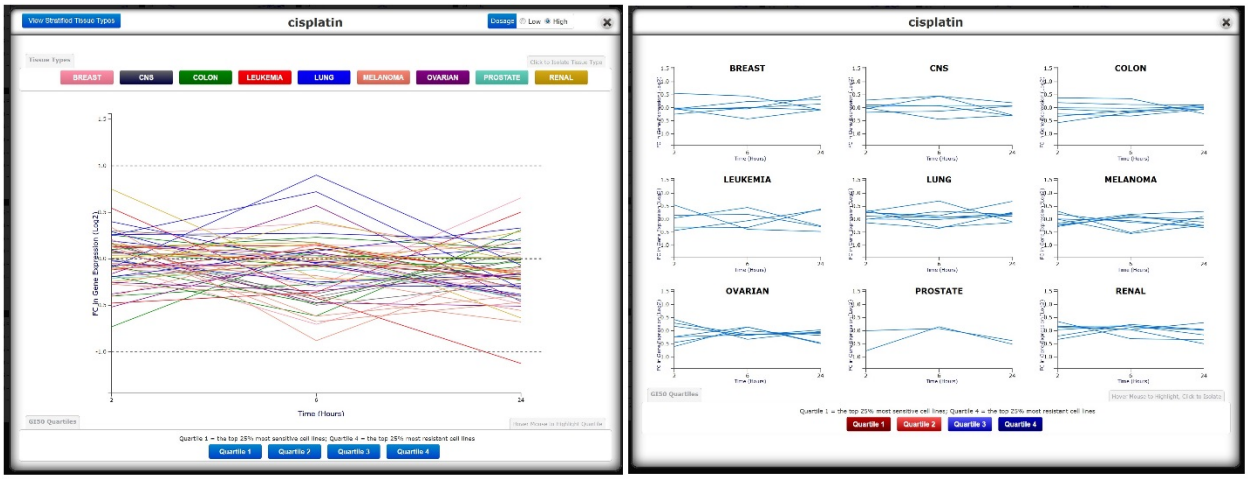


Figure 7: the NCI TPW results of query gene BRAF time courses related to cisplatin using dynamic plots. Refer to the text for more details.

In Figure 7A, each line in the plot represents a cell line, color coded according to 9 different tissue types. When moving the mouse cursor on any of the lines, the cell line name, tissue type, $\log_{10}$(GI50) and its quartile are shown on top of the page. When clicking on "Melanoma" (one of the colored buttons at the top), only melanoma cell lines in orange are highlighted as shown. There are four drug sensitivity buttons in the bottom panel of the pop up window (Figure 7A). NCI-60 cell lines are sorted into quartiles by their drug sensitivity (i.e., $\log_{10}$GI50 value) from the most sensitive (1st quartile) to the most resistant (4th quartile). Hovering the mouse over the GI50 Quartile buttons highlights only cell lines with drug sensitivity in the selected quartile.

Clicking on the button "View Stratified Tissue Types" at the top left corner of the window, a second pop-up window shows nine time course plots for the current drug, each plot displays the cell lines in one of the nine tumor tissue types (Figure 7B). Again, hovering on each line shows the cell line name, tissue type, and $\log_{10}$(GI50) value for the highlighted cell lines. The GI50 Quartile buttons are located at the bottom panel of the window, allowing the user to use the mouse to highlight quartiles of interest and isolate the cell lines by drug sensitivity.

“Correlation analysis” tab

Under this functional module, the NCI TPW provides a heatmap for a group of genes whose gene expression shows the highest correlation with one of several phenotypes: $\log_{10}$GI50, doubling time, multidrug resistance, gene mutation data, and protein expression data (Figure 8).

Baseline gene expression data is also an available choice in the first drop-down menu. If the user selects the “*baseline gene expression” option, an additional field will be displayed, and the user will be asked to type the gene name for which the baseline data is queried. Since the query is a “correlation analysis”, the user will have to select additional information about the drug to use for the correlation analysis. If the user selects the “baseline, no drug” in the second dropdown, an error message will be displayed and no plot will be generated.

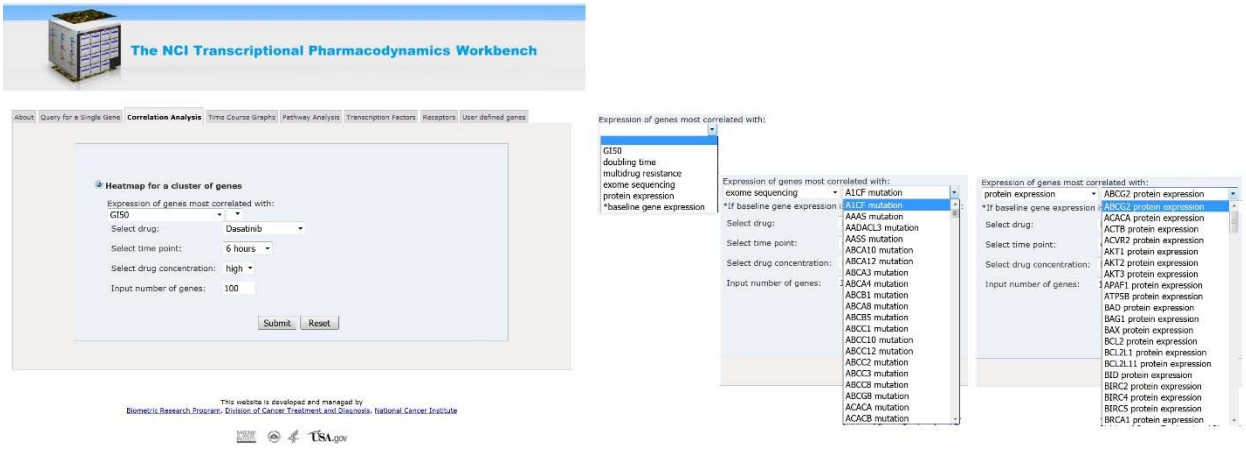


Figure 8: the NCI TPW Correlation Analysis. Refer to the text for more details.

Doubling time information of NCI-60 cell lines can be found at https://dtp.cancer.gov/discovery_development/nci-60/cell_list.htm

Multi-drug resistance (MDR) functional assay results of NCI-60 cell lines can be found in the following publication (Lee, et al., Mol Pharmacol. 1994 Oct;46(4):627-38).

The user can select to query drug, concentration level, time point, and the number of most significant genes (maximum 100 genes). The result of the query of the 100 genes with the largest absolute correlation of gene expression with the GI50 phenotype in cell lines treated with high dose of dasatinib at 6 hours is shown in Figure 9.

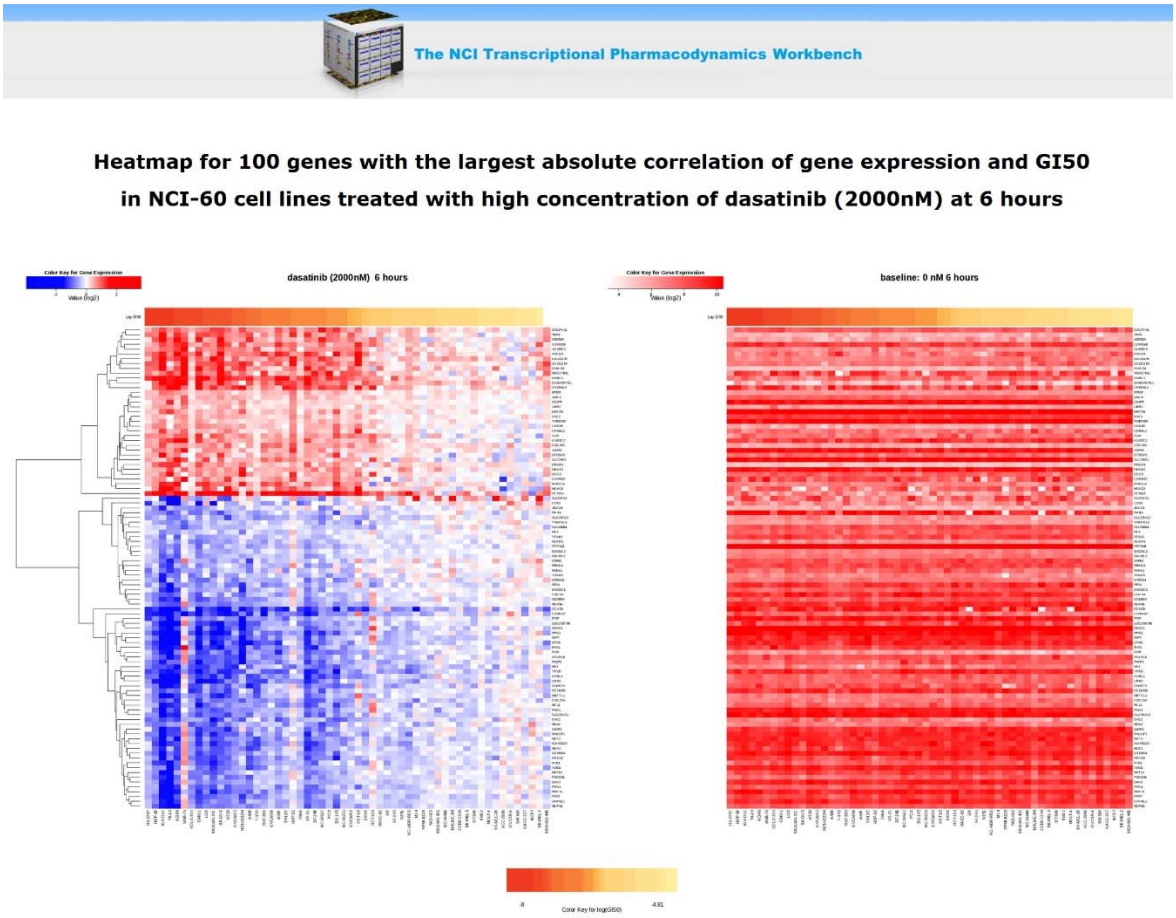


Figure 9: the NCI TPW results of a correlation analysis. Refer to the text for more details.

For the gene mutation phenotype (exome sequencing option in the drop-down menu), the n genes with the largest absolute t-statistics of gene expression in gene-mutant versus wild-type cell lines are selected. The t-statistics are calculated based on Welch two sample t-test. For the other phenotypes, the n genes with the largest absolute correlation of gene expression and phenotype in cell lines are selected. The correlation is calculated based on Pearson method. In the output page as shown in Figure 9, a heatmap is displayed with cell lines in y axis and genes in x axis. The top color legend indicates the ranges for log ratio data, when compared to the base line data. The genes are clustered using the hierarchical clustering method implemented in the R function "heatmap", while the cell lines are ordered by $\log_{10}$GI50 from the most sensitive to the most resistant (from left to right). The color legend for $\log_{10}$GI50 is located at the bottom panel of the heatmap. A JavaScript magnifier is provided to zoom in when moving the mouse cursor on the heatmap, making it easy for user to see details like gene names. There are two data tables listed below the heatmap. The top table lists genes that are positively correlated with GI50. Those

genes are sorted by the mean log fold changes in resistant cell lines, with gene names linked to the corresponding GeneCards® website (http://www.genecards.org). In this table, additional information is included, like the Pearson correlation coefficients, mean log fold changes in sensitive cell lines, mean log fold changes in resistant cell lines, and the differences of the two mentioned fold changes between sensitive and resistant cell lines. The bottom table lists genes that are negatively correlated with drug sensitivity using the same indexes as in the first table. Resistant cell lines are defined as cell lines whose growth inhibition for this drug are in the top 25 percentile of NCI-60 cell lines when ordered by $\log_{10}$GI50. Sensitive cell lines are defined as cell lines whose growth inhibition for this drug are in the bottom 25 percentile of NCI-60 cell lines when ordered by $\log_{10}$GI50. By analyzing the two data tables, the user can easily identify genes that are over or under expressed in resistant cell lines. At the bottom of the page, a link is provided for users to download the raw data used to generate the heatmap and the tables.

"Time Course Graphs" tab

Using this tab, given a specific drug and concentration level, the user can generate a series of time profiles for the top 50 genes and two different measures:

- the top 50 genes with the largest average fold changes across cell lines, (Figure 10)
- the top 50 genes whose gene expression are most correlated with drug sensitivity, i.e., GI50 (Figure 11). For each gene, correlation coefficients between gene expression and GI50 for three time points are calculated. The genes are sorted by the maximum absolute value of the correlation coefficients among the three time points.

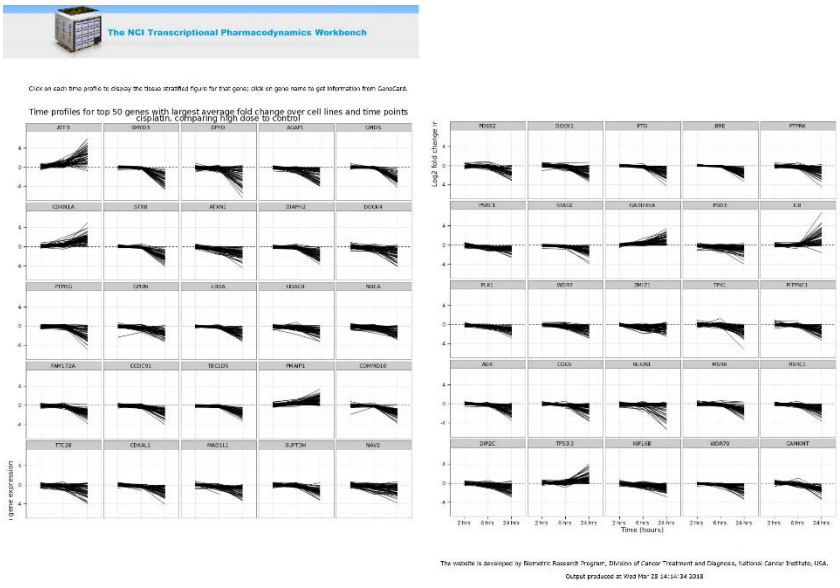


Figure 10: the NCI TPW results of a time course analysis. Refer to the text for more details.

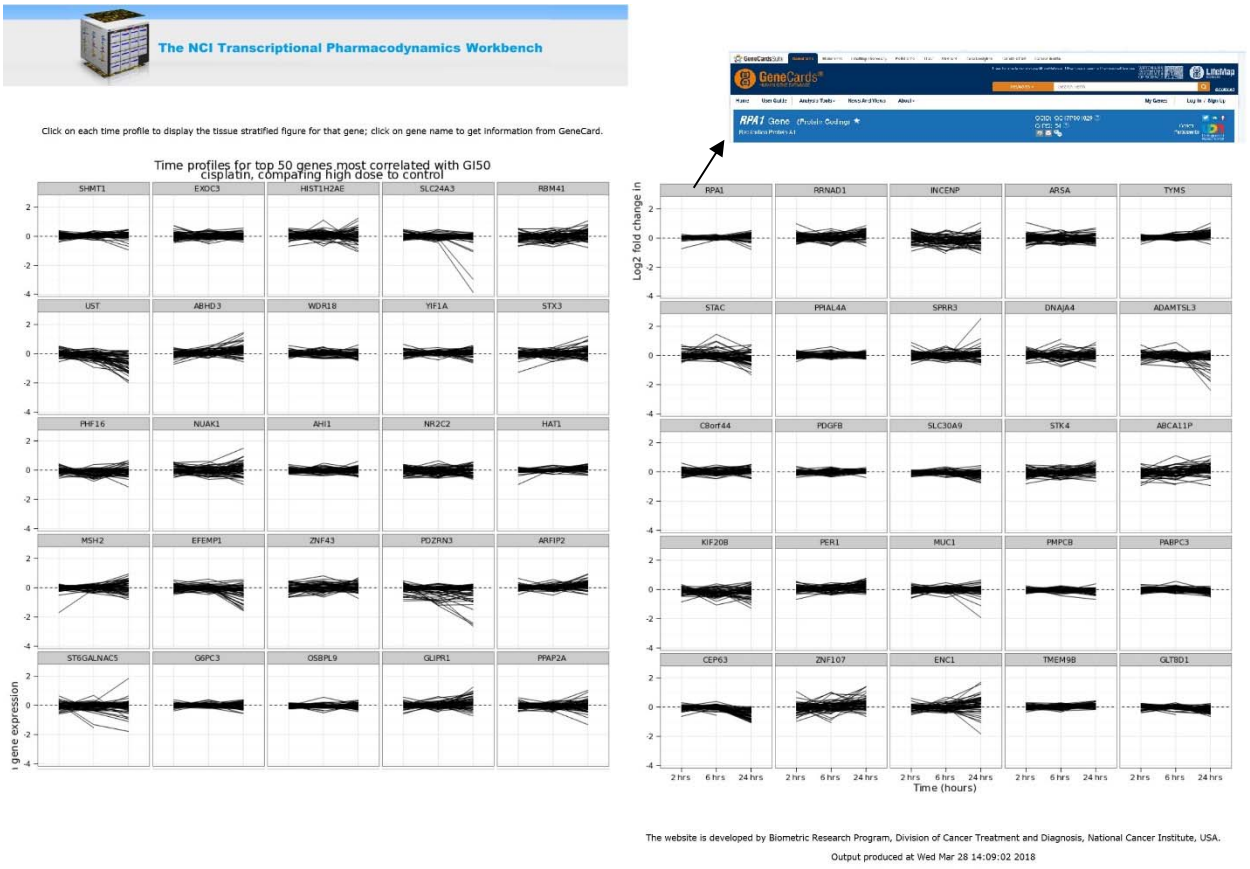


Figure 11: the NCI TPW results of a time course analysis. Refer to the text for more details.

The NCI TPW outputs the top 50 gene list and generates the time profile plots for these 50 genes. For each of the 50 time profile plots in the output page, the y-axis indicates the $\log_2$ fold change in gene expression and the x-axis is composed of the three time points for 2hr, 6 hr, and 24 hrs. Clicking on each individual time profile will display the tissue stratified figure for that gene, while clicking on gene name will redirect the user to the corresponding gene annotation page on GeneCards® website (http://www.genecards.org). In order to increase the processing speed to display this data, all gene lists and graphs are pre-generated and stored on the server.

"Pathway Analysis" tab

The analysis available under this tab allows the user to study how biological relevant patterns are affected by the 15 treatment drugs.

The gene lists for 65 BioCarta pathways were obtained from the Cancer Genome Anatomy Project (CGAP) website. Six heatmaps are displayed in the output html page, to account for the

three time points and two concentrations available. The genes (rows) and the cell lines (columns) are both clustered by default (Figure 12). The user can click on "View larger image" to get an enlarged heatmap and improve readability. Additionally, by clicking "Download data" the user can save the data used to generate the heatmap into a CSV format file, that can be opened in any spreadsheet software (e.g., MS Excel) and used for local analysis.

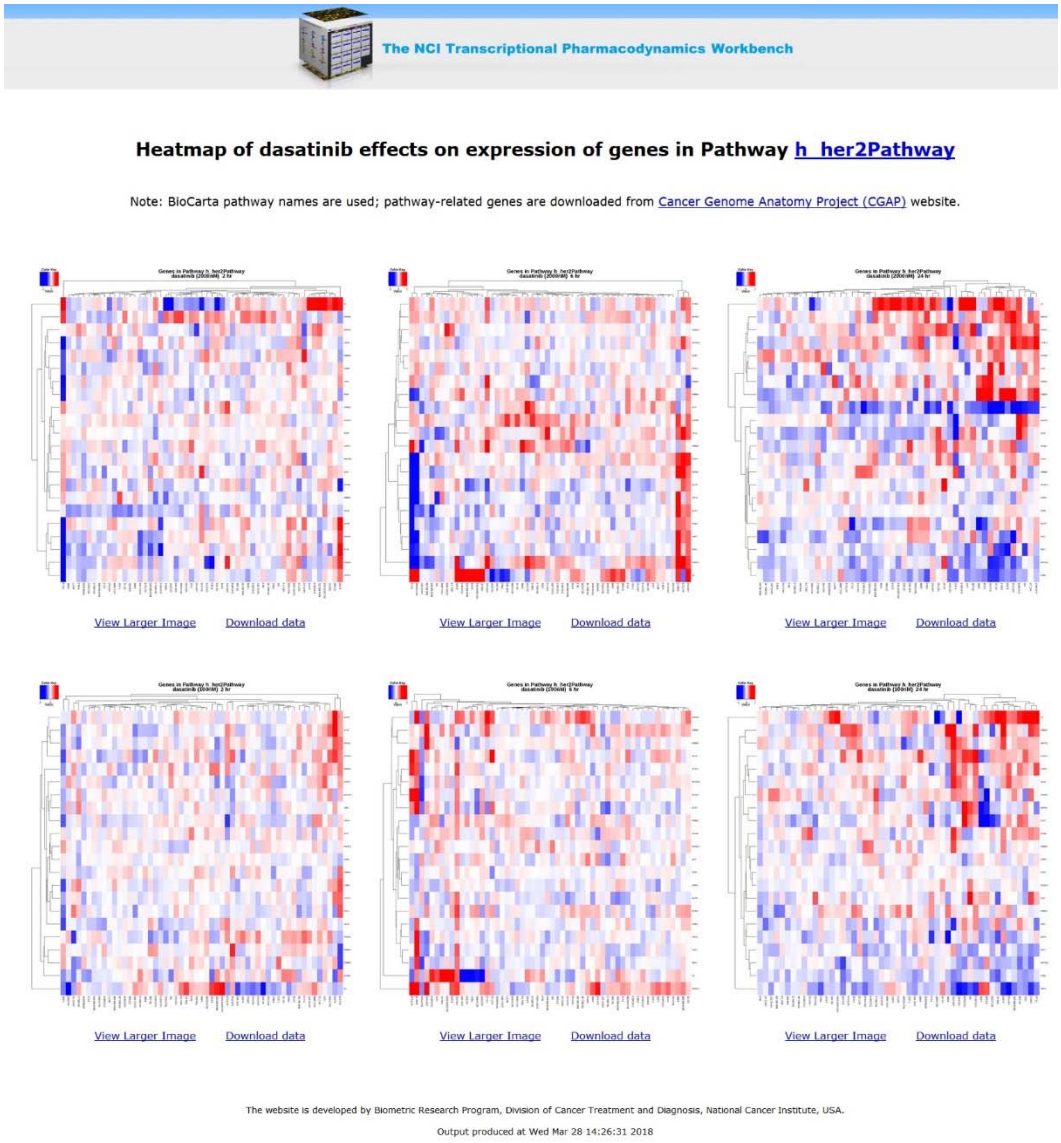


Figure 12: the NCI TPW results of a pathway analysis. Refer to the text for more details.

From the main "Pathway Analysis" tab, users can also choose to sort the cell lines by drug sensitivity ($\log_{10}$GI50) so that the orders of cell lines across all six heatmaps is kept consistent, making it easy to compare the difference among different concentrations and time points (Figure 13).

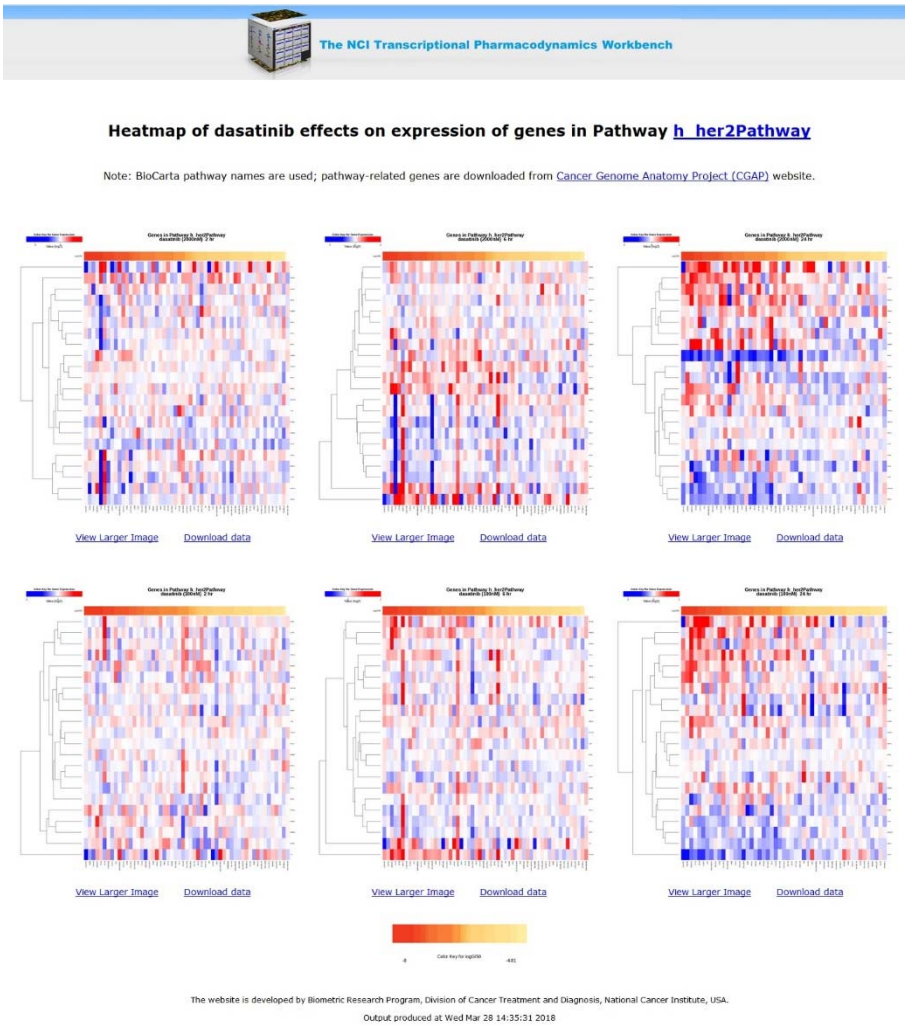


Figure 13: the NCI TPW results of a pathway analysis. Refer to the text for more details.

"Transcription Factors" tab

The 256 transcription factors and their targeted genes are experimentally verified and downloaded from the website developed and managed by Dr. Michael Zhang's lab (Jiang, C., et al. "TRED: a transcriptional regulatory element database, new entries and other development." Nucleic acids research 35.suppl_1 (2007): D137-D140).

There are three options to generate the heatmaps:

- the heatmap with target genes of a specific transcription factor (Figure 14). By selecting the transcription factor and drug of interest, the NCI TPW will generate six heatmaps of drug effects on expression of target genes of the specified transcription factor at three time points and two concentrations. The cell lines (x-axis) and the target genes (y-axis) are both clustered by default.

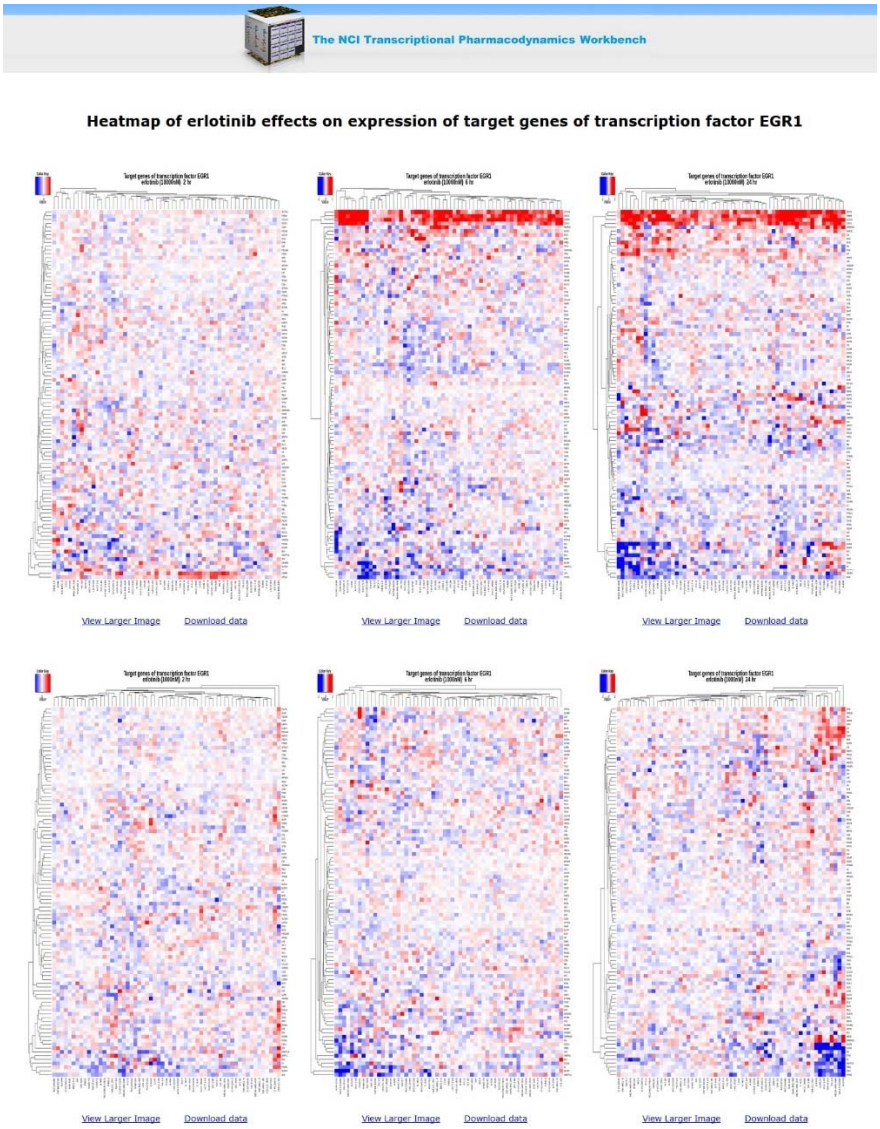


Figure 14: the NCI TPW results of a transcription factors analysis. Refer to the text for more details.

- The heatmap of drug effects on expression of all transcription factors (Figure 15). By selecting a drug name, the NCI TPW will generate six heatmaps for all 256 transcription factors in three time points and two concentrations. The cell lines (x-axis) and the transcription factor genes (y-axis) are both clustered by default.

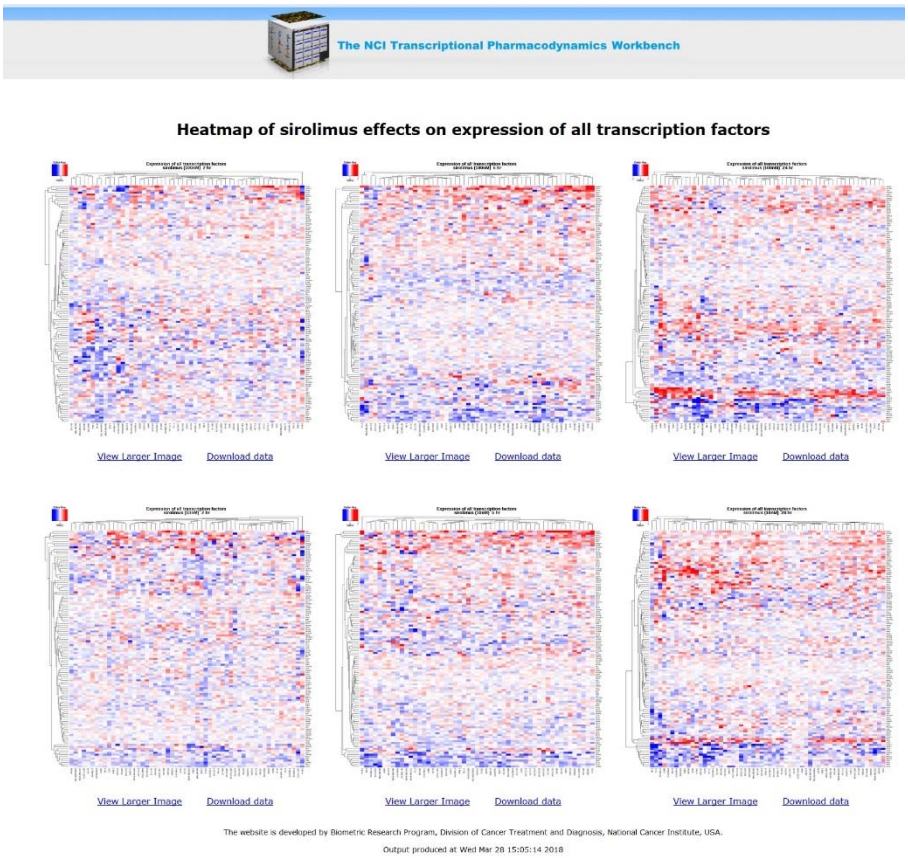


Figure 15: the NCI TPW results of a transcription factors analysis. Refer to the text for more details.

- heatmap of drug effects on gene expression of a specific transcription factor (Figure 16). By selecting one of the 256 transcription factors in the drop-down menu, the NCI TPW will generate a heatmap with all the cell lines at the three time points and two concentrations. The cell lines (y-axis) and the drugs (x-axis) are both clustered by default.

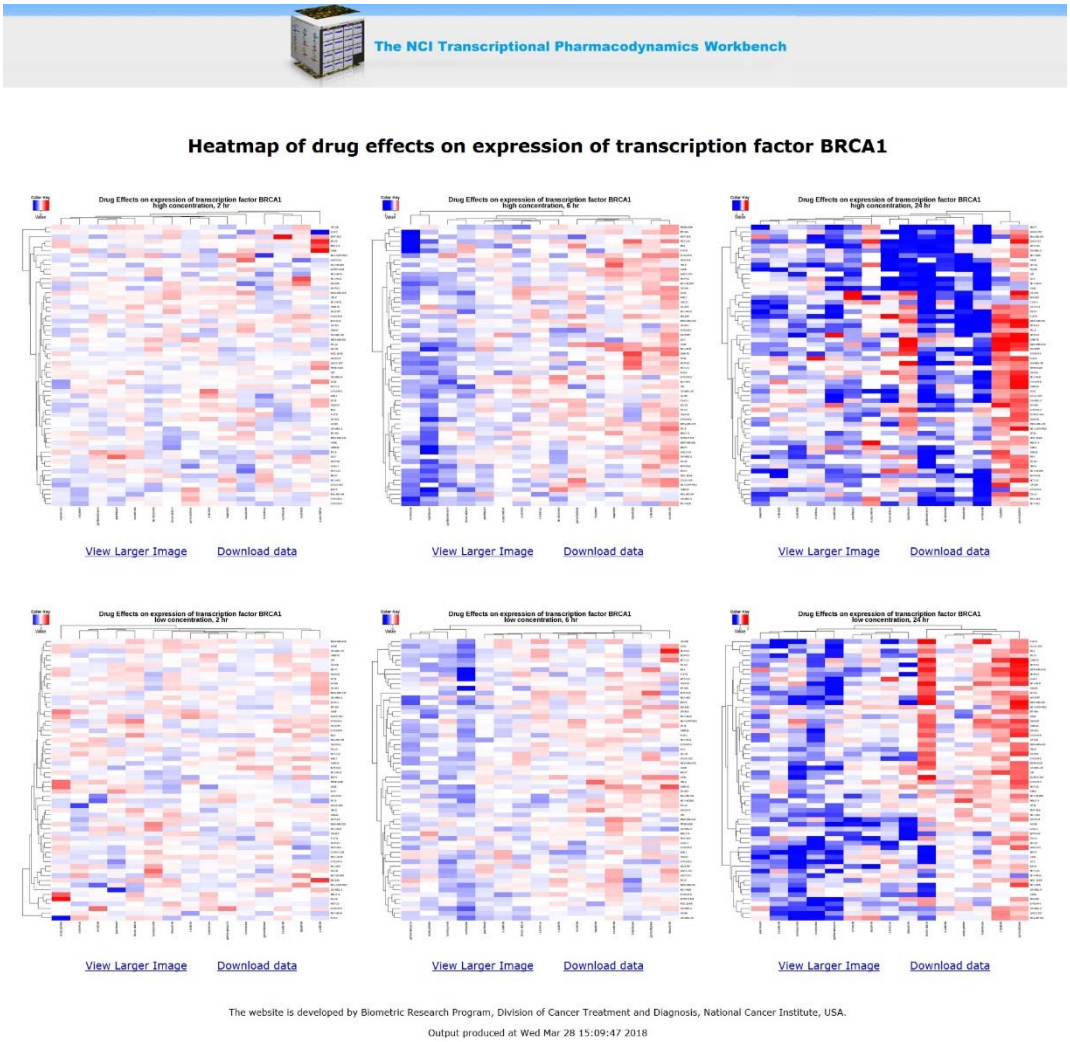


Figure 16: the NCI TPW results of a transcription factors analysis. Refer to the text for more details.

In all the pages displaying heatmaps, the user can click on “View larger image” to get an enlarged heatmap and improve readability. Additionally, by clicking “Download data” the user can save the data used to generate the heatmap into a CSV format file, that can be opened in any spreadsheet software (e.g., MS Excel) and used for local analysis.

“Receptors” tab

Examining the expression pattern of genes in certain receptor group treated with anti-cancer agents can help us understand mechanisms of action and resistance to these drugs. Abnormal expression of receptors and their ligands lead to tumorgenesis by disruption of cell cycle, apoptosis and DNA repair. Discovery and development of mechanism-based therapies targeting cancer related receptors have improved outcome for many cancer patients. For this reason, the NCI TPW provides the option to explore 55 receptor groups from the IUPHAR Targets database (http://www.guidetopharmacology.org/).

In the NCI TPW, the user can select a receptor group and a drug name and click “Submit” (Figure 17). The result of the query is shown in Figure 18: heatmaps for all the genes in the chosen receptor group in three time points and two concentrations are shown.

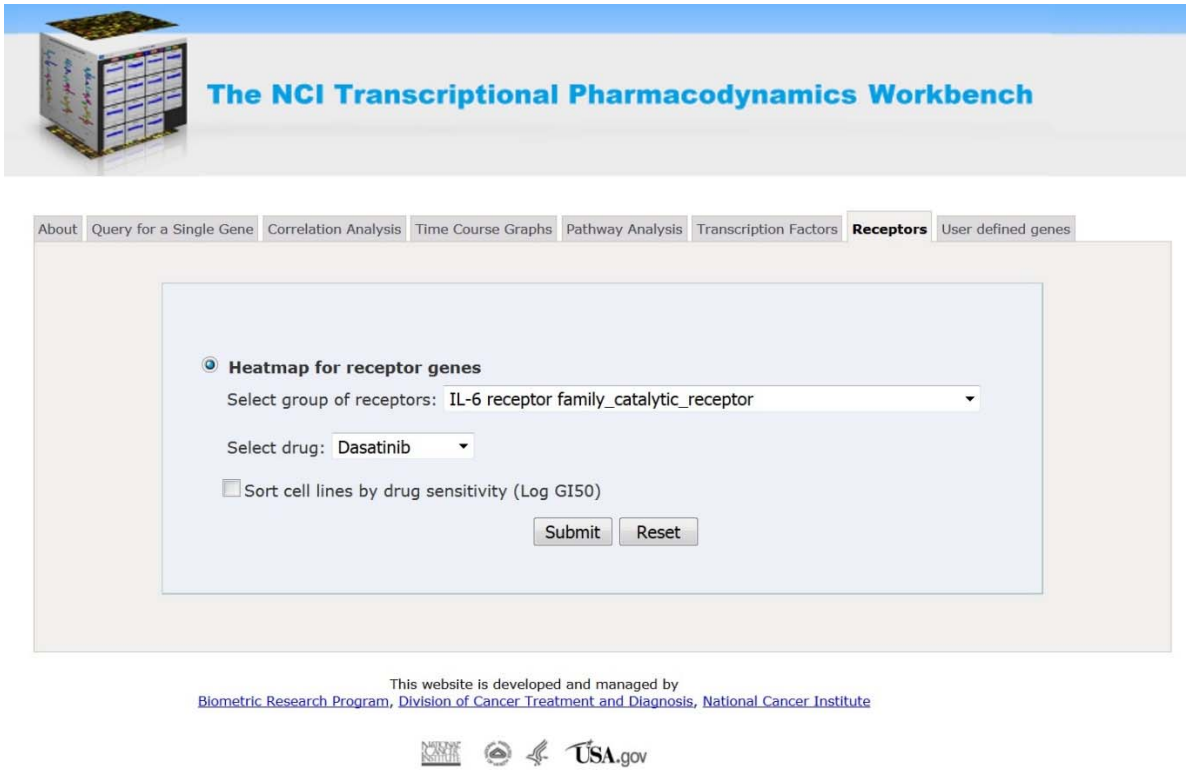


Figure 17: the NCI TPW tab used to query the “Receptors” data.
Refer to the text for more details.

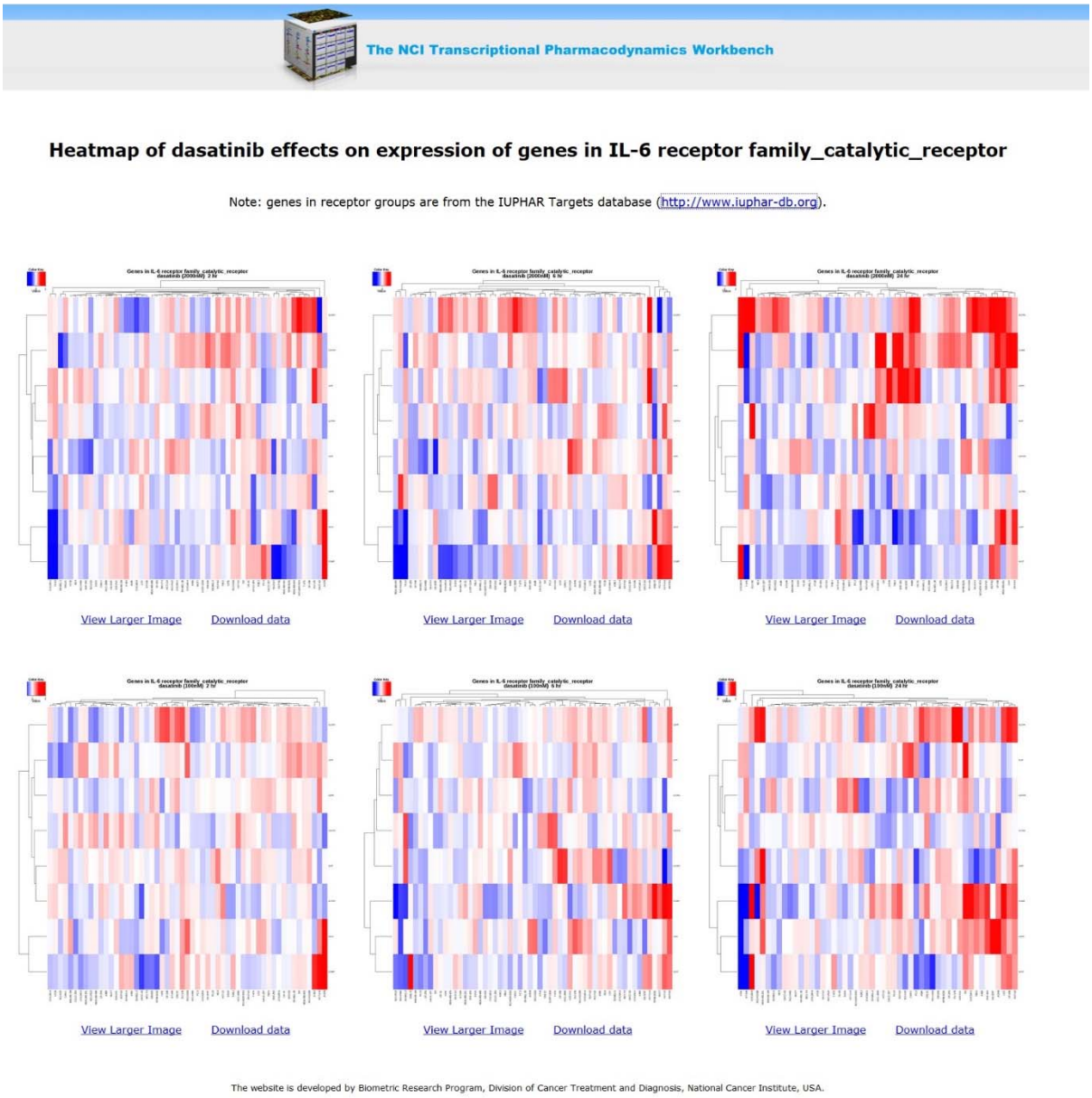


Figure 18: the NCI TPW results of a receptors analysis. The cell lines (x-axis) and the genes (y-axis) are both clustered by default. Refer to the text for more details.

“User defined genes” tab

This feature of the NCI TPW gives users the flexibility to generate a heatmap of any set of genes of interest. Users can simply enter the gene symbols in a list in the “Enter gene symbol” field (Figure 19). After selecting the drug and clicking “Submit”, six heatmaps of gene expressions are generated for the three time points and two concentrations, respectively.

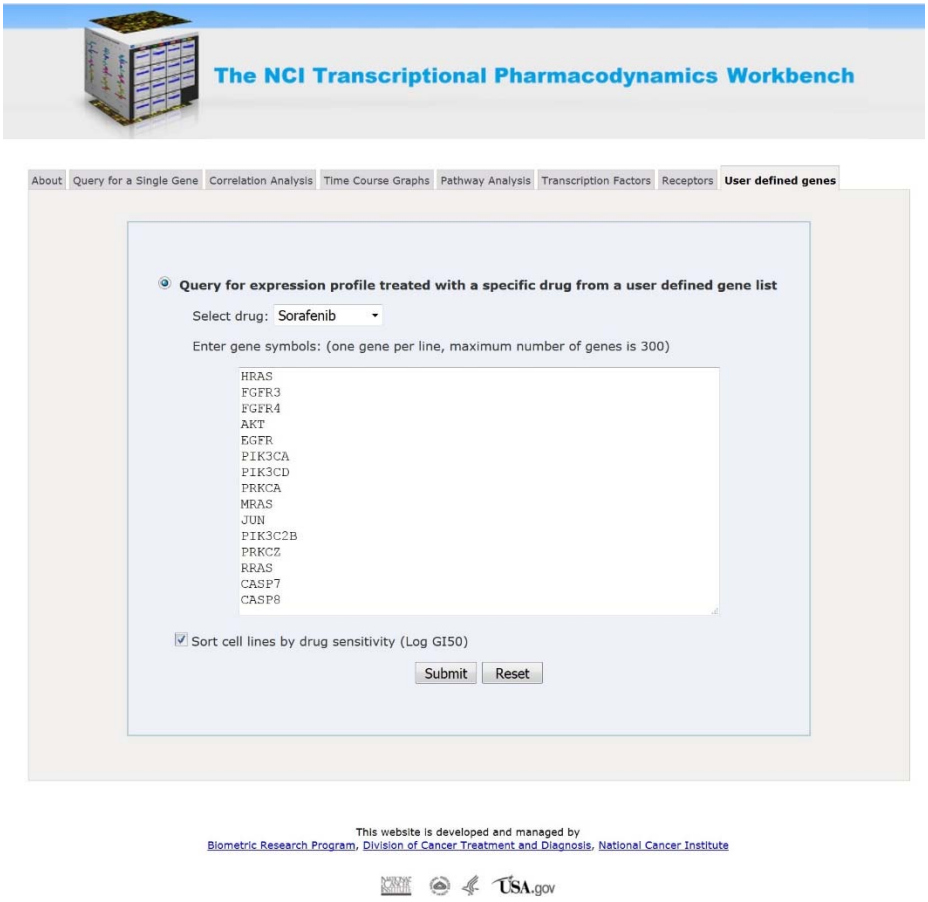


Figure 19: the NCI TPW tab used to query the “User defined genes” data. Refer to the text for more details

By default, the cell lines on x-axis and the user-defined genes on y-axis are both clustered. The user is presented the additional option to sort the cell lines on x-axis by drug sensitivity ($\log_{10}$GI50). All data used to generate these heatmaps can be downloaded in CSV format file by clicking the “Download data” link.

In Figure 20, we see an example of using 58 genes for sorafenib pharmacodynamic superpathway that are curated in Pathcard by the Weizmann institute (http://pathcards.genecards.org/Card/vegf_pathway_(tocris)?queryString=Sorafenib%20Pharmacodynamics). The heatmap at high concentration at 24 hours reveals that HRAS, PRKCD and AKT1 are down-regulated while PIK3C2B, PRKCZ, PIK3C2A, MAPK9, PK2, JUN, CASP7, CASP8 are upregulated.

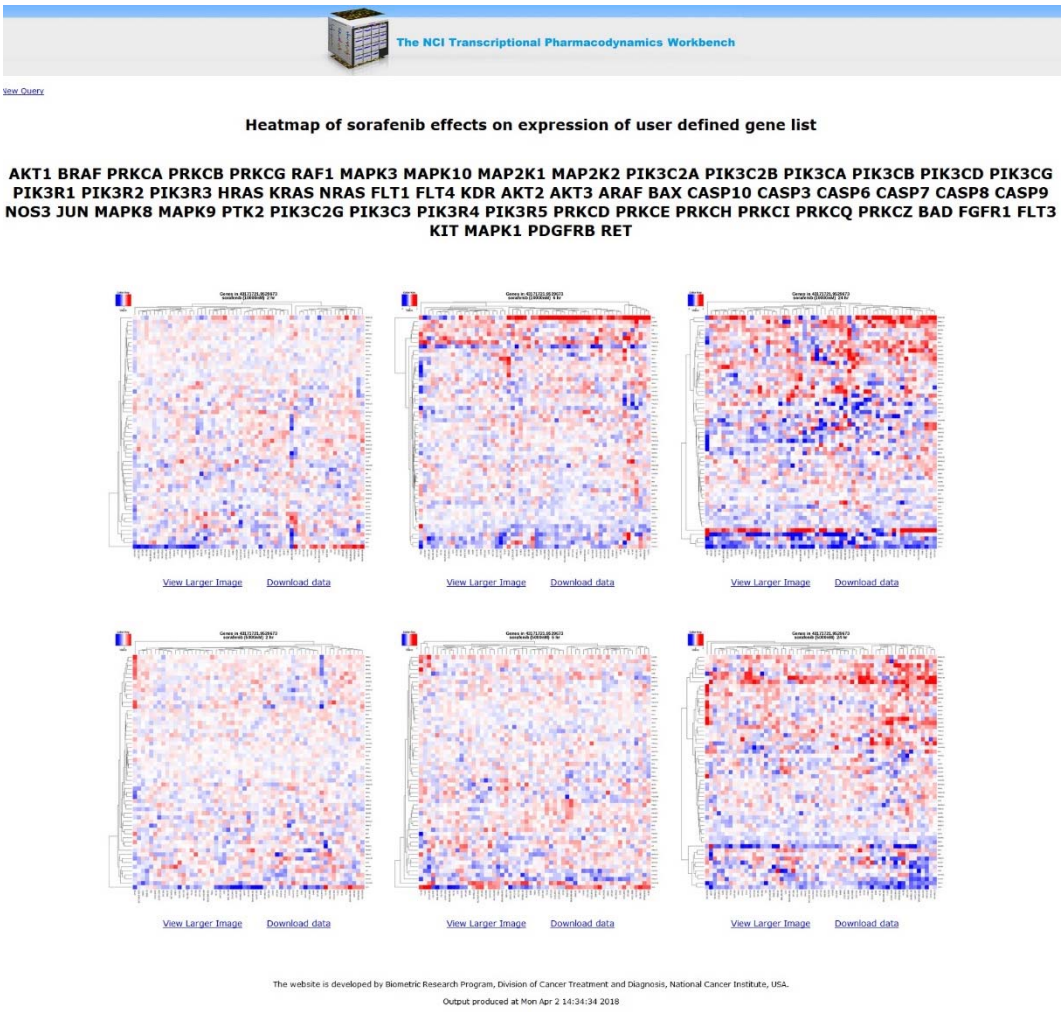


Figure 20: the NCI TPW results of a user defined gene list analysis. Refer to the text for more details.