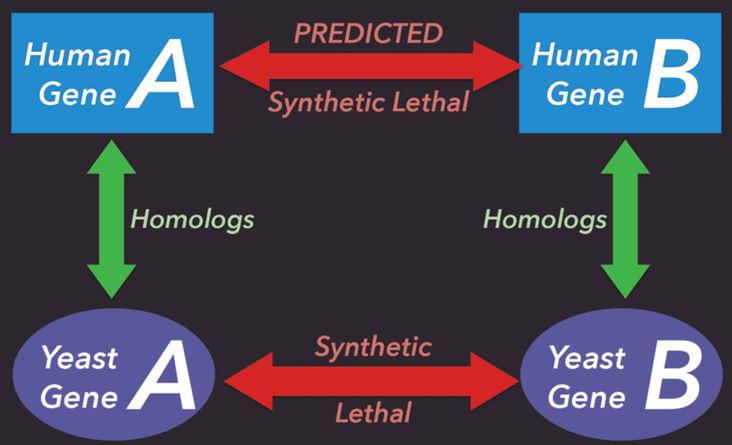
Background

Synthetic lethality is a type of genetic interaction where loss of two or more genes, such as PARP and BRCA1/2, results in loss of cell viability.

Some tumors lose BRCA1/2 function. Because of the synthetic lethal interaction between PARP and BRCA1/2, drugs that inhibit PARP can be used to specifically target & kill tumor cells.

Synthetic lethal interactions are therefore of great interest to precision medicine, but not all interactions of this type are known in humans.



To predict cancer-relevant synthetic lethal interactions in the human genome, we can turn to the wealth of data available on *S. cerevisiae*.

In the following tutorial, we will import a list of human tumor suppressors into YeastMine in order to identify yeast homologs with potentially conserved synthetic lethal interactions.

yeastmine.yeastgenome.org

The YeastMine tutorial presented here is also available as a YouTube video:

http://bit.ly/SGDchemotherapy

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For more step-by-step help on YeastMine, check out:

SGD YouTube • Video Tutorials

youtube.com/SaccharomycesGenomeDatabase

Or contact us directly:

Questions, suggestions?

sgd-helpdesk@lists.stanford.edu

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YeastMine is populated by the Saccharomyces Genome Database (SGD; yeastgenome.org) and powered by InterMine (intermine.org)

SGD Saccharomyces GENOME DATABASE

InterMine

Quick Guide

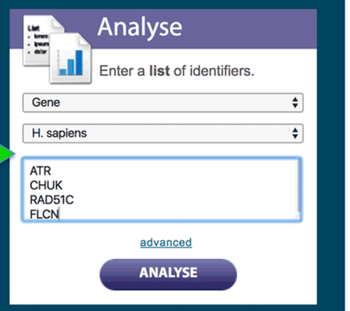
SGD YeastMine

Predicting Chemotherapy Targets

yeastmine.yeastgenome.org

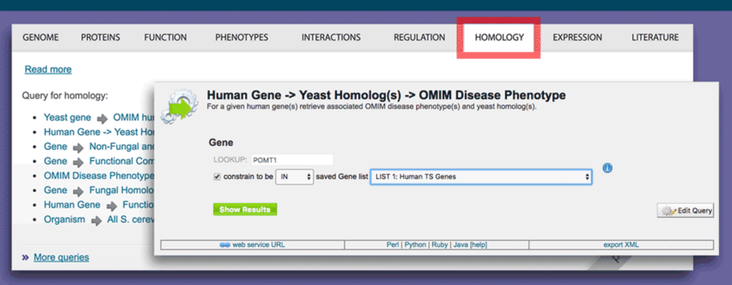
Step 1: Import human tumor suppressors

ATR
CHUK
RAD51C
FLCN



On the YeastMine homepage, import human tumor suppressor genes through the **"Analyse"** feature. You can try the four genes listed here as an example. Name this list: **"LIST 1: Human TS Genes"**

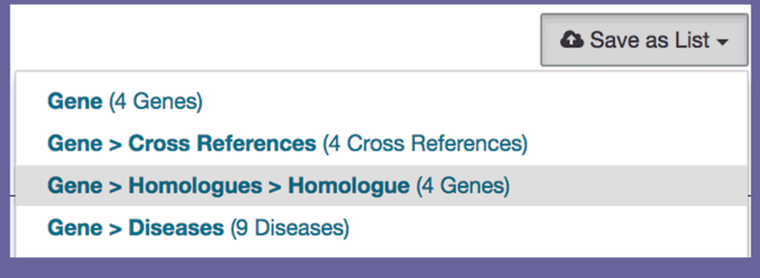
Step 2: Find yeast homologs (of human tumor suppressors)



I) Open the HOMOLOGY tab in the query toolbar.

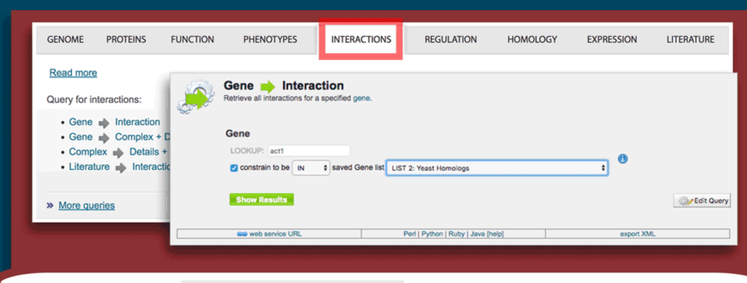
Select the query:
- Human Gene -> Yeast Homolog(s) -> OMIM Disease Phenotype

Input: **LIST 1: Human TS Genes** and hit "Show Results"



II) After the results table is produced, click on the **"Save as List"** button. Save the yeast homologs as: **"LIST 2: Yeast Homologs"**

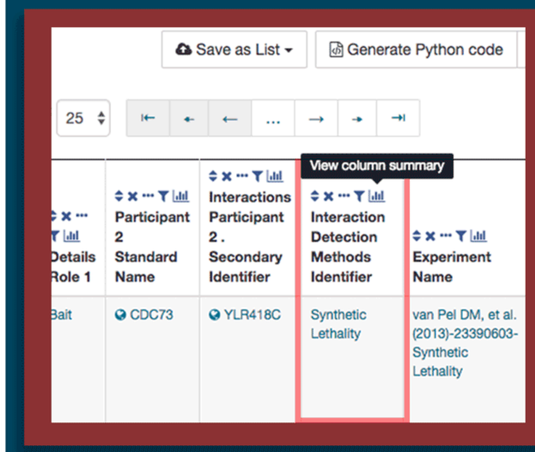
Step 3: Find synthetic lethal interactors (of the yeast homologs)



I) Open the INTERACTIONS tab in the query toolbar.

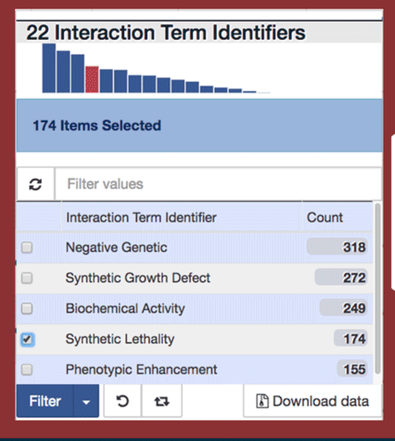
Select the query: • Gene ➡ Interaction

Then, input: **LIST 2: Yeast Homologs** and run the query.

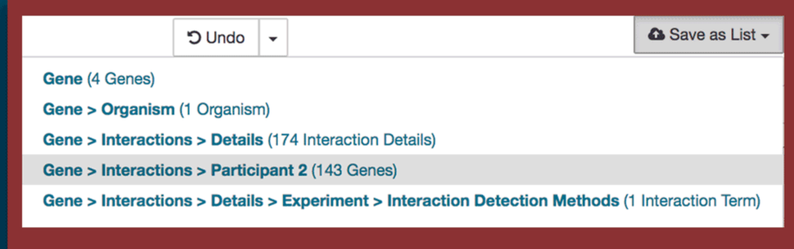


II) In the results table, find the column shown here:

Click on the icon.

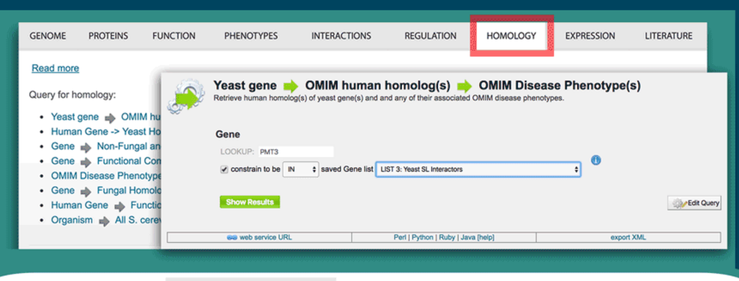


III) Filter the table for "Synthetic Lethality" as shown here.



IV) Save the synthetic lethal interactors as: **"LIST 3: Yeast SL Interactors"**

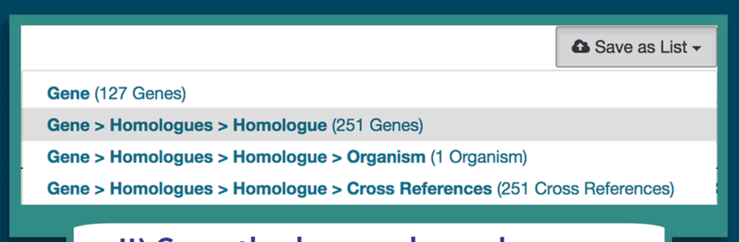
Step 4: Find human homologs (of the yeast synthetic lethal interactors)



I) Open the HOMOLOGY tab in the query toolbar.

Then, select the query:
- Yeast gene ➡ OMIM human homolog(s) ➡ OMIM Disease Phenotype(s)

Input **LIST 3: Yeast SL Interactors** and hit "Show Results"



II) Save the human homologs as: **"LIST 4: Human SL Interactors"**

Interpreting Results

To predict synthetic lethal interactions for the human tumor suppressors, browse through each of the query results that were produced during steps 2-4.

Example findings from each step:

Step 2
Human ATR is homologous to yeast MEC1.

Step 3
Yeast MEC1 has a synthetic lethal interaction with yeast POL3.

Step 4
Yeast POL3 is homologous to human POLD1.

Conclusion:

Because yeast MEC1 and POL3 have a synthetic lethal interaction, their human homologs (ATR and POLD1) are predicted to have one as well!