

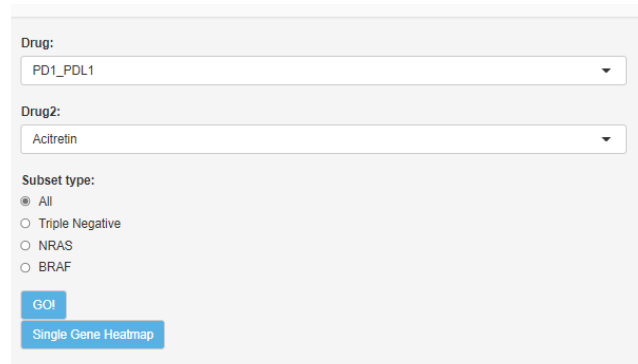
DRepMel - Drug combinations

User manual

DRepmel is a shiny application found at <http://drepmel.moffitt.org/>. The home page of the application is the “About” tab. The application loads a large amount of data and loading icons will be present while the data is loading. Once they disappear the data is loaded and you can select treatments.

Figure 1 displays the initial input panel. Once the data is loaded choose two drugs from the drop down lists, the subset of patients (all patients, TN, NRAS, BRAF) and click “GO!”. The loading icons on the tabs will appear again while the plots are being redrawn. Also, the target gene drop down lists will appear for the TME tab. Click “Single gene heatmaps” after selecting the desired genes to draw the single gene heat maps.

Figure 1: Initial input panel after data loads



Drug:
PD1_PDL1

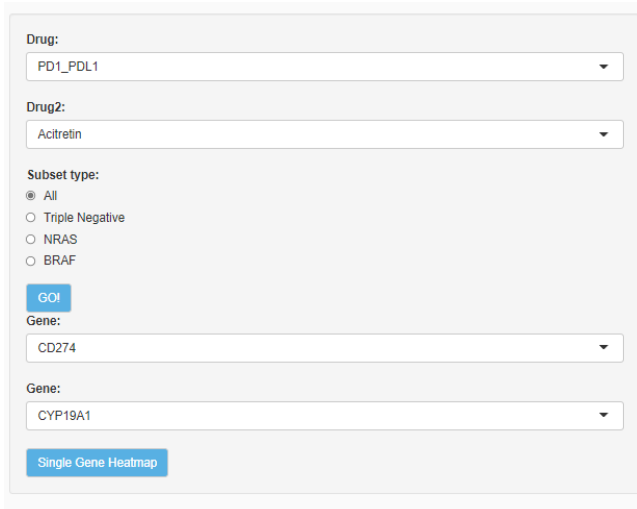
Drug2:
Acitretin

Subset type:
 All
 Triple Negative
 NRAS
 BRAF

GO!

Single Gene Heatmap

Figure 2: Input panel after GO button is clicked



Drug:
PD1_PDL1

Drug2:
Acitretin

Subset type:
 All
 Triple Negative
 NRAS
 BRAF

GO!

Gene:
CD274

Gene:
CYP19A1

Single Gene Heatmap

Figure 3: Tabs



There are 5 tabs that contain KM plots, heat maps, violin plots, boxplots and tables.

Top combinations tab

The top combination tab displays the top combinations as determined by the ranking method (see paper). The subtype radio button will subset the table to ALL, NRAS, BRAF, or Triple wild type. The table will show 10 combinations by default and searchable using the box in the upper right corner.

Show <input type="text" value="10"/> entries				Search: <input type="text"/>
Cohort	Drug 1	Drug 2	combinedP	
ALL	CTLA-4	prochlorperazine_MCF7_UP	0.01171388	
ALL	TIM-3	Prestwick-682_PC3_UP	0.000310514	
ALL	IDO	Prestwick-682_PC3_UP	0.003881395	
ALL	CTLA-4	Prestwick-682_PC3_UP	0.00435293	
ALL	LAG3	Prestwick-682_PC3_UP	0.007384449	
ALL	CTLA-4	acetohexamide_PC3_UP	0.005991421	
ALL	IDO	acetohexamide_PC3_UP	0.008642617	
ALL	Gleevec (Imatinib)_MRC.d2	acetohexamide_PC3_UP	0.009696378	
ALL	CTLA-4	mephentermine_MCF7_UP	0.003508011	
ALL	CTLA-4	diloxanide_MCF7_UP	0.008920694	

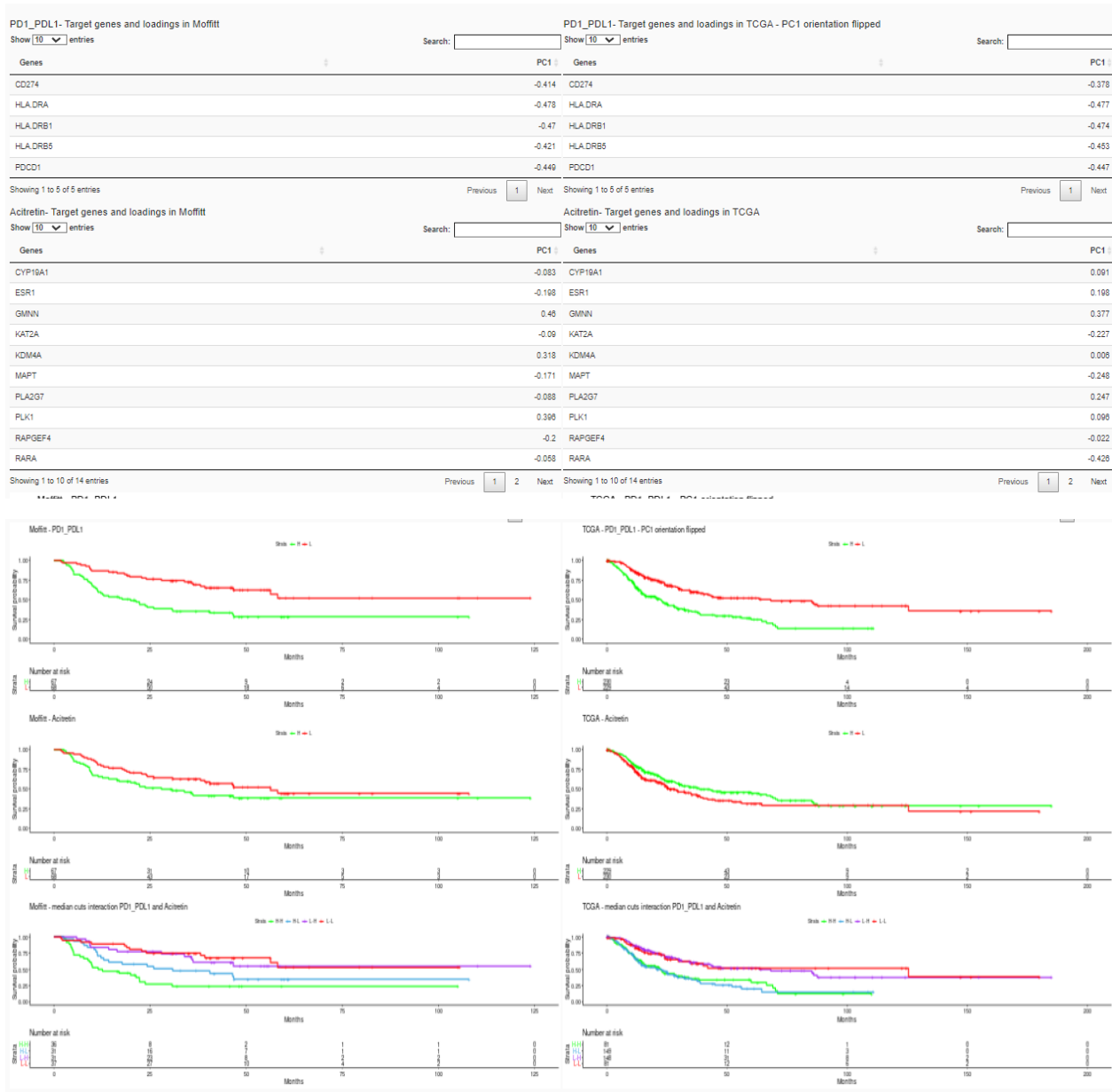
Showing 1 to 10 of 65 entries

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PC1 and Survival tab

The PC1 and survival tab contains tables of target genes and their PC1 loadings for the two drugs in the Moffitt and TCGA cohorts. By default, the tables will show at most 10 genes, the user can change the number shown with the drop down menu in the upper left of each table. The user can also search for a specific gene using the search field in the upper right of each table. Also displayed are KM plots for both treatments in each cohort. The PC1 of the target genes is dichotomized at the median.

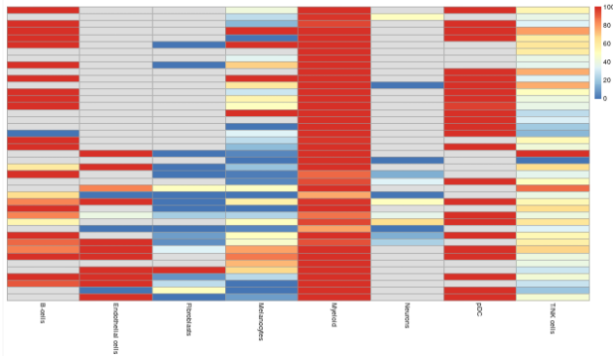
Figure 4: PC1 and Survival tab tables



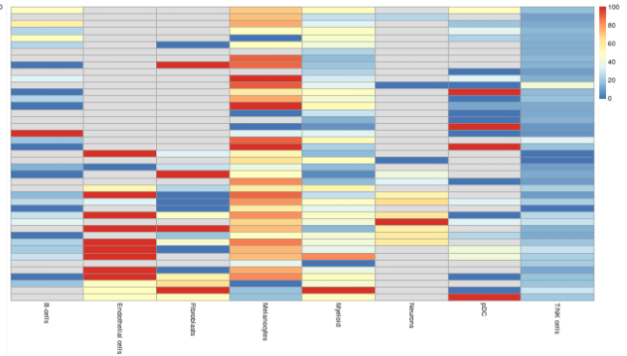
TME (Tumor immune microenvironment) tab

The TME tab contains single cell gene expression heat maps and violin plots. There are heat maps for expression of all the target genes of a drug and single gene heatmaps. These plots are not affected by the subset radio buttons. This data is from a separate cohort described in the paper.

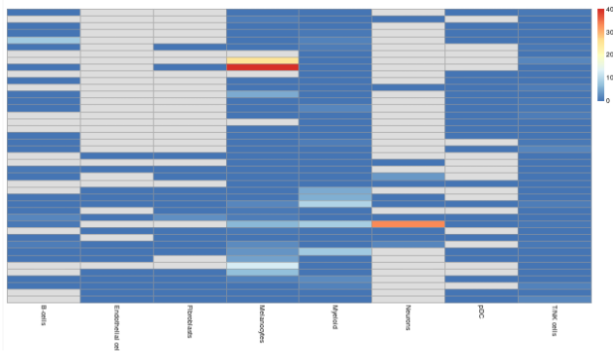
Single cell gene expression for PD1_PDL1 gene set



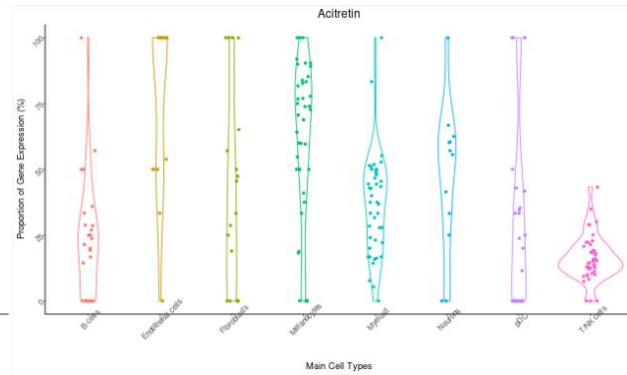
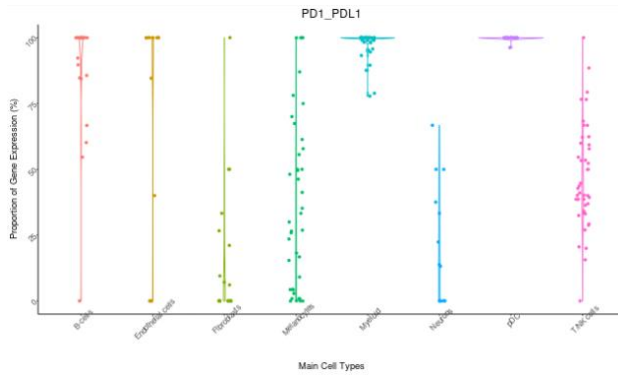
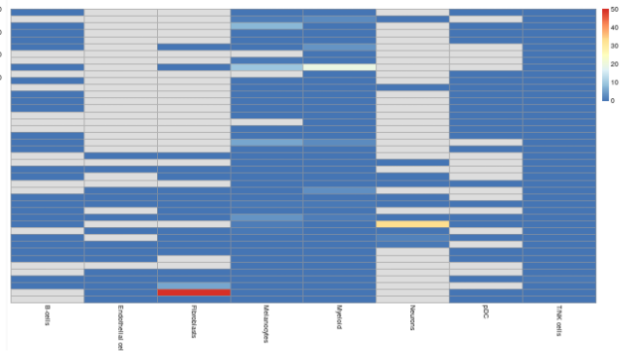
Single cell gene expression for Acitretin gene set



Single cell gene expression for CD274

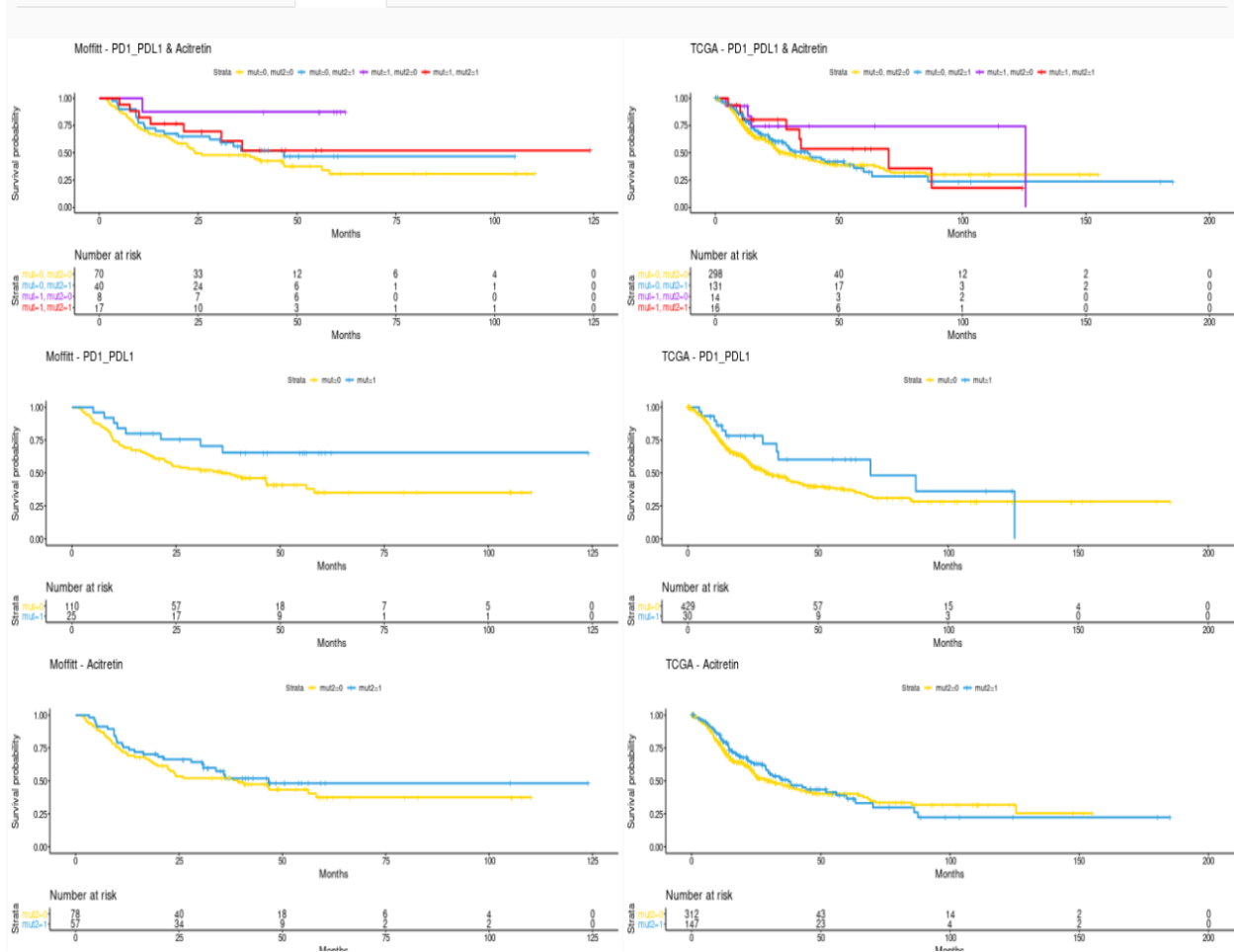


Single cell gene expression for CYP19A1



Mutation & survival tab

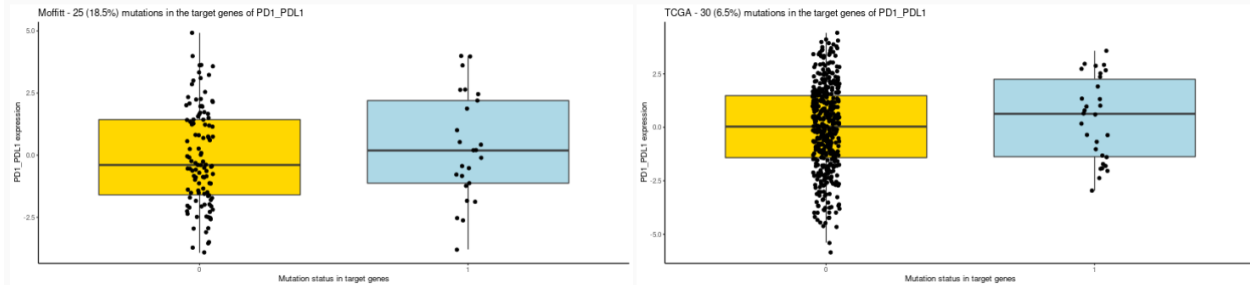
The mutation status and survival tab displays KM plots for mutation status in the target genes of drug 1 and drug 2 in both cohorts along with the combination of mutation status for both drugs. If there is a mutation in any of the target genes of a treatment for a patient it is considered a mutation.



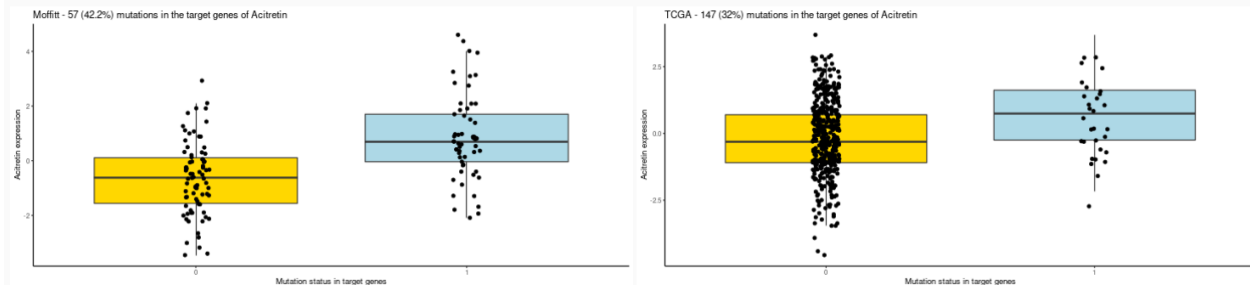
eQTL tab

The eQTL tab displays box plots of the PC1 of the expression of the target genes of each drug by mutation status in the target genes. If there is a mutation in at least one target gene of a drug then the mutation status is 1, otherwise 0. The percentage of patients with a mutation in the target genes is specified and the data is overlaid on the box plots.

PC1 by mutation status in target genes of PD1_PDL1



PC1 by mutation status in target genes of Acicretin



This tab also shows a table of the summary statistics of the PC1 of the expression in the target genes of each drug and cohort.

Show entries Search:

	PC	Min.	1st Qu.	Median	3rd Qu.	Max.
1	Moffitt PD1_PDL1	-3.91	-1.54	-0.38	1.53	4.93
2	Moffitt Acicretin	-3.45	-1.15	-0.05	0.88	4.6
3	TCGA PD1_PDL1	-5.85	-1.42	0.07	1.49	4.42
4	TCGA Acicretin	-4.55	-0.97	0.03	0.96	3.69

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Methods tab

This tab shows an example of the flipping of the PC1 for a drug, when the loadings of the cohorts are opposite signs in more than 50% of the target genes the orientation of PC1 for the TCGA cohort is flipped (the signs of the loadings are multiplied by -1) and thus the KM plot is reversed.

If the signs of the loadings of the principle components between BMS and TCGA disagree in more than 50% of them the orientation of the PC1 in TCGA is flipped. The PC1 of one or both drugs may be flipped

PD1-PDL1 - Target genes and loadings in TCGA

Show entries

Search:

Genes	PC1
CD274	0.378
HLA.DRA	0.477
HLA.DRB1	0.474
HLA.DRB5	0.453
PD1	0.447

PD1-PDL1 - Target genes and loadings in TCGA - PC1 orientation flipped

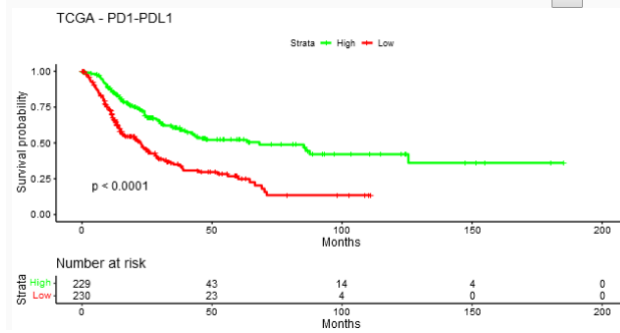
Show entries

Search:

Genes	PC1
CD274	-0.378
HLA.DRA	-0.477
HLA.DRB1	-0.474
HLA.DRB5	-0.453
PD1	-0.447

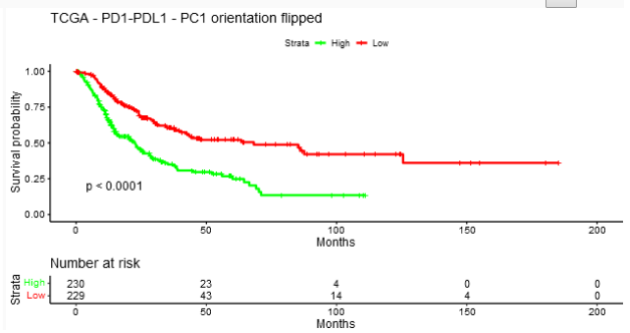
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