LINCS Canvas Browser v1.0 - Tutorial

Written by

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Abstract

The Library of Integrated Network-based Cellular Signatures (LINCS) project has produced masses of gene expression signatures using the L1000 technology. The L1000 technology measures 1000 genes' mRNAs and estimates the rest of the transcriptome based on a model built from a large set of microarray data from GEO. The L1000 technology is cost-effective and suitable to measure gene expression in large scale. So far gene expression profiles have been collected for 15 human cell lines responding to 16,425 chemical reagents and 5,806 genetic reagents in different time points and concentrations for a total of over one million experiments. Visualizing and analyzing such large dataset for biological knowledge extraction is challenging. Fast querying of signatures and integration with other sources of data is also a desired functionality that would bridge LINCS L1000 data with existing high-throughput data collection efforts. To begin addressing these challenges we introduce LINCS Canvas Browser (LCB), an interactive HTML5 web-based software application that facilitates querying, browsing and interrogating almost all LINCS L1000 gene expression experiments. LCB implements two compacted layered canvases, one to visualize the L1000 expression data and the other to display enrichment analysis results. Clicking on an experimental condition highlights gene-sets enriched for the differentially expressed genes in the clicked experimental condition experiment. A search interface in LCB allows users to input gene lists and query the lists against a dataset of 140,000 conditions to find the top matching experiments. LCB is implemented in HTML5 using state-of-art JavaScript libraries including Backbone, Underscore, D3 and JQuery.

Installation and Requirements

LCB requires a working internet connection and modern browser capable of displaying and operating dynamic SVG images. Current versions of the browsers FireFox, Opera, Chrome, Safari, and Internet Explorer should work. LCB should also work on mobile devices and respond to touch gestures. LCB is available on various web-sites in different versions:

http://www.maayanlab.net/LINCS/LCBL

http://apps.lincscloud.org/LCBL/

http://lincs.hms.harvard.edu/explore_/canvasbrowser/

Each version provides almost the same functionality but it is slightly customized. LCB on the HMS site only displays the LJP datasets and has links to Enrichr. This version of LCB also has functionality that show other layers of regulation such as Akt and Erk levels and results from cell viability assays.

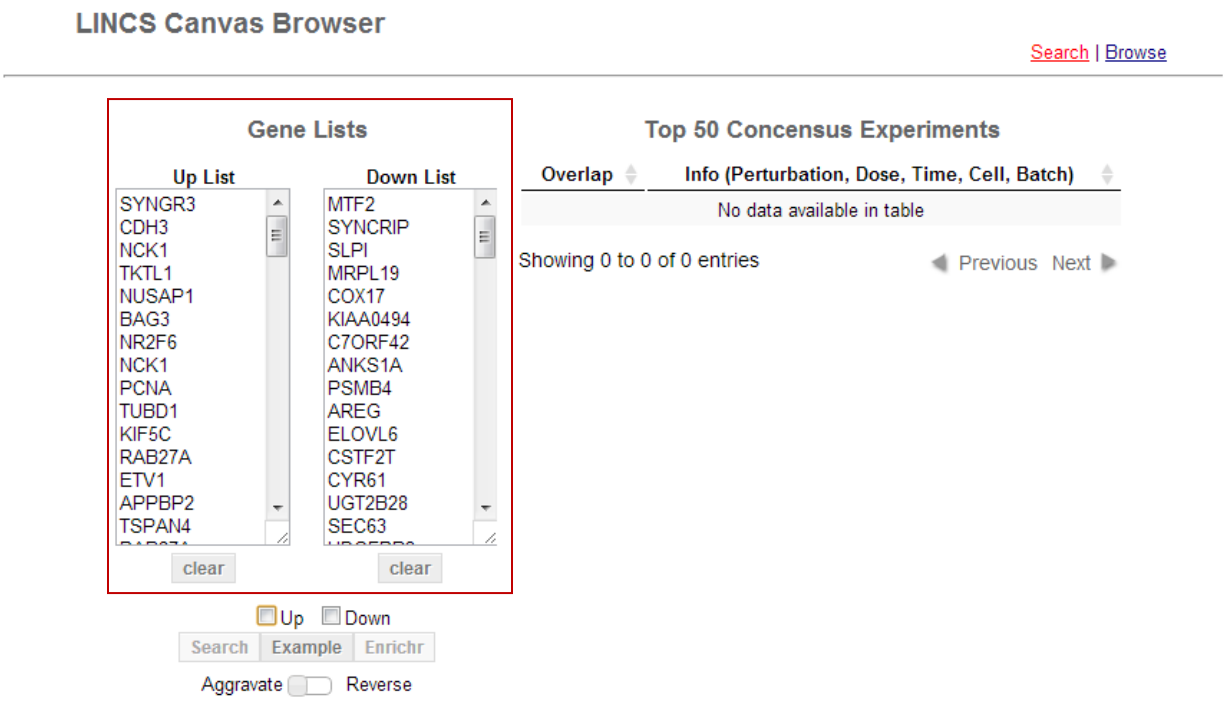
LCBL, these versions available on the LINCS apps cloud and the maayanlab.net sites, cover all the L1000 datasets and have search engine functionality. The version on the maayanlab.net web-site maybe more updated and is used for beta-testing.

Instructions

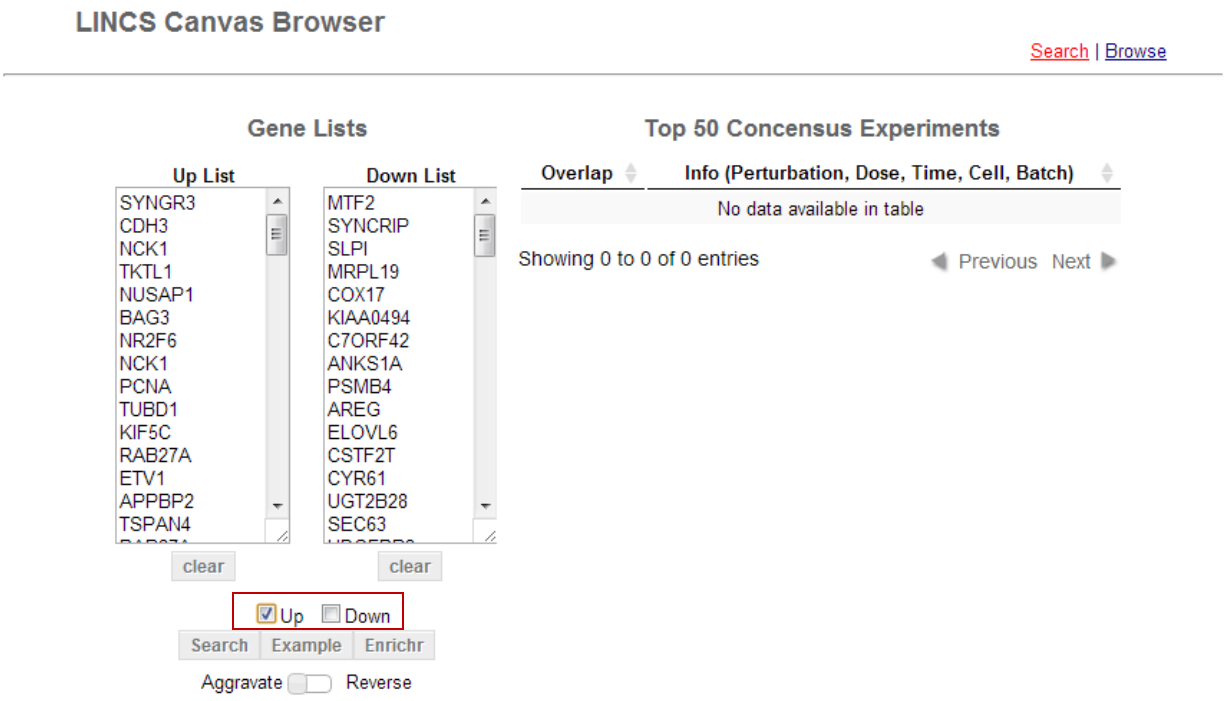
I. Querying for consensus experiments

First, navigate to the Search page of LCB at http://www.maayanlab.net/LINCS/LCBL or

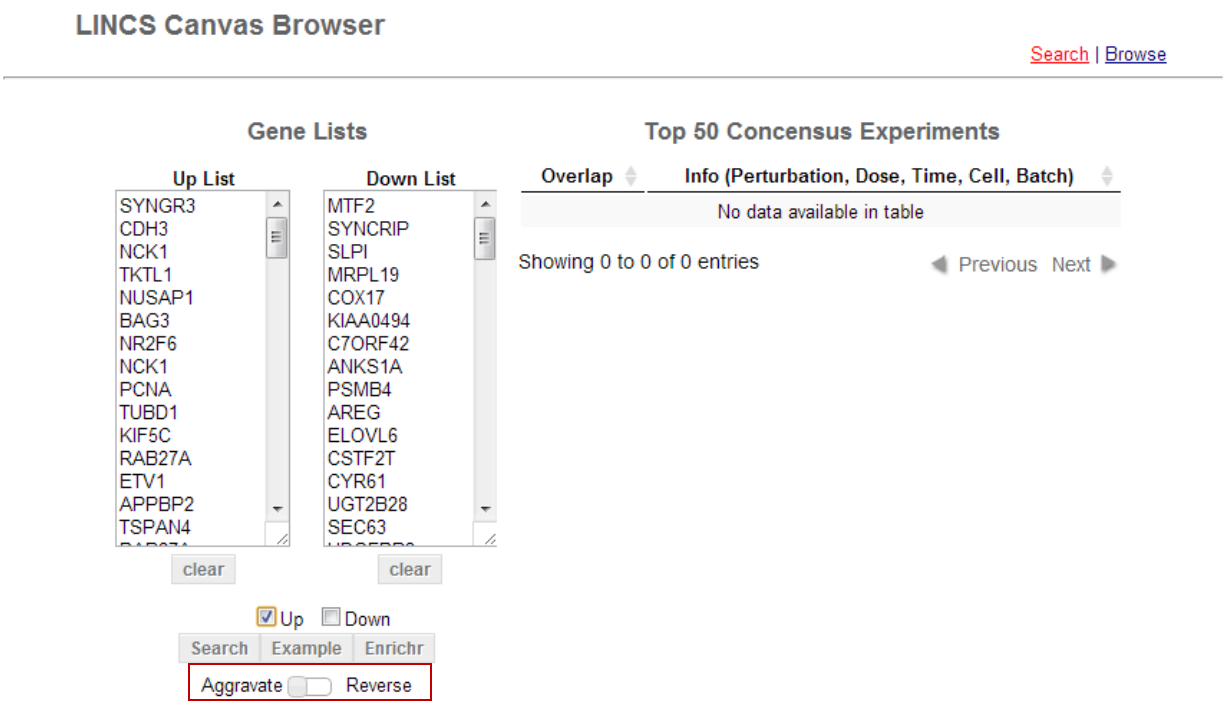
http://apps.lincscloud.org/LCBL/



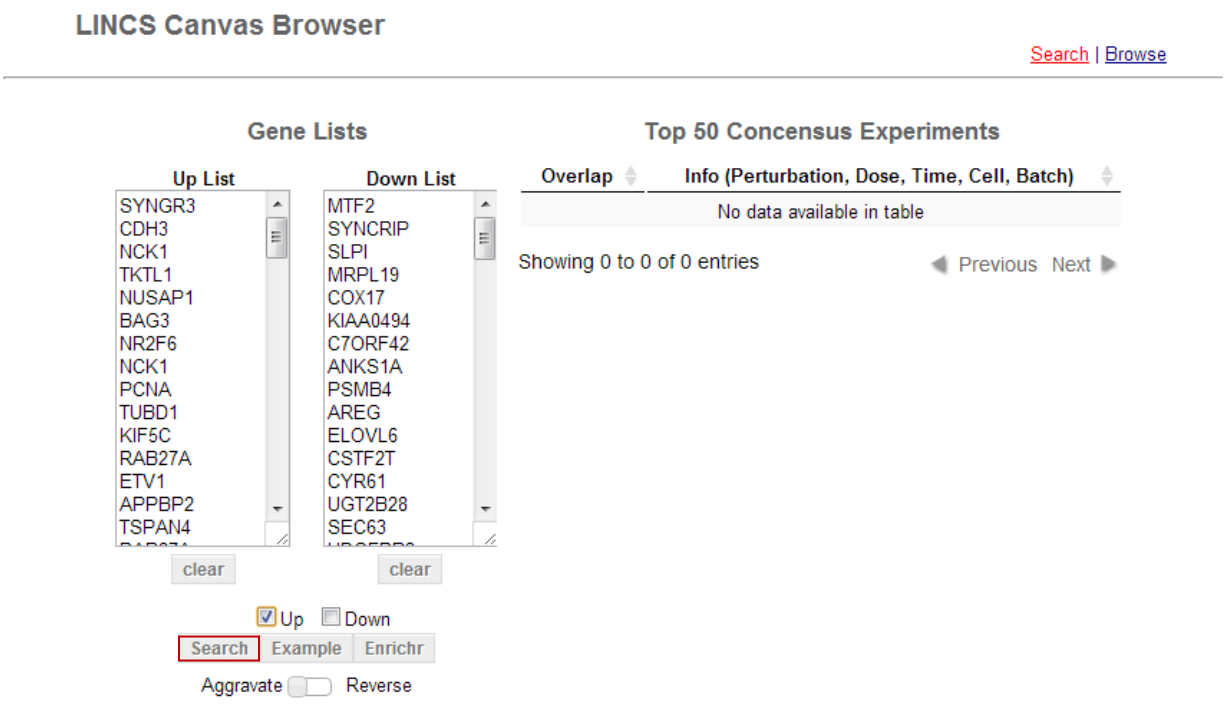
Step 1. Fill in up/down gene lists in the text boxes.



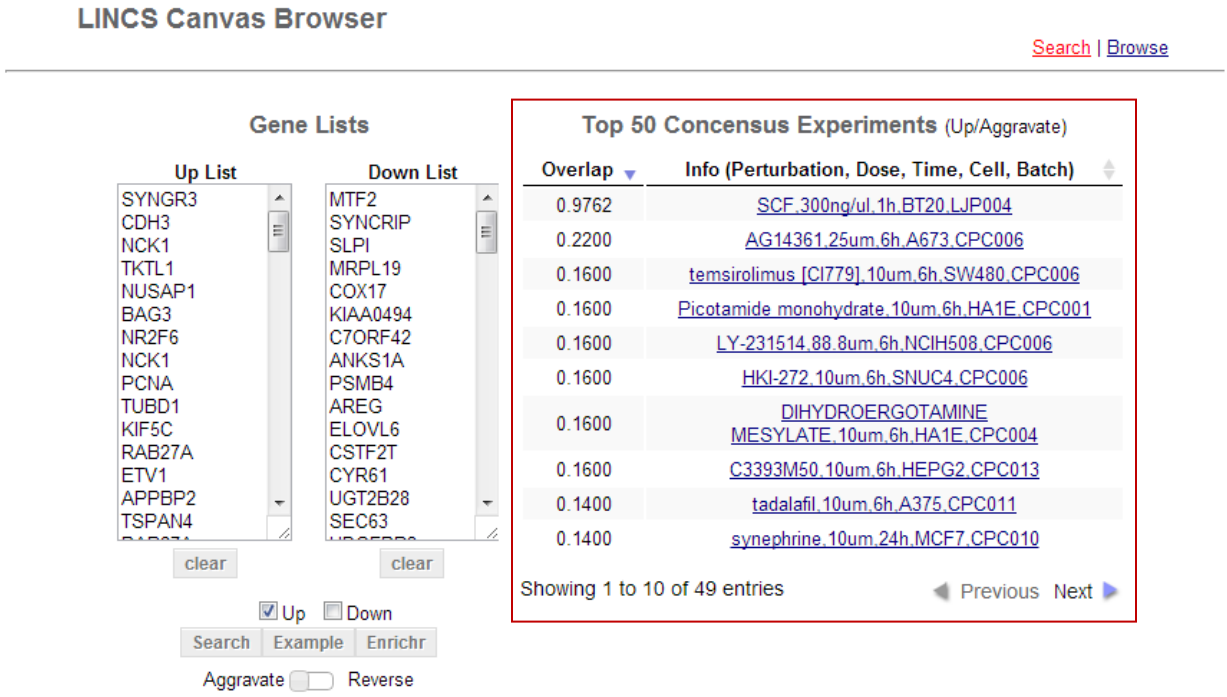
Step 2. Select the search options using the up and down checkboxes. By checking up only, LCB would only query for experiments that have a similar set of differentially expressed up gene list in the database. By checking the down box, LCB would only query for experiments that have a similar down gene list. Checking both boxes would query for experiments that have both a similar up gene list and a similar down gene list. The Search and Enrichr buttons are only enabled after making the up/down selections.



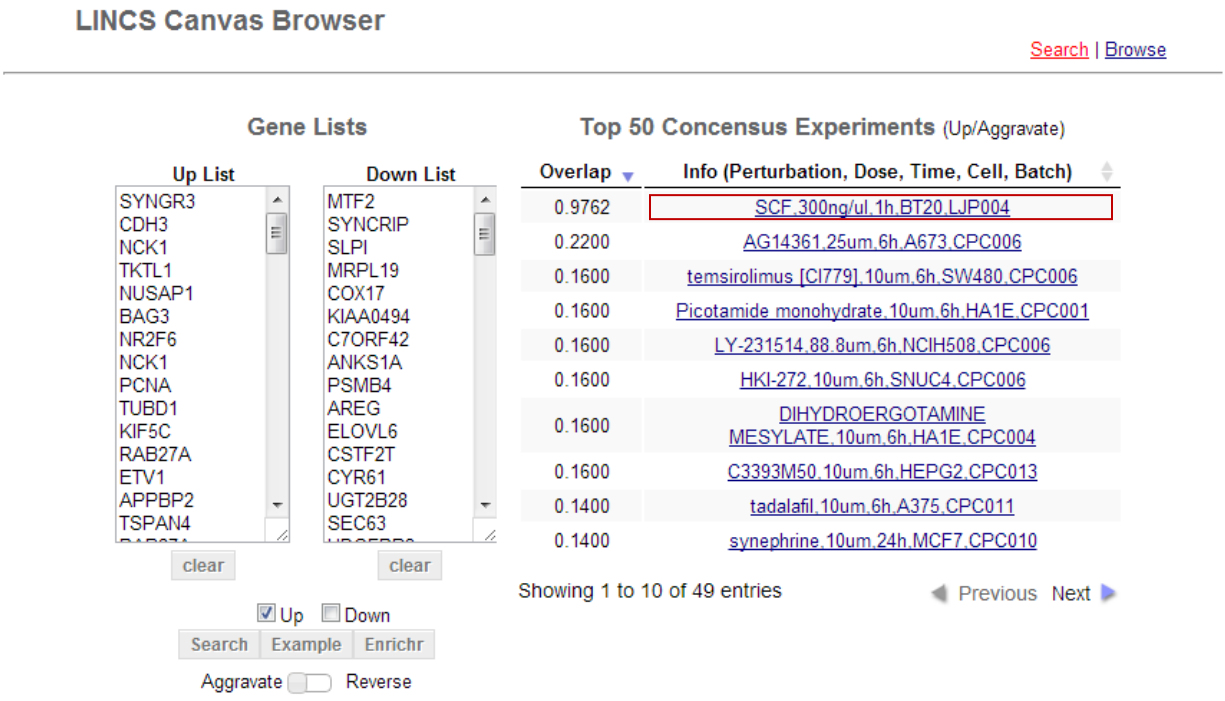
Step 3. Choose either aggravate or reverse search. If reverse search is chosen, LCB would query for experiments with up gene-list similar to the input down gene-list and the down gene-list is similar to input up gene-list. This option may be used to search perturbations that would reverse a disease condition. The aggravate option will simply do the opposite, matching the up with the up and the down with the down.



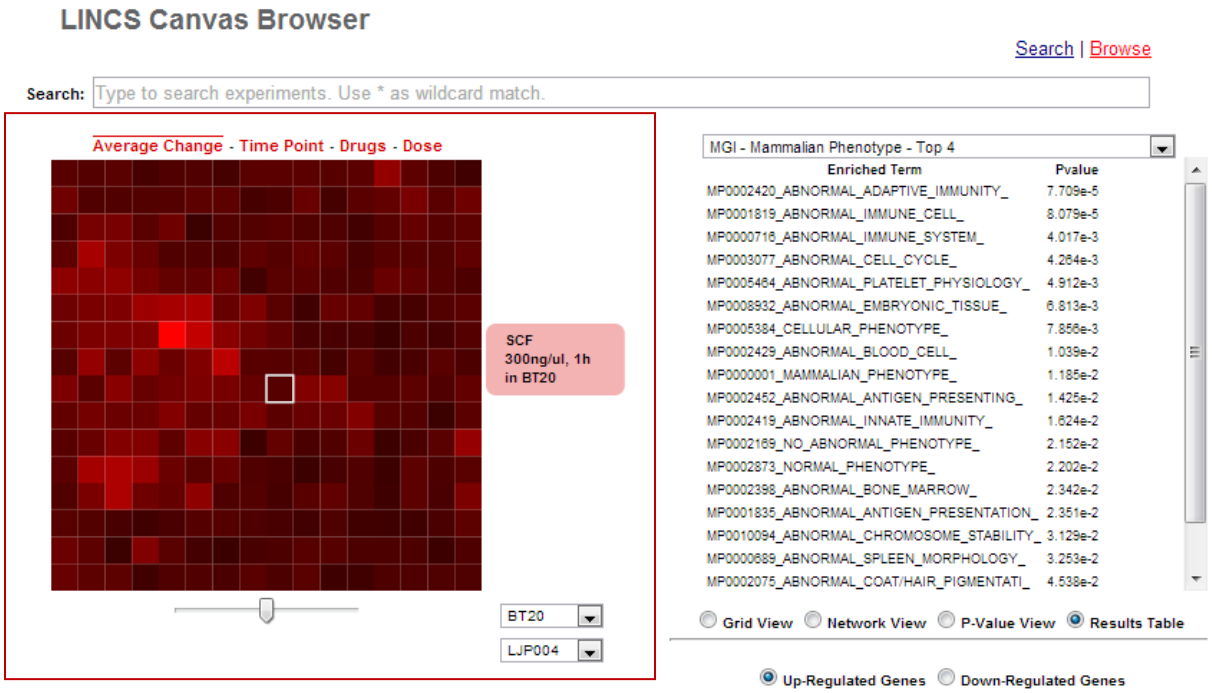
Step 4. Clicking the search button will initiate querying the database. It will usually take less than 20 seconds to complete the search.



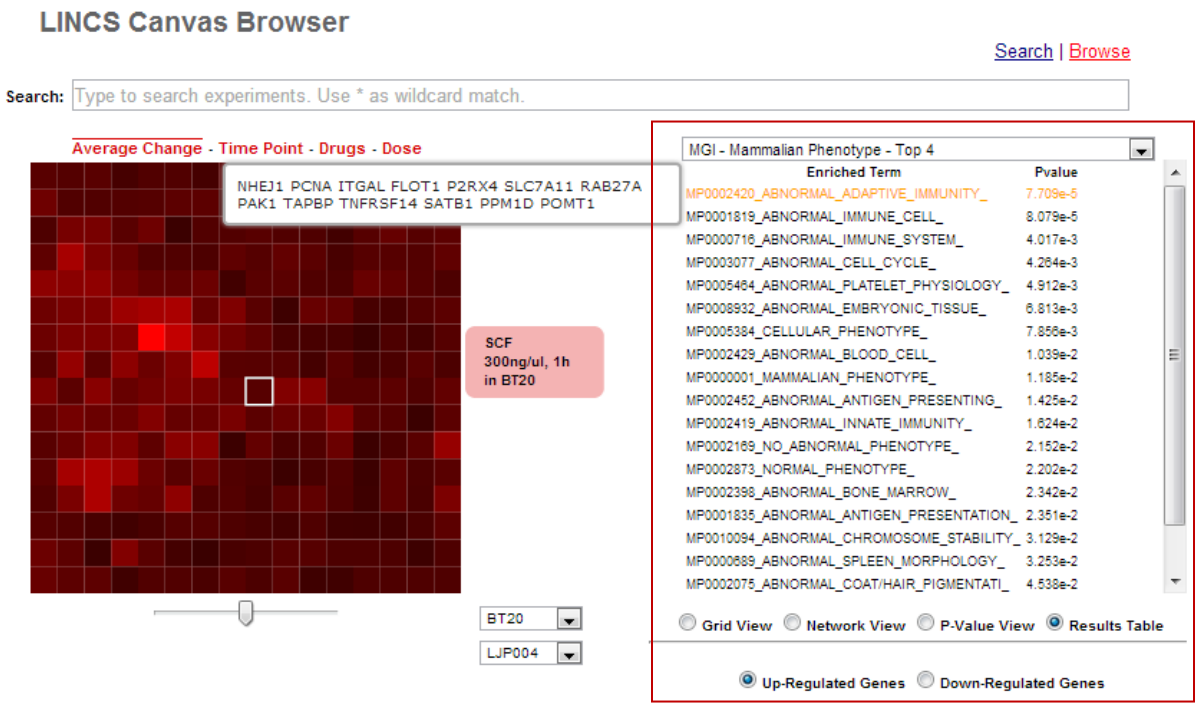
Step 5. Browse consensus experiments. After the search is complete, the top 50 consensus experiments are listed in a table as sown above. The table has 5 pages with each page displaying 10 entries. Use the next and previous buttons at bottom to navigate through these pages. The first column of the table shows a similarity score with 1 representing a perfect match and 0 representing no match. The second column of the table shows descriptive information of each experimental condition. The information provided includes perturbation, dose, time point, cell-line and batch ID.



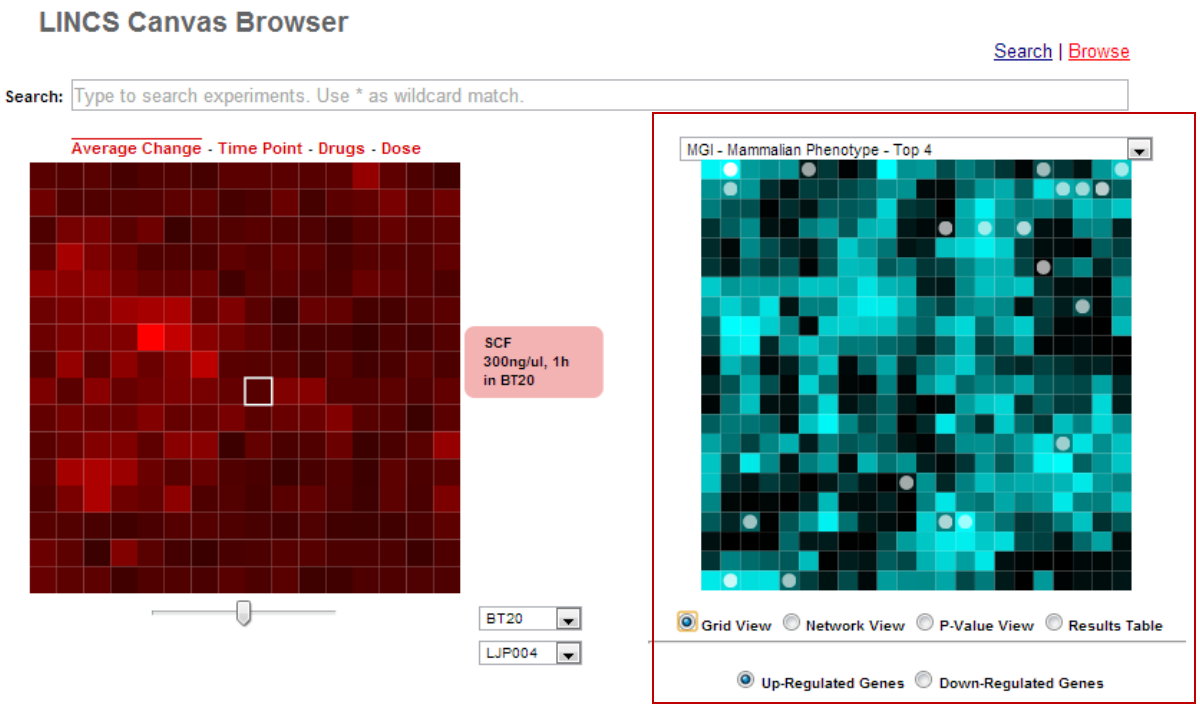
Step 6. Click on an entry to visualize the experiment and its enrichment analysis results on canvases in a new tab.



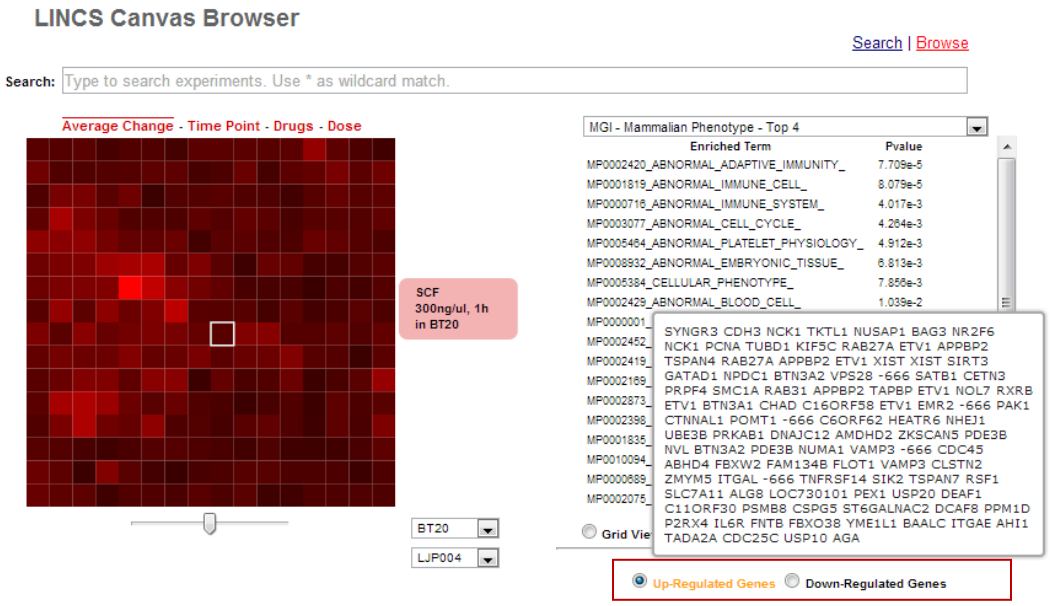
Step 7. Experiments displayed on a canvas. The red canvas on the left visualizes all the experiments applied on one cell-line in one batch. Each experiment is represented by a tile on the canvas. The canvas in the figure shows all the experiments applied on the BT20 cell-line in the LJP004 batch. The tiles are arranged by gene expression similarity so that neighboring tiles have similar gene expression profiles. The coloring on the canvas indicates signal strength. A bright red tile represents a strong perturbation while a darker tile a weak perturbation. Different coloring schemes that represent other aspects of the data could be chosen by click on the navigation bar above the canvas. The experiment that was clicked on in the search results page is highlighted by a white square.



Step 8. Enrichment results table. The enrichment results table lists all the significantly enriched terms for the up-regulated genes of the consensus experiment using the Mammalian Phenotype gene-set library created from the MGI mouse phenotypes ontology browser. Enrichment is computed using the Fisher exact test with BH correction. Selection of the down-regulated genes radio button would display significantly enriched terms for the down-regulated genes for that experiments. A tooltip showing the overlapping genes between the up-regulated genes and the genes of a gene-set entry would pop-up after mouse hovering on that entry. Different gene-set libraries could be selected using the dropdown menu above the enrichment results table.

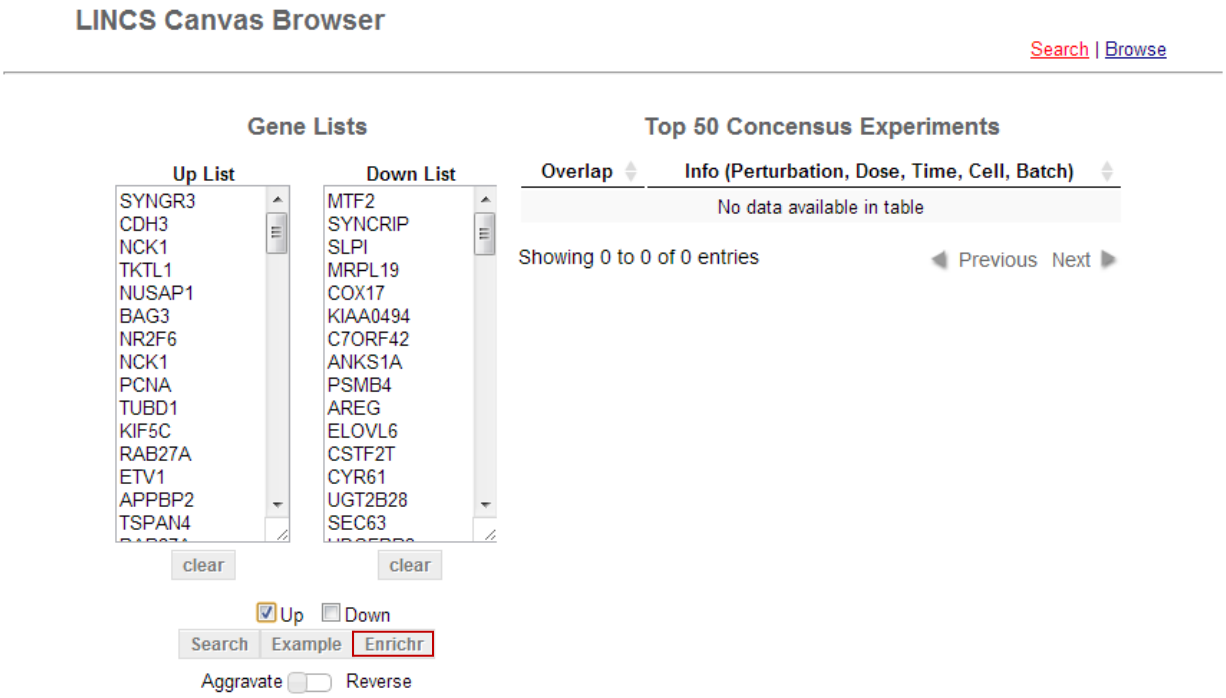


Step 9. Alternative views. Enrichment analysis results could also be visualized on gene-set library canvases by selecting the grid view radio button. These gene-set library canvases show all gene-sets in a specific gene-set library organized by their gene content similarity. Significantly enriched gene-sets that match the selected L1000 experiment are highlighted by white circles where brighter circles denote stronger enrichment scores.



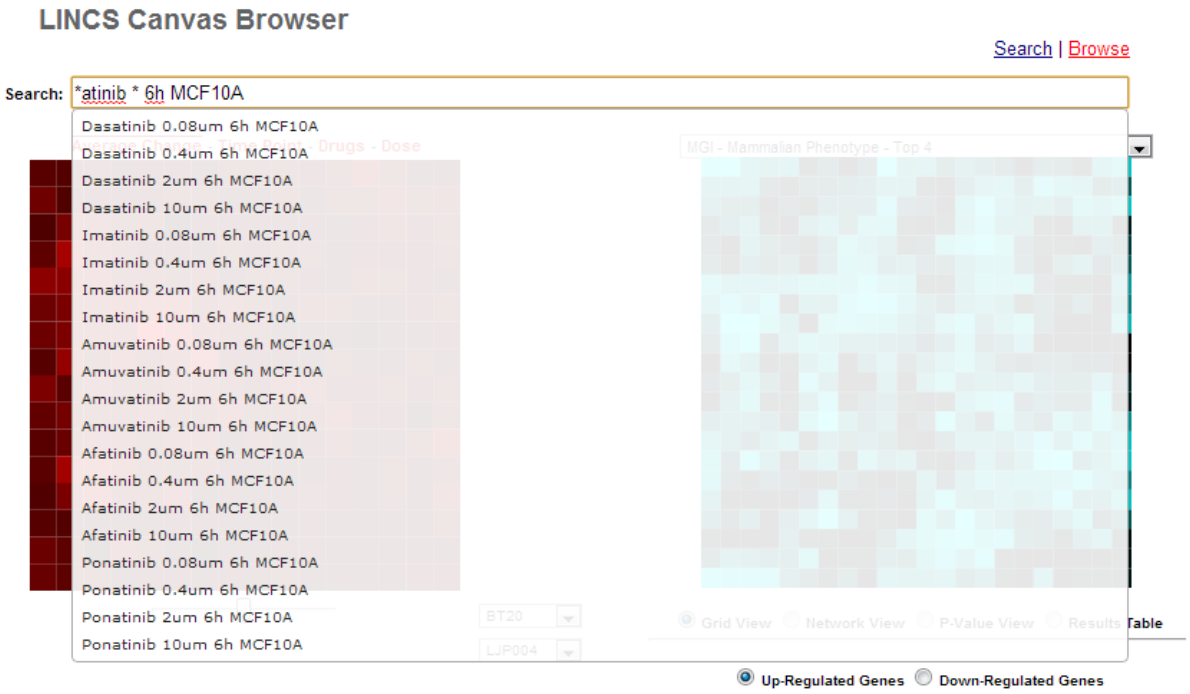
Step 10. Display up- or down-regulated genes. Mouse over the “Up-Regulated Genes” text or the “Down-Regulated Genes” text would display respective gene lists.

II. Enrichment analysis on the input gene lists with Enrichr



You can perform enrichment analysis on your input gene lists by click on the Enrichr button. The Enrichr button would send your input gene lists to the Enrichr web service. The up/down checkboxes determine which gene list to send. If both are checked, the up and down gene lists will be merged into one gene list and sent to Enrichr. You can learn more about how to use Enrichr at http://amp.pharm.mssm.edu/Enrichr/index.html#help.

III. Search for and visualize perturbations



You can search for a specific perturbation using the search bar above the canvas viewers. The search bar supports "*" as a wildcard. The example in the figure above searches for all experiments that use MCF10A cell line, have a perturbation name ended with atinib and a time-point of 6 hours. Selection of a matched experiment on the dropdown menu would visualize the experiment in the appropriate canvas and show its enrichment analysis results in a table as in show in step 6 of part I.