



REUTERS/Jim Young

METACORE – MAKING THE MOST OUT OF YOUR OMICS DATA

Matthew Wampole, PhD. – Solution Scientist

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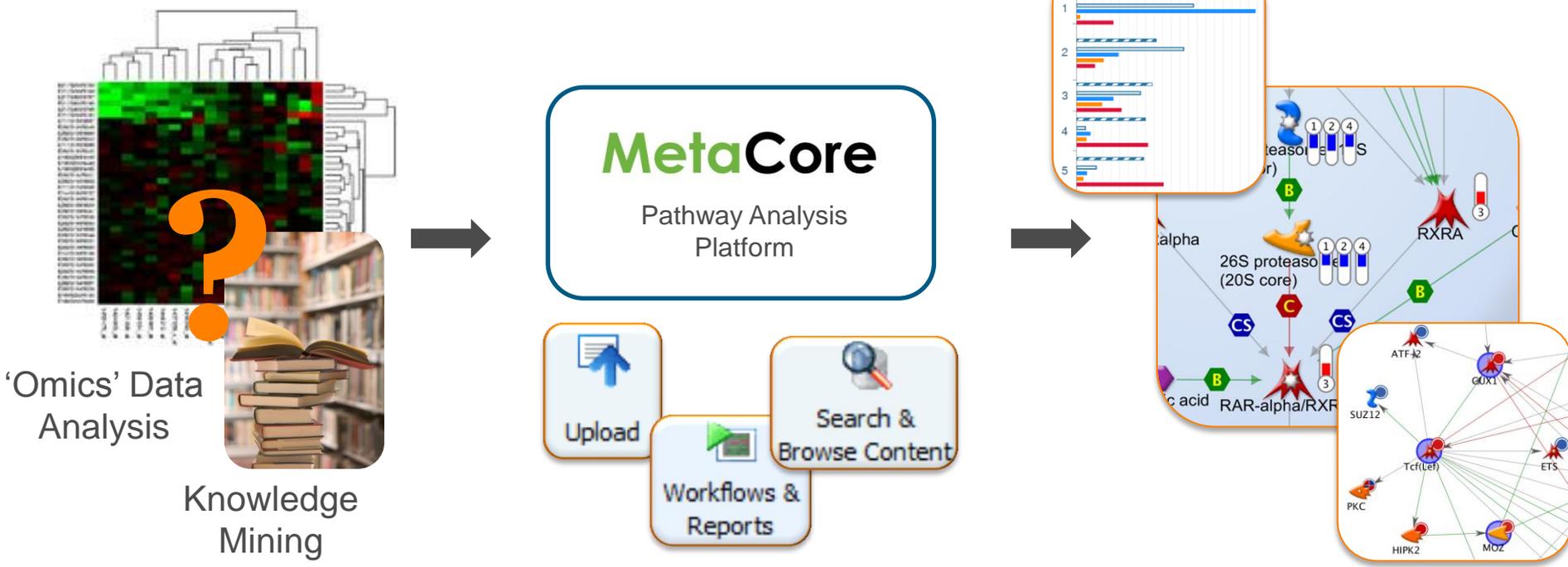
THOMSON REUTERS

AGENDA

- **Morning Session (Introductory Topics) – 9:30 AM to 12:30 PM**
 - 9:30-10:00 – General Overview: Thomson Reuters Systems Biology Solutions
 - 10:00-10:30 – Knowledge Mining: Explore the database and exporting
 - 10:30-11:00 – Uploading, filtering and setting a background
 - 11:00-11:45 – Running Functional Enrichments and exploring Pathway Maps
 - 11:45-12:30 – Running Workflows
- **Lunch Break – 12:30 PM to 1:30 PM**
- **Afternoon Session (Advanced Topics) – 1:30 PM to 4:30 PM**
 - **Topics of Interest** (will discuss these or other topics of interest to attendees)
 - 30-45 min – Key Pathway Advisor – Hypothesizing key hubs using the causal reasoning algorithm
 - 45-60 min – Building Networks with MetaCore
 - 30-45 min – Using the Microarray repository for gene comparisons against public data
 - 30-45 min – Multi-omics analysis with miRNA & mRNA data
 - 45-60 min – Multi-omics analysis with Metabolomics & mRNA data

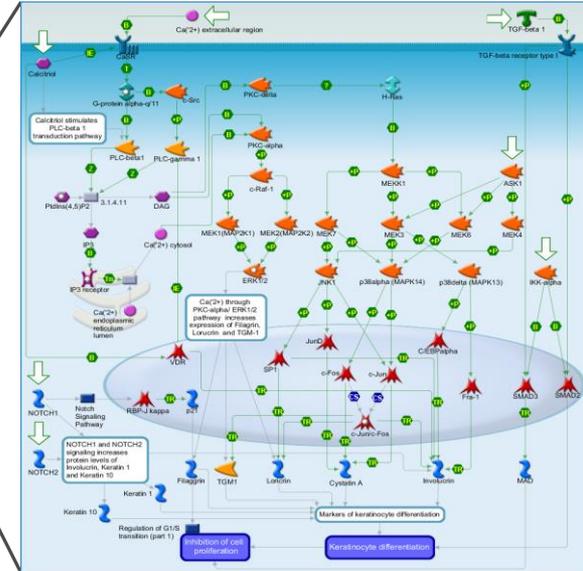
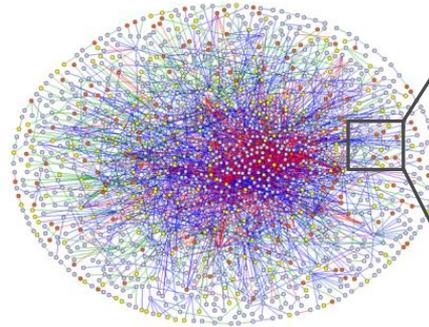
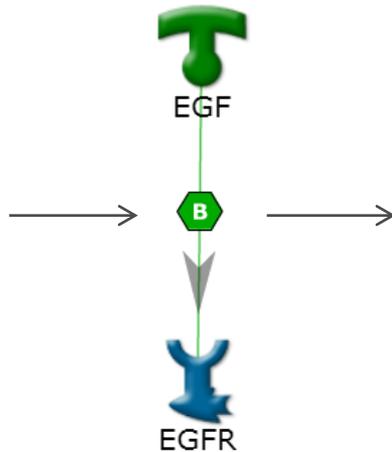
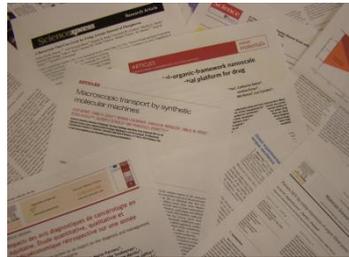


METACORE: YOUR GPS IN PATHWAY ANALYSIS



- Gain molecular understanding of disease
- Analyze and understand experimental findings (Omics data) in the context of validated biological pathways.
- Generate and confirm hypotheses for novel biomarkers, targets, mechanisms of action

FROM PEER REVIEWED ARTICLES TO SIGNALING PATHWAYS



PUBLICATIONS
(195 for EGF-EGFR interaction)

MOLECULAR INTERACTION

GLOBAL NETWORK:
~ 1,600,000
molecular interactions

~ 3,000 canonical and disease signaling pathways

- Manual annotation from publications
- Team of PhDs, MDs
- More than 10 years

WHAT'S IN AN INTERACTION?

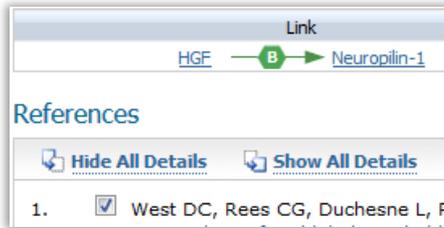
When you click



HGF
Network object |  B

Table of Contents

General



Link

HGF  Neuropilin-1

References

 Hide All Details  Show All Details

1. West DC, Rees CG, Duchesne L, P



Neuropilin-1
Network object |  Bu

Table of Contents

General

What you see

Icon of network object

Effect

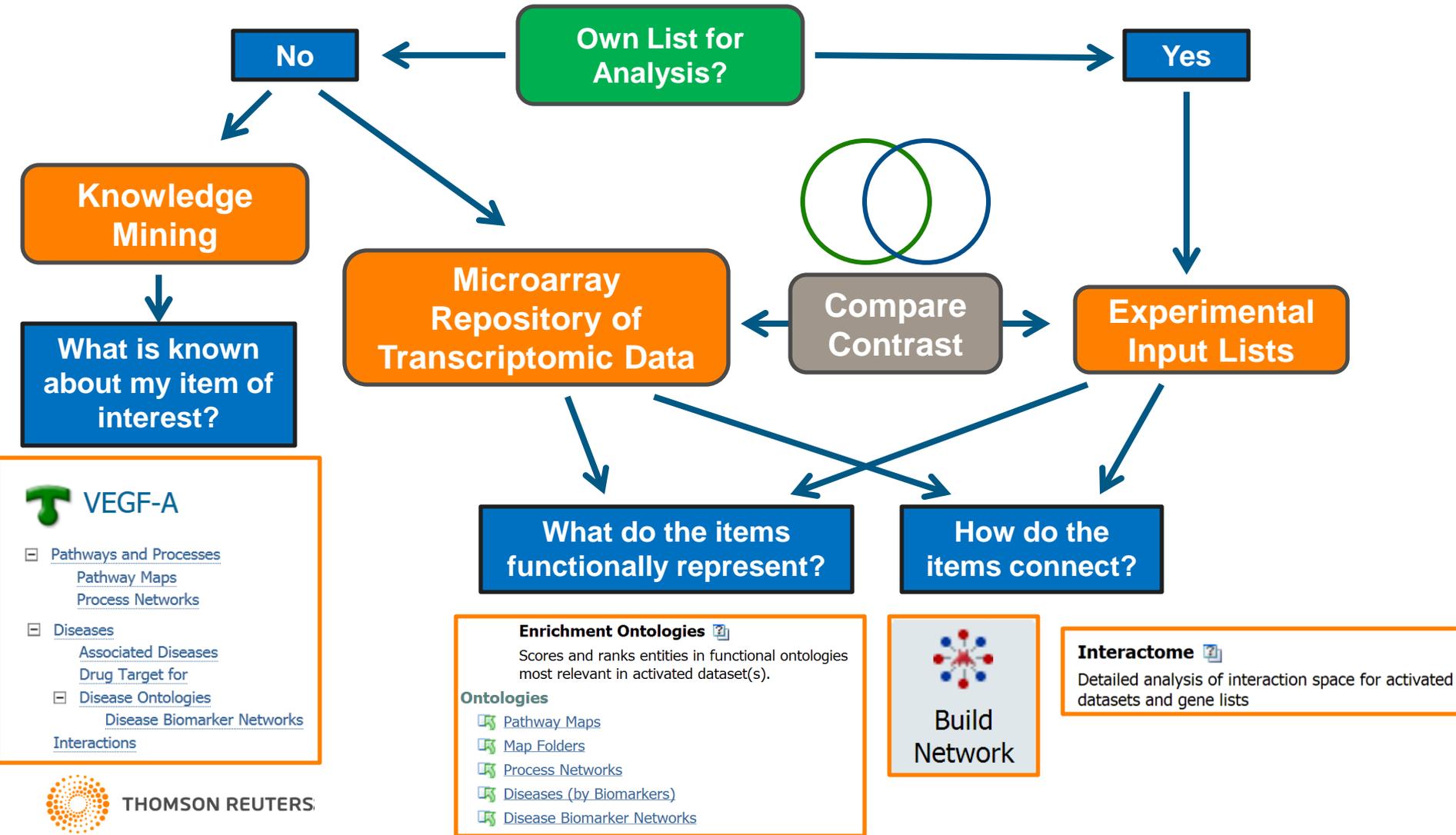
-**activating**
-**inhibiting**

Mechanism
-B=binding

Directionality

Neuropilin-1

WAYS TO APPROACH METACORE

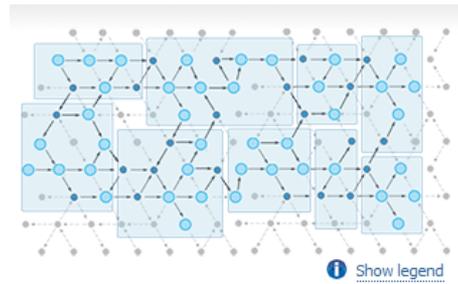


FLEXIBILITY IN DATA ANALYSIS TOOLS

11 Different Network Building Algorithms, all with written and visual descriptions

Choose building algorithm

- Analyze network
- Analyze network
- Analyze network (transcription factors)
- Analyze network (receptors)
- Transcription regulation
- Shortest paths
- Trace pathways
- Direct interactions
- Self regulation
- Auto expand
- Expand by one interaction
- Manual expand



Multiple automated Workflows to save, share and export



Data Analysis Workflows

A set of simple step-by-step wizards for analysis of your data.

- Enrichment Analysis
- Analyze Single Experiment
- Compare Experiments
- Compare Compounds
- Toxicity Analysis
- Biomarker Assessment
- Interactome Analysis

Causal reasoning algorithm to find key hubs

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METACORE KPA

GSE3744_Breast tumor vs Bulk normal breast(FC_5_pval_01) Download Report

Key Processes

39 key pathway maps

335 diseases (by biomarkers)

12 process networks

31 map folders

KEY PROCESSES - KEY PATHWAY MAPS

Pathway maps are graphic images representing complete biochemical pathways or signaling cascades in a commonly accepted sense. All maps listed below are enriched with both input genes and Key Hubs.

| # | Name | Input Objects p-value | Key Hubs p-value | Union Objects p-value | stacked | grouped |
|---|---|-----------------------|------------------|-----------------------|--------------------------|--------------------------|
| 1 | Cytoskeleton remodeling_TGF, WNT and cytoskeletal remodeling | 1.056E-5 | 1.121E-7 | 4.745E-13 | <input type="checkbox"/> | <input type="checkbox"/> |
| 2 | Cell cycle_Role of APC in cell cycle regulation | 1.785E-9 | 7.218E-5 | 1.353E-12 | <input type="checkbox"/> | <input type="checkbox"/> |
| 3 | Cell cycle_Initiation of mitosis | 2.073E-5 | 6.316E-8 | 1.497E-10 | <input type="checkbox"/> | <input type="checkbox"/> |
| 4 | Immune response_ETV3 affect on CSF1-promoted macrophage differentiation | 1.114E-3 | 1.769E-6 | 4.305E-9 | <input type="checkbox"/> | <input type="checkbox"/> |

But also One-Click analysis for instant answers



Enrichment Ontologies

- Pathway Maps
- Map Folders
- Process Networks
- Diseases (by Biomarkers)
- Disease Biomarker Networks
- Drug Target Networks
- Toxic Pathologies
- Drug and Xenobiotic Metabolism Enzymes
- Toxicity Networks
- Metabolic Networks
- Metabolic Networks (Endogenous)

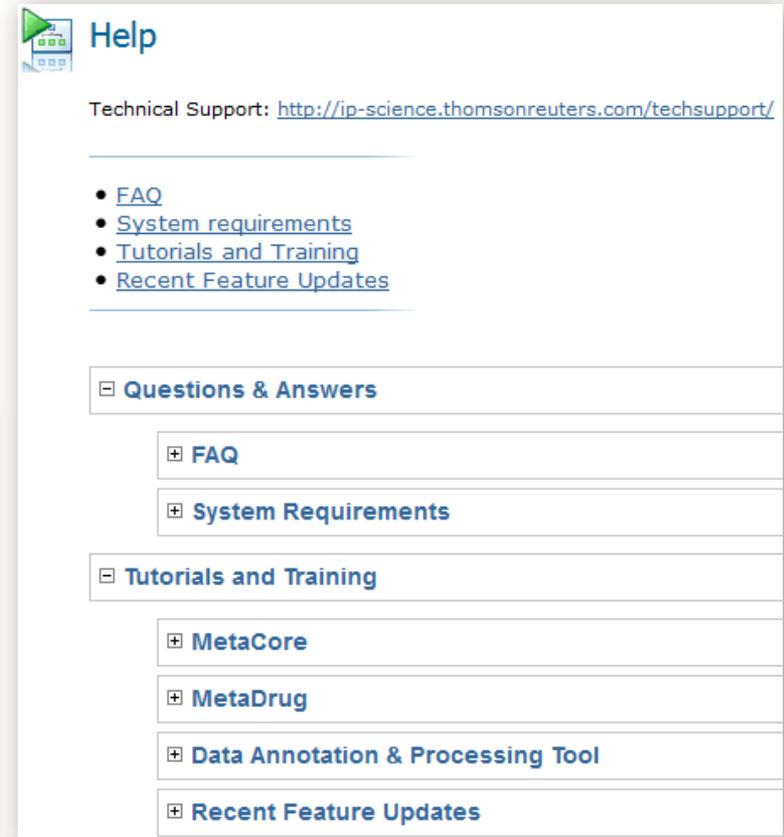
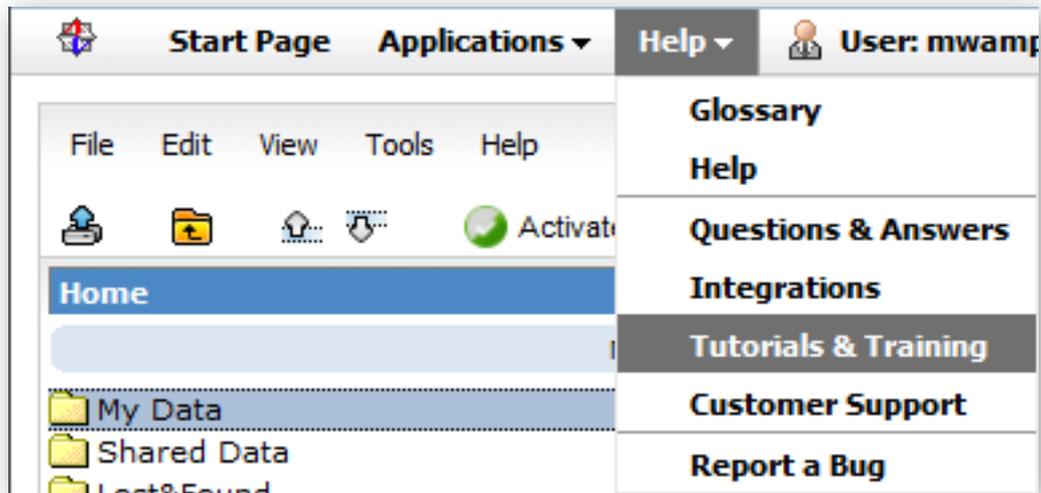
Interactome

- Interactions by Protein Function
 - Transcription Factors
 - Significant Interactions Within Set(s)
 - Interactome Topology
 - Enrichment by Protein Function
 - Interactions Between Datasets (all)
 - Interactions Between Datasets (TR)
 - Drug Lookup for Your Gene Lists and Datasets
- Microarray Repository**
- Similarity search by Genes
 - Similarity search by Functional Descriptors

GETTING SUPPORT

Technical Support & questions:
sbsupport@thomsonreuters.com

Monthly Training webinar recordings
available at:
www.lsresearch.thomsonreuters.com
(in the Knowledge section)



PUBLISHING WITH METACORE

1. Make sure to cite “Thomson Reuters MetaCore”
2. Include the version and build found at the bottom left corner of MetaCore `MetaCore+MetaDrug™ version 6.24 build 67895`

*important because the database is updated every quarter

3. Ensure reproducibility by detailing the steps you take:
 1. What background did you use?
 2. Did you apply some filter?
 3. Did you change the order of how you sorted the results?
4. You can export images and graphs to use in your papers and presentation!

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KNOWLEDGE MINING MANUALLY CURATED CONTENT FROM PEER REVIEWED SOURCES

EZ search

Advanced Search

Objects Found

- Genes (110)
- Gene Aberrations (26411)
- Proteins (589)
- RNA (682)
- Network Objects (75)
- Interactions (305)
- Diseases (6)**
- Drugs (302)
 - Small Molecule Drugs (255)
 - Biologics (47)
- Potential Disease Biomarkers (7730)
- Maps (160)
- Reactions (1)

Conditional Search. Choose a query and click "Search".

Find Alterations and Aberrations (RNA Level) with increased level or with decreased level that are associated with Diseases Breast Neoplasms ... with increased level or with decreased level and are associated with Diseases Melanoma ...

Find:

- **Question:**

- What can I learn about genes being overly expressed in breast cancer?
- What RNA has a change in abundance in both breast cancer and melanoma?

EZ SEARCH FOR INFORMATION RELATED TO BREAST CANCER

Start Page Applications Help User: mwampolemc

breast cancer Search Advanced Search

File Edit View Tools Help

Genomic Analysis Most Popular Questions Upload Workflows & Reports One-click Analysis Build Network

EZ Search

Name: breast cancer Search Exact match

Objects Found

- Genes (110)
- Gene Aberrations (26411)
- Proteins (589)
- RNA (682)
- Network Objects (75)
- Interactions (305)
- Diseases (6)
- Drugs (302)

Selected Diseases

Results

Show tree with all diseases

Disease Details

- Hereditary breast cancer**
Synonyms: Hereditary breast cancer
- Breast Neoplasms**
Mesh Reference: D001943
Synonyms: Breast Cancer, Breast Carcinoma, Breast Cancer
- Inflammatory Breast Neoplasms**
Mesh Reference: D058922
Synonyms: Breast Cancer, Inflammatory, Breast Cancer

Breast Neoplasms

Disease Export Build Network Include Subfolders Show low trust content

Table of Contents

- Summary
- Causal Associations (by Gene)
- Causal Associations (Endogenous Compounds)
- Drugs & Therapeutic Agents
- Pathway Maps

Summary

Description

Tumors or cancer of the human BREAST.

Entry Terms

Breast Neoplasms; Breast Cancer; Breast Carcinoma; Breast Neoplasm; Cancer of Breast; Cancer of the Breast; Cancer, Breast; Carcinoma, Human Mammary; Human Mammary Carcinoma; Human Mammary Carcinomas, Human Mammary; Human Mammary Neoplasms; Malignant Neoplasms, Human Mammary; Mammary Carcinoma, Human; Mammary Carcinomas, Human; Mammary Neoplasms, Human; Neoplasm, Breast; Neoplasm, Human Mammary; Tumor, Breast; Tumors, Breast

External Databases

| | |
|------|--------------------------------|
| Mesh | D001943 |
| OMIM | 113705, 114480, 600048, 605365 |

WHAT CAN I LEARN ABOUT GENES BEING OVERLY EXPRESSED IN BREAST CANCER?

Causal Associations (by Gene)

Search: 1/4

Result pages: 1 * 6 7 8 9 10 * 168 (Showing results 141 to 160 of 334)

| # | Gene | Alteration Level | Alteration Type | Alteration Subtype | Details | Abundance | Activity/Gain/Loss of Function | Normal/Pathology Concentration | Subcellular Localization Change | Organ/Tissue Distribution | Disease | Info |
|-----|-----------------------|------------------|-----------------|----------------------|---------------------------------------|-----------------------|--------------------------------|--|---------------------------------|---|--|------|
| 156 | ESR1 | Protein level | Protein | | ESR1_HUMAN | up, Indifferent, down | | 0.07074±0.06045 → 0.0856±0.06719 ug/L, 0.012±0.0083 → 0.0203±0.0116 ug/kg | | Serum, Skin, Lung, Bone and Bones, Prostate, Stromal Cells, Mammary Glands, Human, Breast, Mucous Membrane, Liver, Gastric Mucosa | Hereditary breast cancer , Inflammatory Breast Neoplasms , Carcinoma, Ductal, Breast , Breast Neoplasms , Male, Breast Neoplasms | |
| 157 | STAT3 | Protein level | Phosphorylation | | STAT3 (HUMAN) Ph_Y705 | up | | | | Mammary Glands, Human | Breast Neoplasms | |
| 158 | CTLA4 | Protein level | Isoform | Alternative splicing | CTLA4_HUMAN_2 | up | | 7.69±4.04 → 23.53±14.96 ug/L | | Serum | Breast Neoplasms | |

Breast Neoplasms

Disease | [Export](#)

Table of Contents

- [Summary](#)
- [Causal Associations \(by Gene\)](#)
- [Causal Associations \(Endogenous Compounds\)](#)
- [Drugs & Therapeutic Agents](#)
- [Pathway Maps](#)

- CTLA-4 expression changes have been seen in blood and tissue of patients
- CTLA-4 protein abundance has seen an increase in serum from patients

USE ADVANCED SEARCH TO FIND GENES ASSOCIATED WITH TWO DISEASE

[Advanced Search](#)
1

Find Alterations and Aberrations (RNA Level) with increased level or with decreased level that are associated with Diseases Breast Neoplasms ... with increased level or with decreased level and are associated with Diseases Melanoma ...

2

Find: that + that

Include Subfold...

Conversion "are associated with"

Abundance: Up Down Indifferent

Activity/Gain/Loss of Functions: Up Down Indifferent Unknown

Subcellular localization change: From: To:

| # | Gene Name | Type | Abundance | Activity/Gain/Loss of Funct... | Pathology |
|----|--------------------------------|------------|--------------------|--------------------------------|---|
| 29 | PROX1 PROX1_(HUMAN)_transcript | Mature RNA | indifferent;down;u | down;up | Carcinoma, L Neoplasms;C |
| 30 | ERBB3 ERBB3_(HUMAN)_transcript | Mature RNA | indifferent;down;u | down;up | Glioblastoma Neoplasms;M Ductal;Endor Breast;Menir |
| 31 | VEGFC VEGFC_(HUMAN)_transcript | Mature RNA | indifferent;down;u | down;up | Glioblastoma Acute;Neuro Carcinoma, F |

LIVE DEMO: DATASET

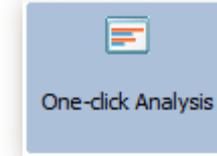
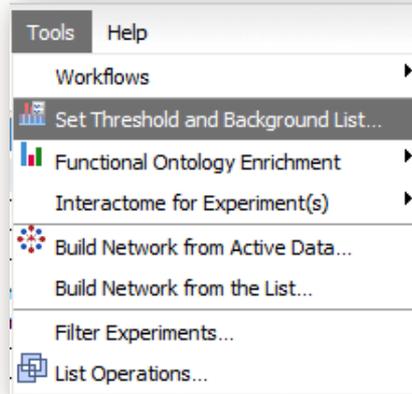
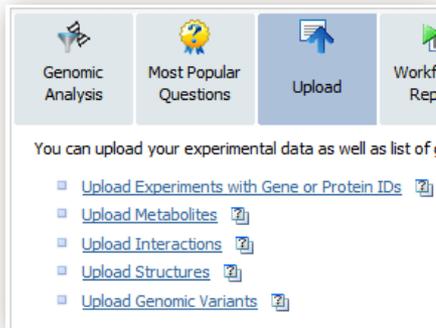
- GSE36765 – Gene expression profiling of CD4+ T cells infiltrating human breast cancer (Discovery Set).
 - Affy/HG-U133_Plus_2
 - Fold change: ≤ -5 or ≥ 5
 - FDR P-value: 0.05
 - Two groups of patients:
 - Breast Tumor CD4+ T-Lymph high infil vs. Patient PB CD4+ T-Lymph high infil. (730 DEGs)
 - Breast Tumor CD4+ T-Lymph low infil vs. Patient PB CD4+ T-Lymph low infil. (778 DEGs)

CASE STUDY ON GENE EXPRESSION PROFILING OF CD4+ T CELLS INFILTRATING HUMAN BREAST CANCER

Upload dataset into MetaCore

Set Threshold/ Background

Analyse Map Folders



- Questions:
 - What overall process is impacted when comparing infiltrating vs. peripheral blood T-lymphocytes?
 - Are there particular pathways showing a difference between high and low infiltrating T-lymphocytes?

UPLOAD TRANSCRIPTOMIC DATA INTO METACORE

1

Genomic Analysis Most Popular Questions **Upload** Workflows & Reports One-click Analysis

You can upload your experimental data as well as list of genes/proteins/metabolites.

- Upload Experiments with Gene or Protein IDs
- Upload Metabolites
- Upload Interactions
- Upload Structures
- Upload Genomic Variants

2

Data Analysis Wizard (General parser)

Step 1

Click "browse" to select file(s) to upload:

Browse... Breast tumor CD4+ T-Lymph Low Infiltration Patients vs. PB CD4+ T-Lymph Low Infiltration Patients.txt

Data format

Warning: do not mix IDs in the same column.
Excel or plain text with tab separated fields formats are supported.

Warning: Currently, Excel 2007 files are not supported older Excel version.

The file has to be in the following format (Column order)

| | A | B | C |
|----|--------------|-------------|----------|
| 1 | AFFY_ID | Fold Change | P-Value |
| 2 | 1552398_a_at | -14.3471562 | 8.54E-05 |
| 3 | 1552797_s_at | 11.07757694 | 0.002814 |
| 4 | 1553434_at | 5.459498006 | 0.045019 |
| 5 | 1553602_at | 115.85537 | 0.025612 |
| 6 | 1553613_s_at | 19.86887452 | 0.000323 |
| 7 | 1553986_at | 14.02880884 | 0.000291 |
| 8 | 1554018_at | 16.6920076 | 0.008601 |
| 9 | 1554600_s_at | 5.360358331 | 0.003606 |
| 10 | 1555778_a_at | 22.14873322 | 0.013634 |

Next >>

3

Data Analysis Wizard (General parser)

Step 2

Only first 10 lines of your file are shown. Use horizontal scrolling if needed.
Use checkboxes against each row to specify table header lines

Specify the column types in your file:

File data

Experiments name prefix: Breast tumor CD4+ T-Lymph Low Infiltration Patients vs. PB CD4+ T-Lymph Low Infiltration Pat

| Type | Affymetrix tag IDs (expression) | Fold-change | P-value |
|-------------------------------------|---------------------------------|--------------|-------------|
| Name | AFFY_ID | Fold Change | P-Value |
| <input checked="" type="checkbox"/> | AFFY_ID | Fold Change | P-Value |
| <input type="checkbox"/> | 1552398_a_at | -14.34715623 | 8.54E-05 |
| <input type="checkbox"/> | 1552797_s_at | 11.07757694 | 0.002813681 |
| <input type="checkbox"/> | 1553434_at | 5.459498006 | 0.04501873 |

<< Back Next >>

4

Data Analysis Wizard (General parser)

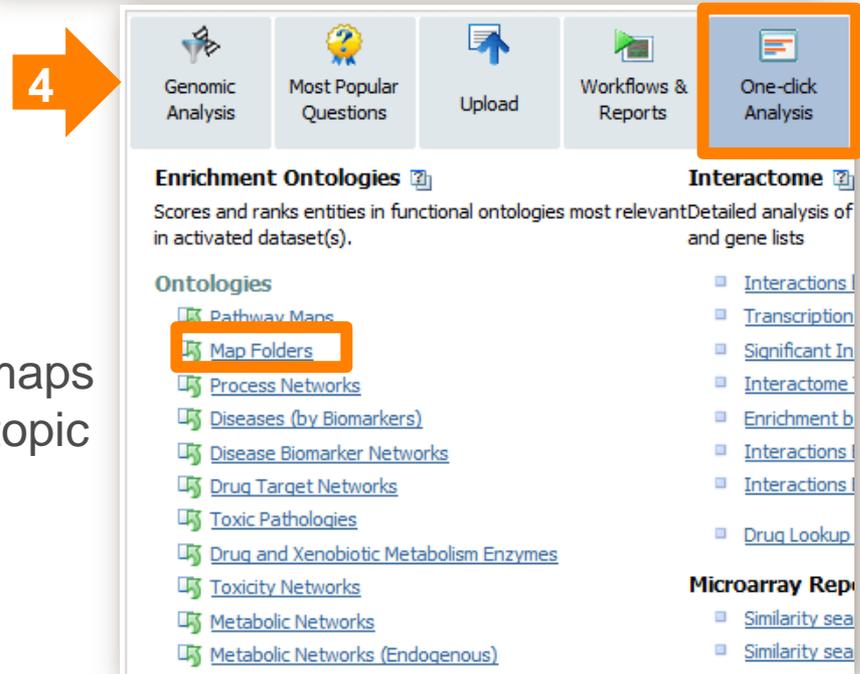
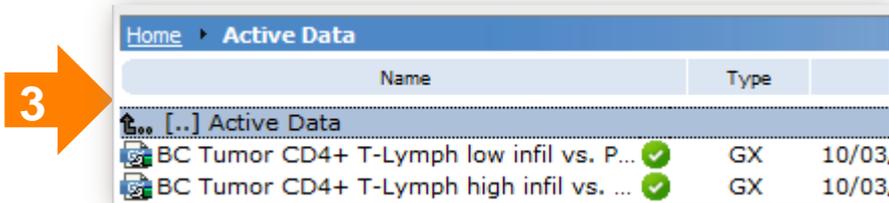
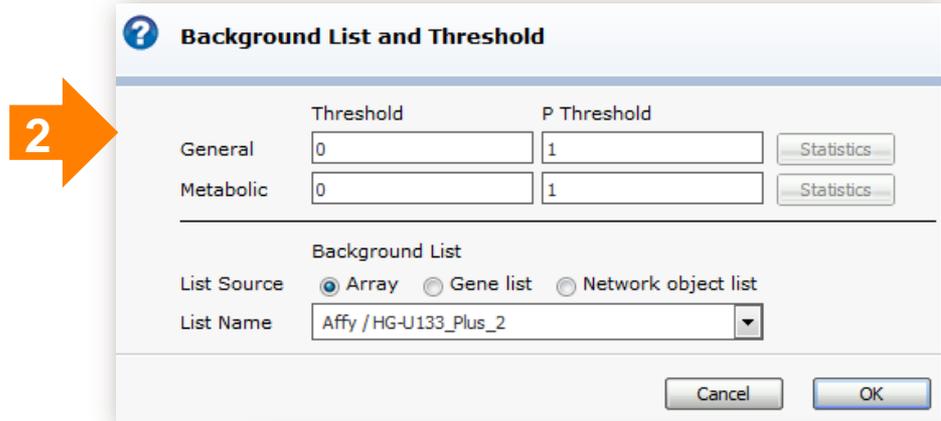
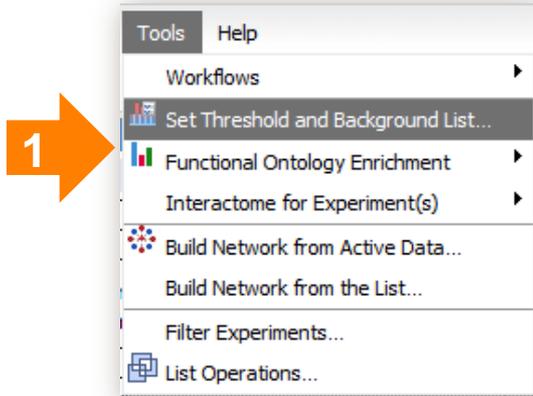
Step 3

Species

Choose species: Homo sapiens

<< Back Next >>

SET THRESHOLD/BACKGROUND AND RUN MAP FOLDER ANALYSIS



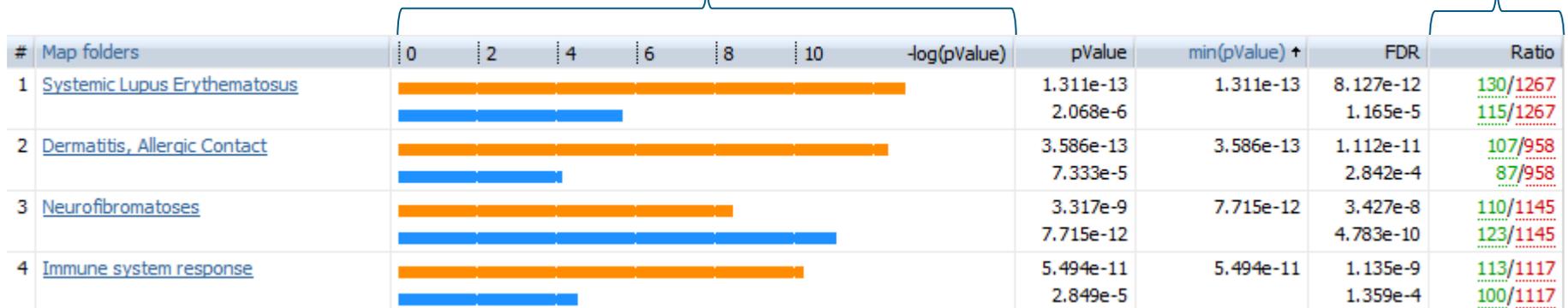
Map Folders are a collection of pathway maps grouped together under one overarching topic such as 'Immune System Response' or 'Breast Neoplasms'

WHAT OVERALL PROCESS IS IMPACTED WHEN COMPARING INFILTRATING VS. PERIPHERAL BLOOD T-LYMPHOCYTES?

| Experiment name | Species | Network Objects |
|---|--------------|-----------------|
| Breast tumor CD4+ T-Lymph High Infiltration Patients vs. PB CD4+ T-Lymph High Infiltration Patients | Homo sapiens | 692 |
| Breast tumor CD4+ T-Lymph Low Infiltration Patients vs. PB CD4+ T-Lymph Low Infiltration Patients | Homo sapiens | 757 |

Ratio of differentially expressed genes from dataset (GREEN) over all network objects in folder (RED)

Graphical representation of $-\log(p\text{Value})$



Map folder name

Significance of overlap of differentially expressed genes in the folder

- Top 3/4 hits are related to immune disease or the immune system processes.
- Marked difference in the presence of differentially expressed genes between low and high infiltrating T-lymphocytes

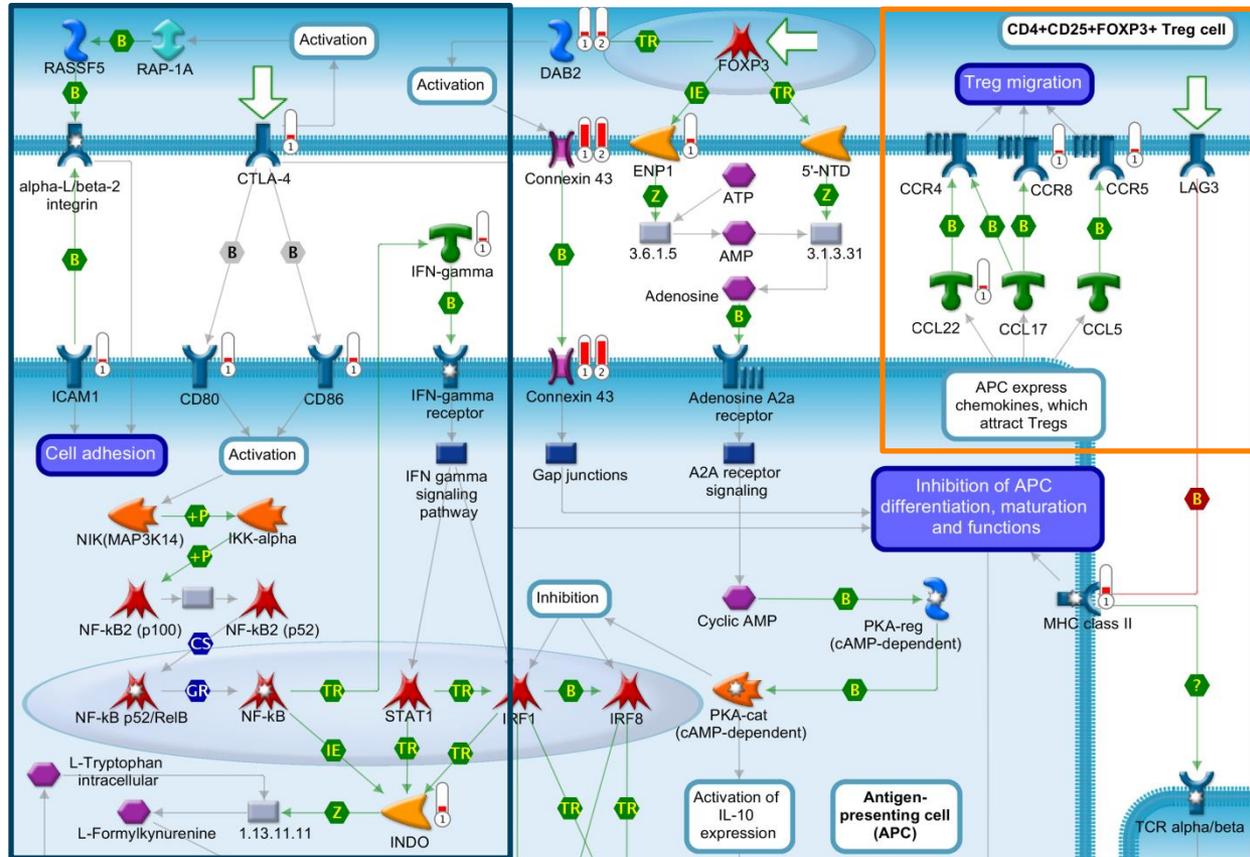
ARE THERE PARTICULAR PATHWAYS SHOWING A DIFFERENCE BETWEEN HIGH AND LOW INFILTRATING T-LYMPHOCYTES?

| Experiment name | Species | Network Objects |
|---|--------------|-----------------|
| <input checked="" type="checkbox"/> Breast tumor CD4+ T-Lymph High Infiltration Patients vs. PB CD4+ T-Lymph High Infiltration Patients | Homo sapiens | 692 |
| <input checked="" type="checkbox"/> Breast tumor CD4+ T-Lymph Low Infiltration Patients vs. PB CD4+ T-Lymph Low Infiltration Patients | Homo sapiens | 757 |

Immune Response T regulatory cell-mediated modulation of antigen-presenting cell functions

CTLA-4 activation of CD80 and CD86 can lead to the expression of IFN-gamma and INDO which can lead to Th1 cell apoptosis.

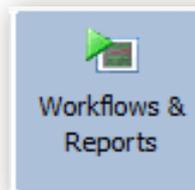
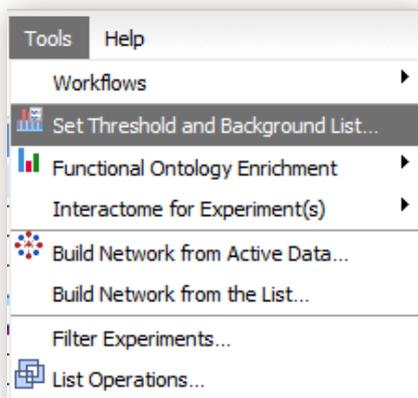
Increased expression of receptors (CCR8 & CCR5) and ligand (CCL22) for T_{reg} migration is seen in high infiltrating T-lymphocytes.



COMPARING TWO DATASETS WITH COMPARE EXPERIMENTS

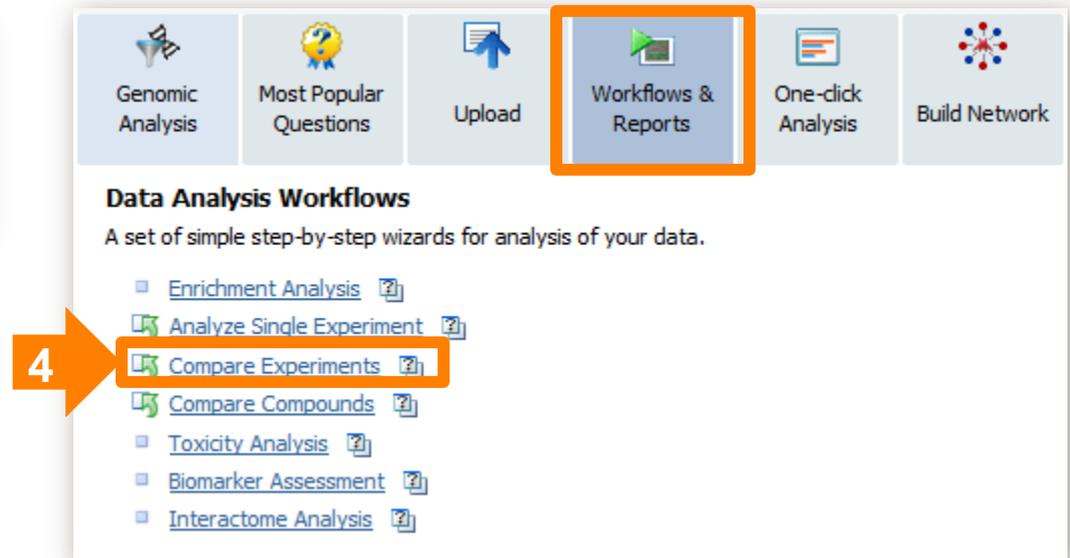
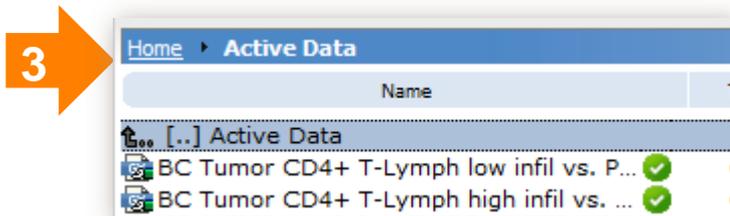
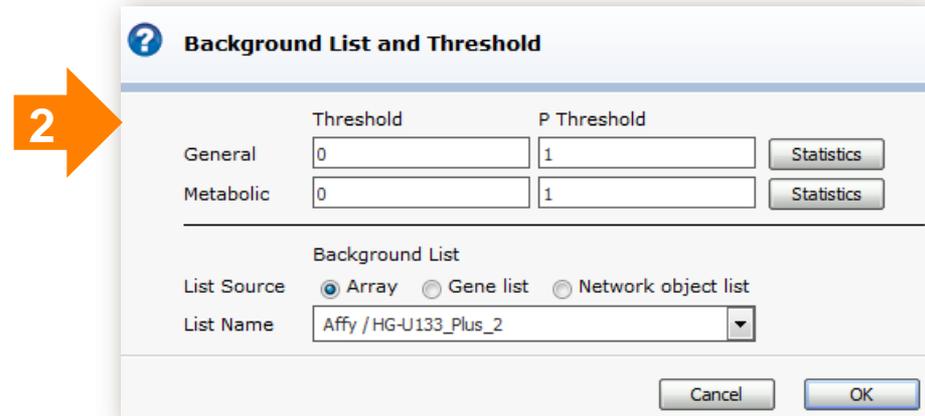
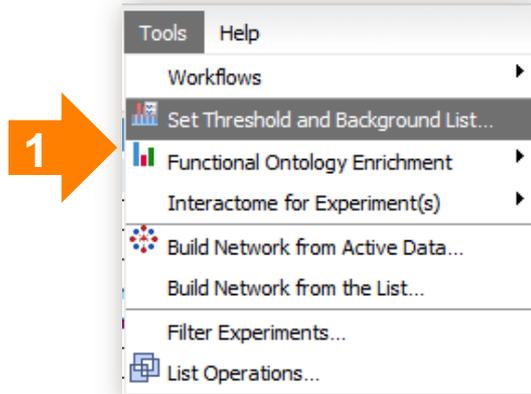
Set Threshold/
Background

Compare Experiments
Workflow



- Question:
 - What pathways and processes are commonly affected by high and low infiltrating T-lymphocytes?

SET THRESHOLD/BACKGROUND AND RUN COMPARE EXPERIMENTS WORKFLOW

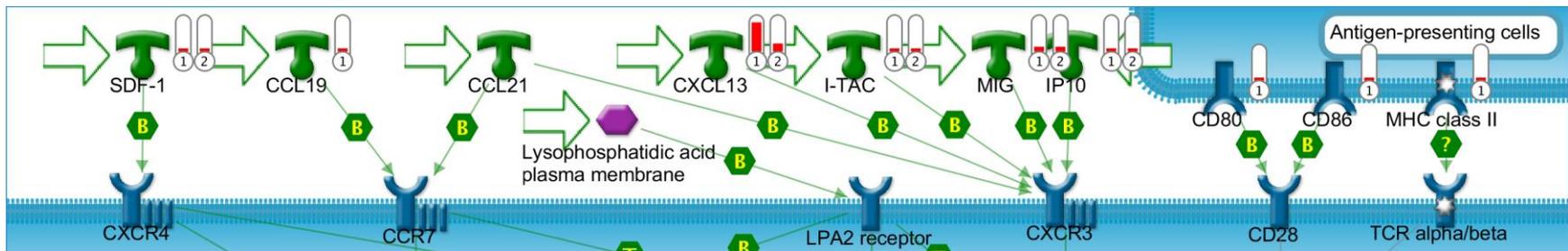


WHAT PATHWAYS ARE COMMONLY AFFECTED BY HIGH AND LOW INFILTRATING T-LYMPHOCYTES?

| <input checked="" type="checkbox"/> | Experiment name | Species | Network Objects |
|-------------------------------------|---|--------------|-----------------|
| <input checked="" type="checkbox"/> | Breast tumor CD4+ T-Lymph High Infiltration Patients vs. PB CD4+ T-Lymph High Infiltration Patients | Homo sapiens | 692 |
| <input checked="" type="checkbox"/> | Breast tumor CD4+ T-Lymph Low Infiltration Patients vs. PB CD4+ T-Lymph Low Infiltration Patients | Homo sapiens | 757 |



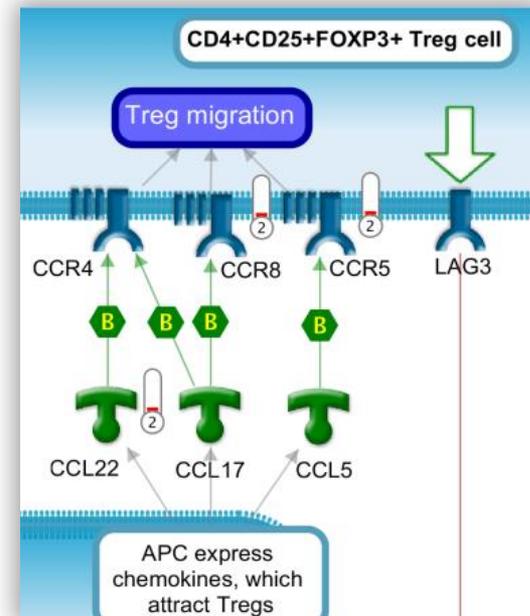
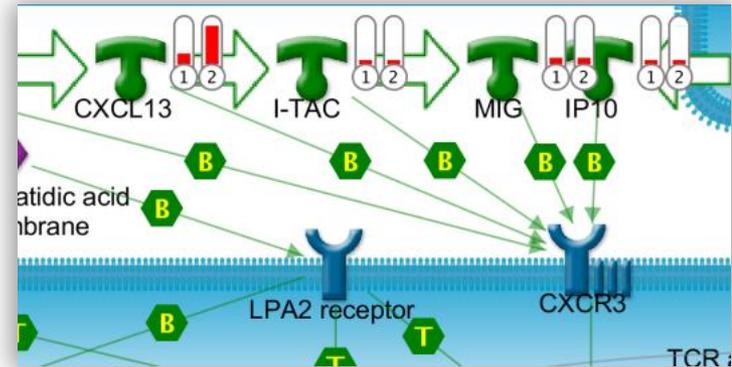
Chemotaxis Leukocyte chemotaxis



- Leukocyte chemotaxis had additional genes unique the highly infiltrating T-lymphocytes.
- CXCL13 has a far higher increase in expression related to highly infiltrating T-lymphocytes.

SUMMARY

- CXCL13 is highly expressed by the CD4+ T-lymphocytes in the patients with high infiltration could be an interesting biomarker to look into.
- A number of receptors and ligands important for T_{reg} migration have been up-regulated in CD4+ T-lymphocytes highly infiltrating breast cancer tumors.



LUNCH BREAK

RETURN @ 1:30PM

AGENDA

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 - 45-60 min – Multi-omics analysis with Metabolomics & mRNA data



KEY PATHWAY ADVISOR

Hypothesizing key hubs using
the causal reasoning algorithm

Key Pathway Advisor (KPA) Features

Comprehensive Pathway Analysis

Differential expression is an *effect* rather than *cause* of disease. *Causal Network Analysis* identifies upstream molecules of DEGs to predict the causes of biological deregulation.

Synergy Pathway Analysis automatically defines processes and pathway maps equally enriched with both experimentally defined and predicted Key Hubs gene sets in order to show connected biologically relevant results.

Integrated OMICs Data Analysis

KPA allows analyzing of gene expression analysis and associated gene variant data. Use *MetaCore Genomic Analysis Tools* to annotate your experimentally defined Gene Variant list and narrow it down to the list of the most promising protein function impact variants.

Resulting list could be uploaded into KPA with expression data in order to identify pathway impact and hypothesize about gain and loss of function effect.

One-Click Analysis

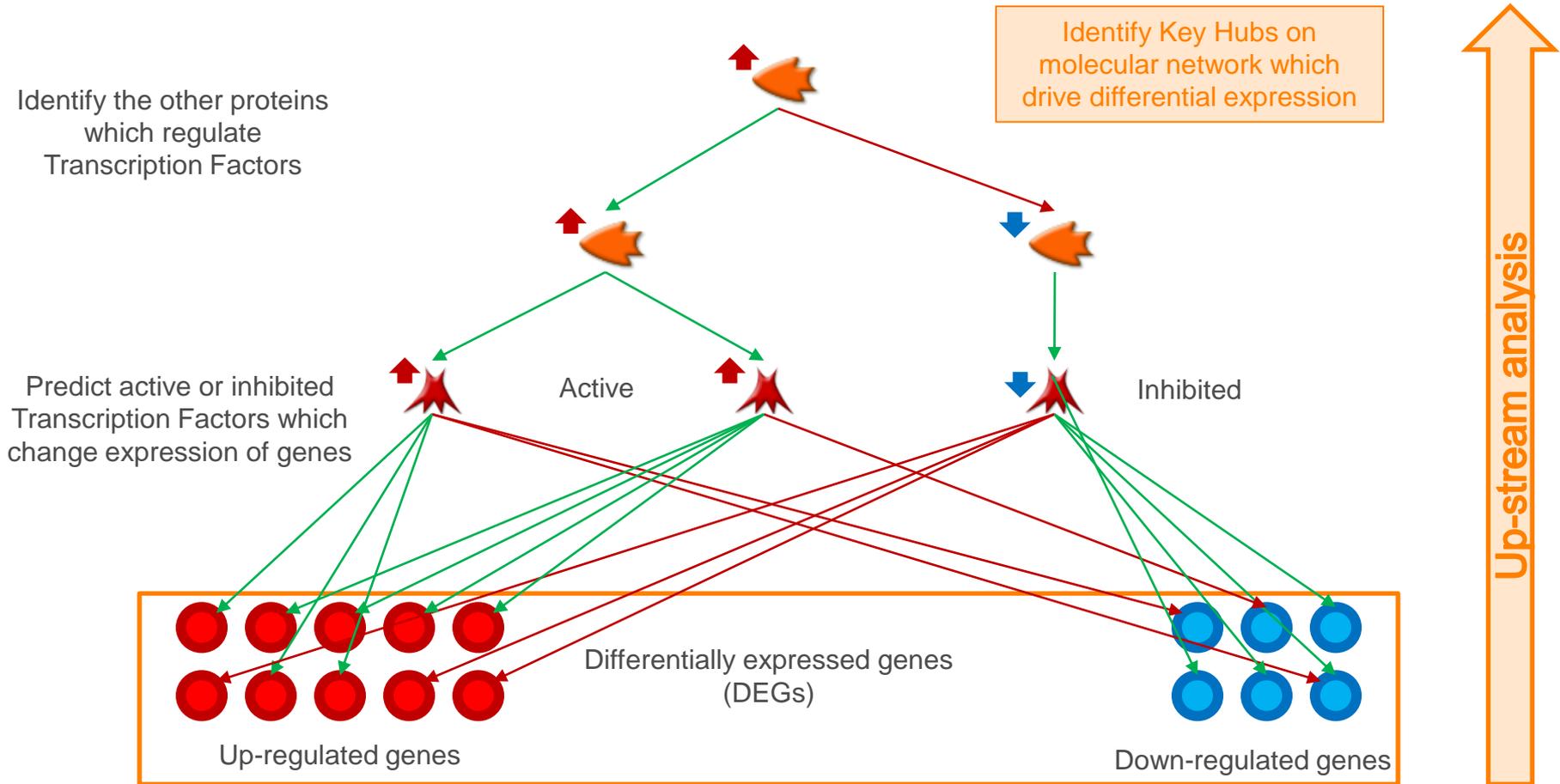
KPA has a simple and intuitive interface. Import your data into analysis and apply default analytical parameters – a whole comprehensive workflow will be calculated on the background showing all results in structured reports.

Study predicted Key Hubs: Identify driver genes and their activity change that regulate differential expression and/or have gene variants – candidate drug targets.

Get better biological understanding analyzing pathway maps enriched by DEGs, Gene Variants and predicted Key Hubs activity change.



CAUSAL REASONING EXPRESSION ANALYSIS



1. Chindelevitch L, Ziemek D, Enayetallah A, Randhawa R, Sidders B, et al. (2012) Causal reasoning on biological networks: interpreting transcriptional changes. *Bioinformatics* 28: 1114-1121.
2. Pollard J Jr, Butte AJ, Hoberman S, Joshi M, Levy J, Pappo J. (2005) A computational model to define the molecular causes of type 2 diabetes mellitus. *Diabetes Technol Ther.* 2005 Apr;7(2):323-36.

HOW TO UPLOAD A DATASET INTO THE KEY PATHWAY ADVISOR

Format and upload data

Choose settings

Analyse and explore results

NEW ANALYSIS

1 | File Upload

2 | Analysis Settings

3 | Run Analysis

Unique genes for high inf...
Affymetrix IDs
Fold change, p-value



Edit File Settings

DRAG A GENE VARIANT FILE 

or

Select file to upload

Supported Formats
Tab-separated TXT, VCF and XLS/XLSX

(Optional)

Analysis Settings x

PROCESSES ONTOLOGIES

- Select all
- Key Pathway Maps
- Diseases (by Biomarkers)
- Process Networks
- Map Folders
- GO Localizations
- GO Processes
- GO Molecular Functions
- Toxicity Networks
- Metabolic Networks (Endogenous)
- Metabolic Networks
- Drug Target Networks (Drug Action Mechanisms)
- Disease Biomarker Networks

Advanced Settings v

SYNERGY ENRICHMENT RESULTS

P-value threshold

KEY HUBS ALGORITHM

Causal Reasoning v P-value threshold

Cancel Save changes

FILE UPLOADED

Once analysis has been completed, the notification will be sent to your email



FORMATTING AND UPLOADING DATA

You can use the same identifiers as in MetaCore

Keep column titles simple

P-values can be included but are not required

1

| | A | B | C |
|---|--------------|--------------|------------|
| 1 | AFFY ID | fold change | p-value |
| 2 | 1405_i_at | -1.981575999 | 0.02476869 |
| 3 | 1552302_at | 2.118812101 | 0.01729475 |
| 4 | 1552303_a_at | 1.908469521 | 0.017252 |
| 5 | 1552309_a_at | 13.04226067 | 2.65E-06 |
| 6 | 1552362_a_at | -2.264977411 | 0.03711153 |
| 7 | 1552370_at | 2.488421551 | 0.00316702 |

WELCOME TO KEY PATHWAY ADVISOR

NEW ANALYSIS

1 File Upload

2 Analysis Settings

3 Run Analysis

Unique genes for high inf...
Affymetrix IDs
Fold change, p-value

Edit File Settings

DRAG A GENE VARIANT FILE

or

Select file to upload

Supported Formats
Tab-separated TXT, VCF and XLS/XLSX

You can upload a gene variant file as an additional data overlay

Restart

3 Next

2

DRAG AND DROP YOUR GENE LIST/EXPRESSION FILE HERE

or

Select file to upload

Click here to find additional information on uploading data

ANALYSIS SETTINGS

Include additional ontologies for enrichment

Analysis Settings

PROCESSES ONTOLOGIES

Select all

Key Pathway Maps Toxicity Networks

Diseases (by Biomarkers) Metabolic Networks (Endogenous)

Process Networks Metabolic Networks

Map Folders Drug Target Networks (Drug Action Mechanisms)

GO Localizations Disease Biomarker Networks

GO Processes

GO Molecular Functions

Advanced Settings

SYNERGY ENRICHMENT RESULTS

P-value threshold

KEY HUBS ALGORITHM

Causal Reasoning

Cancel

2 | Analysis Settings

Report Name

Unique genes for high infiltrating T-Lymph

Prior Knowledge Data

Biomarkers Drug Targets

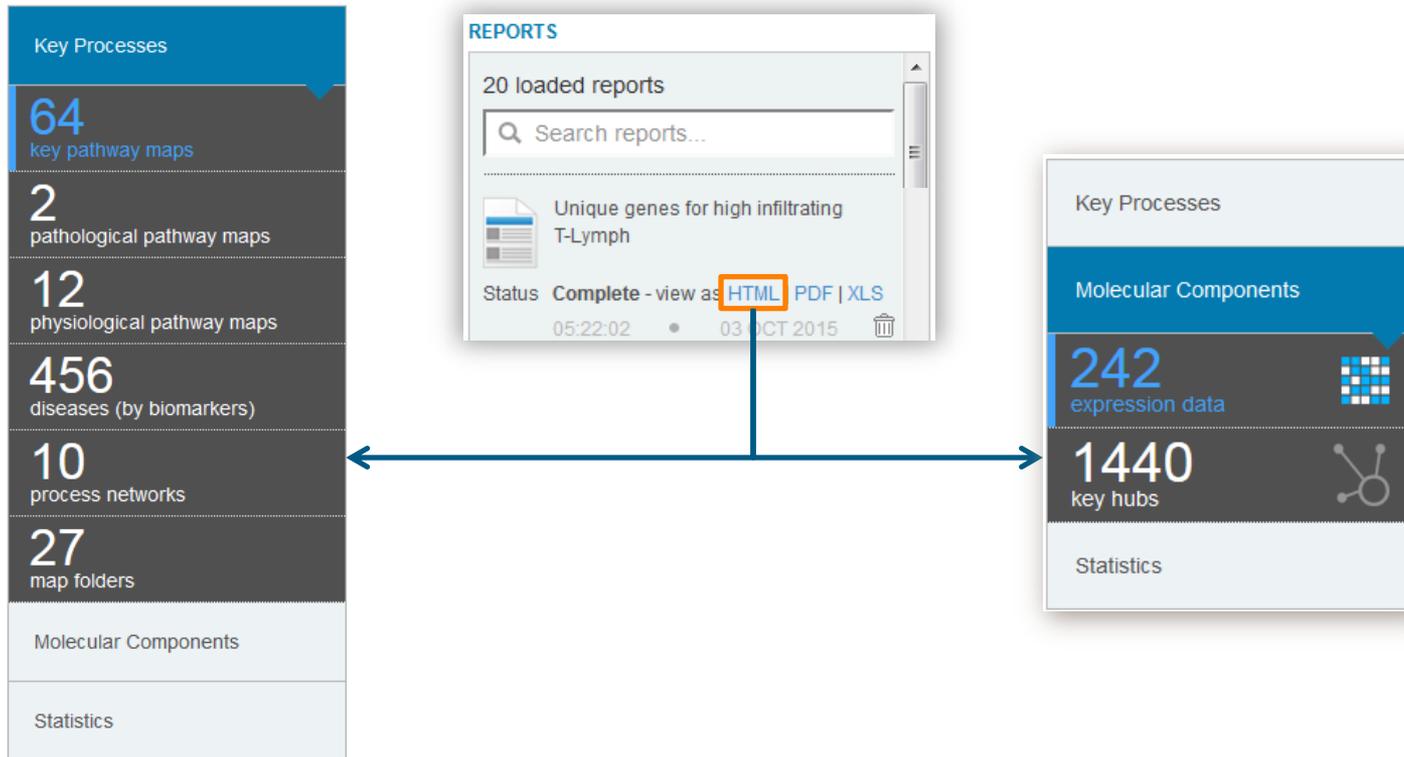
Default Processes Ontologies **NEW!**

- Key Pathway Maps
- Diseases (by Biomarkers)
- Process Networks
- Map Folders

[Edit Settings](#) | Use Default

Find overlap of results with information from curated literature

USE HTML INTERFACE TO EXPLORE RESULTS



- Question:

- What key pathways are linked with the unique differentially expressed genes from high infiltrating T-lymphocytes?

- Question:

- What direct and indirect regulators could be responsible for the unique gene signature for high infiltrating T-lymphocytes?

WHAT KEY PATHWAYS ARE LINKED WITH THE UNIQUE DIFFERENTIALLY EXPRESSED GENES IN HIGH INFILTRATING T-LYMPHOCYTES?

Unique genes for high infiltrating T-Lymph

Download Report

Key Processes

- 64 key pathway maps
- 2 pathological pathway maps
- 12 physiological pathway maps
- 456 diseases (by biomarkers)
- 10 process networks
- 27 map folders

KEY PATHWAY MAPS

Pathway maps are graphic images representing complete biochemical pathways or signaling cascades in a commonly accepted sense. All maps listed below are enriched with both input genes and Key Hubs. The enrichment analysis was done for whole set of pathway maps including physiological and pathological processes.

| # | Name | Input Objects p-value | Key Hubs p-value | Union Objects p-value | stacked <input type="checkbox"/> grouped <input checked="" type="checkbox"/> |
|---|---|-----------------------|------------------|-----------------------|--|
| 1 | Development_Cytokine-mediated regulation of megakaryopoiesis | 0.005264 | 1.363E-14 | 3.108E-16 | |
| 2 | Immune response_IL-22 signaling pathway | 7.681E-4 | 2.025E-13 | 5.072E-16 | |
| 3 | SLE genetic marker-specific pathways in T cells | 3.943E-6 | 5.004E-10 | 1.868E-15 | |
| 4 | Immune response_Role of PKR in stress-induced antiviral cell response | 0.005264 | 1.472E-13 | 3.726E-14 | |
| 5 | Immune response_Differentiation and clonal expansion of CD8+ T cells | 7.278E-6 | 5.429E-8 | 3.414E-13 | |
| 6 | Immune response_IL-12 signaling pathway | 0.00271 | 1.619E-10 | 2.683E-12 | |

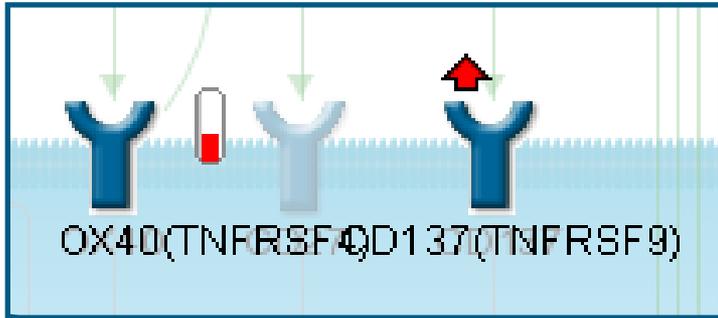
Enrichment p-value of differentially expressed genes

Enrichment p-value of key hubs

Enrichment p-value using union of key hubs and DEGs

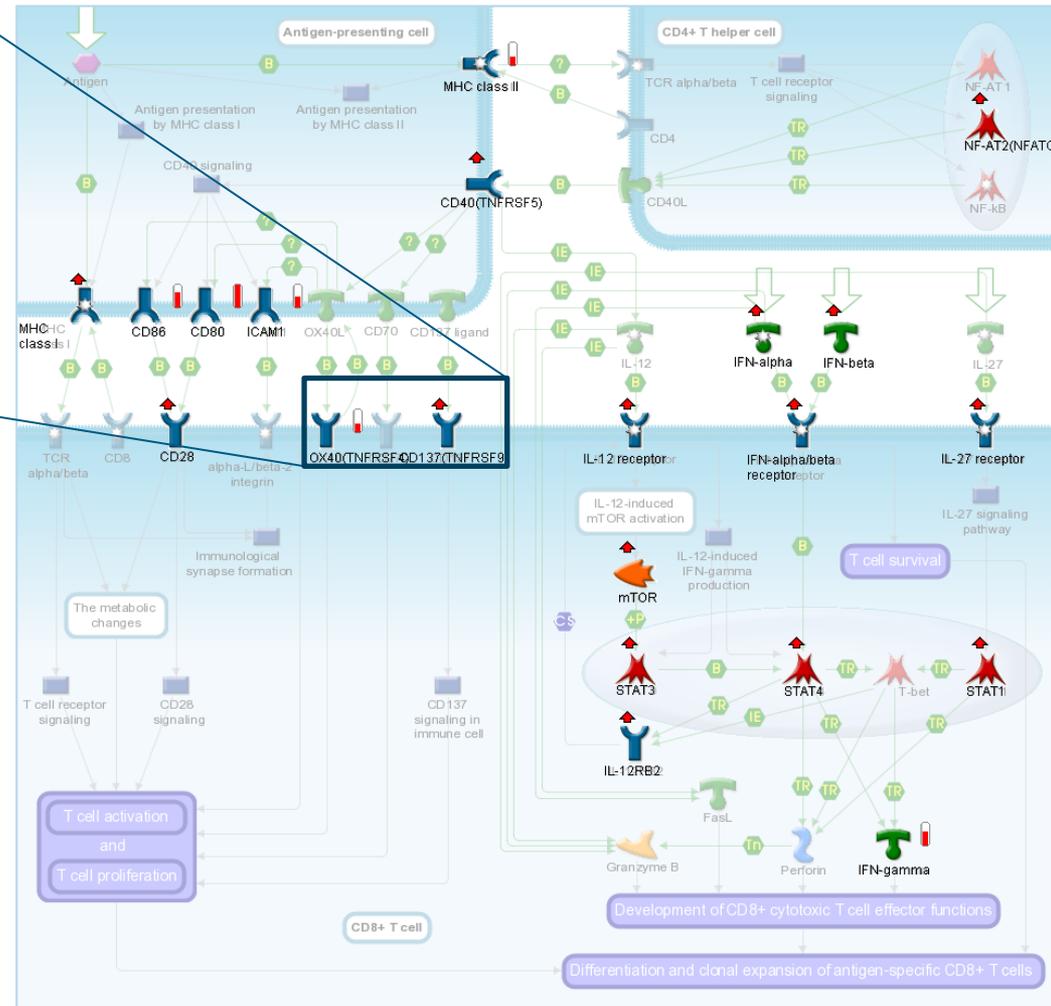
HOW IS THIS SIGNATURE IMPACTING CD8+ DIFFERENTIATION AND EXPANSION?

Immune Differentiation and clonal expansion of CD8+ T cells



OX40 is uniquely over-expressed in the highly infiltrating T-lymphocytes.

CD137 is predicted to have an increase in activity due to the gene signature



WHAT DIRECT OR INDIRECT REGULATORS COULD BE RESPONSIBLE FOR THE GENE SIGNATURE?

Unique genes for high infiltrating T-Lymph

Download Report

Key Processes

Molecular Components

242 expression data

1446 key hubs

Statistics

KEY HUBS

A list of network objects (proteins, protein complexes, miRNAs) that regulate expression of uploaded differentially expressed genes or molecules overconnected with the uploaded gene list.

| # | Network Object | Gene | Molecular Function | Activity | Correct/All prediction | p-value | Distance |
|---|----------------|---------|-------------------------|----------|------------------------|-----------|----------|
| 1 | MafK | MAFK | Transcription factor | ▲ | 90/101 | 7.118E-17 | 3 |
| 2 | MSK1 | RPS6KA5 | Protein kinase | ▲ | 85/97 | 5.216E-15 | 3 |
| 3 | LRP16 | MACROD1 | Generic binding protein | ▲ | 78/89 | 6.837E-14 | 3 |
| 4 | NIK(MAP3K14) | MAP3K14 | Protein kinase | ▲ | 80/93 | 3.112E-13 | 3 |
| | KIR2DL3 | KIR2DL3 | Generic receptor | ▼ | 29/33 | 5.464E-06 | 3 |
| | PD-1 | PDCD1 | Generic receptor | ▼ | 29/33 | 5.464E-06 | 3 |
| | CD137(TNFRSF9) | TNFRSF9 | Generic receptor | ▲ | 14/15 | 0.0004883 | 3 |

Indicates if a gene is being activated (+) or inhibited (-)

The correct number of DEGS at the specified distance from the key hub vs. all DEGs at that distance

significance of overlap between the correct and all predictions

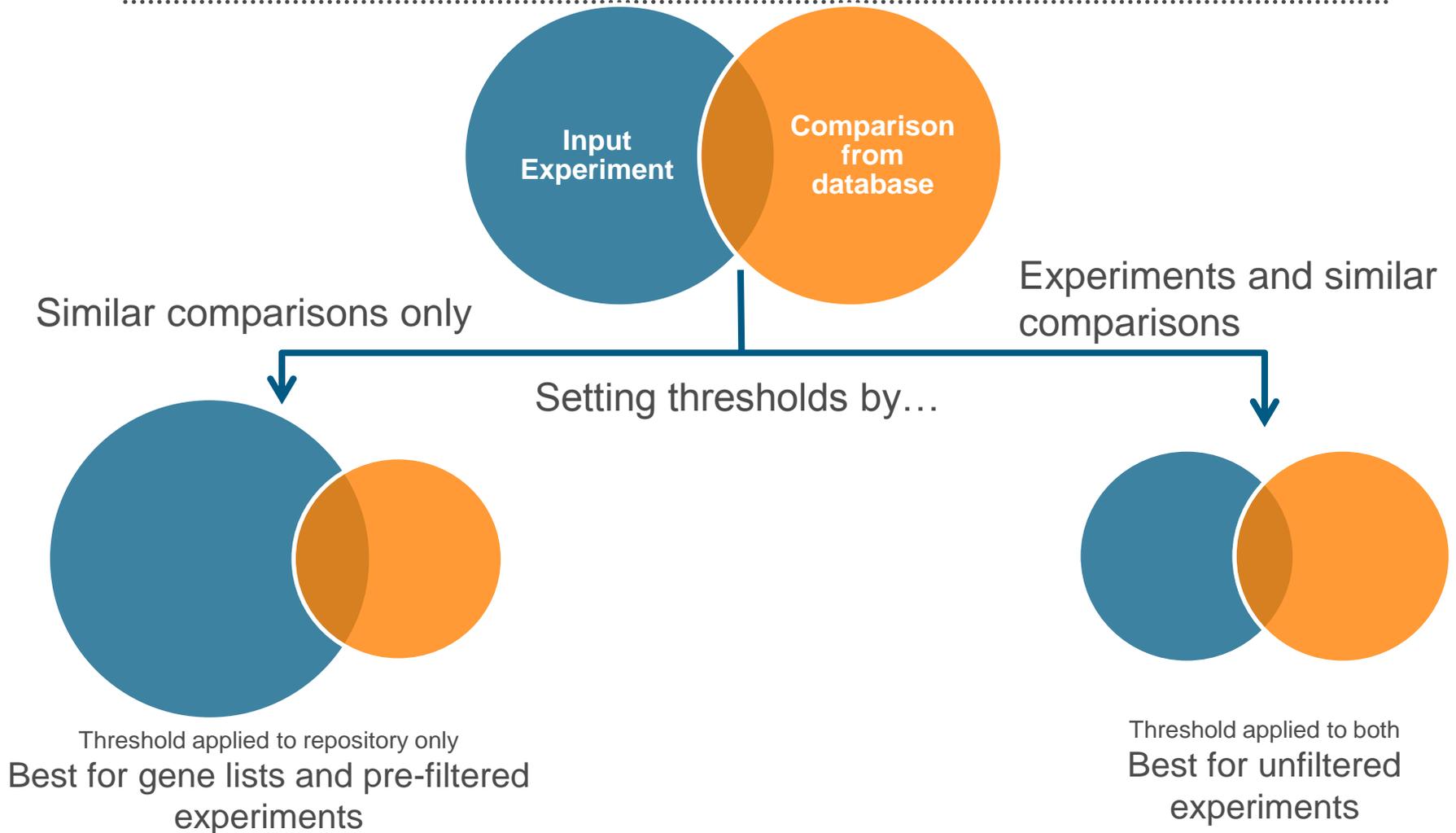
Distance of key hub from DEGs

Indicates key hub is also a DEG

MICROARRAY REPOSITORY

Using the Microarray repository
for gene comparisons against
public data

SIMILARITY SEARCH BY GENES



DATASET BACKGROUND

- Patients were recruited at Hospital Santa Creu i Sant Pau (Barcelona, Spain)
 - 15 patients diagnosed with ulcerative colitis
 - 13 patients diagnosed with Crohn's disease
 - 7 health controls
- Samples were taken by endoscopic pinch biopsies of macroscopically un-inflamed mucosa from the ascending colon.

Identification of Novel Predictor Classifiers for Inflammatory Bowel Disease by Gene Expression Profiling

Trinidad Montero-Meléndez, Xavier Llor, Esther García-Planella, Mauro Perretti, Antonio Suárez 

Published: October 14, 2013 • DOI: 10.1371/journal.pone.0076235



TRAINING DATASET

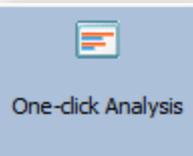
- GSE36807 – Genome-wide analysis of Crohn’s disease and ulcerative colitis biopsy samples.
 - Affymetrix Human Genome U133 Plus 2.0
 - Thresholds
 - Fold change: ≤ -2 or ≥ 2
 - P-value: 0.05 FDR adjusted
 - Comparison:
 - Ulcerative Colitis vs. Normal (772 Network Objects)

| Series GSE36807 | | Query DataSets for GSE36807 |
|-----------------|--|---|
| Status | Public on Sep 23, 2013 | |
| Title | Genome-wide analysis of Crohn's disease and ulcerative colitis biopsy samples. | |
| Organism | Homo sapiens | |
| Experiment type | Expression profiling by array | |
| Summary | Gene expression patterns of Crohn's disease (CD) and ulcerative colitis (UC) colonic specimens were analyzed using whole-genome microarrays. Healthy control samples were included in order to detect gene expression changes associated with CD or UC. CD and UC samples were also compared in order to identify the molecular mechanisms that distinguish both phenotypes of inflammatory bowel disease. | |

USE SIMILARITY SEARCH BY GENES TO FIND DATASETS WITH SIMILAR GENE SIGNATURES

Similarity Search by Genes

Export Similar Comparisons



Interactome [?](#)

Detailed analysis of interaction space for activated datasets and gene lists

- [Interactions by Protein Function](#)
- [Transcription Factors](#)
- [Significant Interactions Within Set\(s\)](#)
- [Interactome Topology](#)
- [Enrichment by Protein Function](#)
- [Interactions Between Datasets \(all\)](#)
- [Interactions Between Datasets \(TR\)](#)
- [Drug Lookup for Your Data](#) [?](#)

Microarray Repository [?](#)

- [Similarity search by Genes](#) [?](#)
- [Similarity search by Functional Descriptors](#) [?](#)

▼ Similar comparisons to experiments

| Export | |
|---|-----------------------|
| <input type="checkbox"/> Case Group | Control Group |
| <input type="checkbox"/> Ulcerative Colitis Colonic Mucosa, without Response to Infiximab Treatment, before Treatment | Normal Colonic Mucosa |
| <input type="checkbox"/> Ulcerative Colitis, Infiximab Treated, Resistant to Treatment | Normal Colon |
| <input type="checkbox"/> Active Ulcerative Colitis, Azathioprine Treatment | Normal Colon |
| <input type="checkbox"/> Crohn Disease Colonic Mucosa, without Response to Infiximab Treatment, before Treatment | Normal Colonic Mucosa |

- Question:
 - What datasets in the Microarray Repository have a similar gene signature to ulcerative colitis?

SET THRESHOLD/BACKGROUND AND RUN COMPARE EXPERIMENTS WORKFLOW

1

| Name | Type | |
|---|------|-----|
| [...] Active Data | | |
| Ulcerative Colitis Intestine vs. Normal ... | GX | 01/ |

2

One-click Analysis Build Network Custom Content Predict Compound Activity (MetaDrug)

Interactome

dataset(s). Detailed analysis of interaction space for activated datasets and gene lists

- Interactions by Protein Function
- Transcription Factors
- Significant Interactions Within Set(s)
- Interactome Topology
- Enrichment by Protein Function
- Interactions Between Datasets (all)
- Interactions Between Datasets (TR)
- Drug Lookup for Your Data

Microarray Repository

- Similarity search by Genes
- Similarity search by Functional Descriptors

3

Similarity search by Genes

Home Add/Remove

My Data Shared Data Lost&Found

Selected Data

| Name | Type | Date |
|---|------|---------------------|
| Ulcerative Colitis Intestine vs. Normal Intestine | GX | 01/28/2016 04:34:42 |

Next>>

4

Settings

Threshold: 4

P-value: 0.05

Signals: up, down, both

Similar comparisons only
 Experiments and similar comparisons

Apply

WHAT DATASETS IN THE MICROARRAY REPOSITORY HAVE A SIMILAR GENE SIGNATURE TO ULCERATIVE COLITIS?

▼ Similar comparisons to experiments

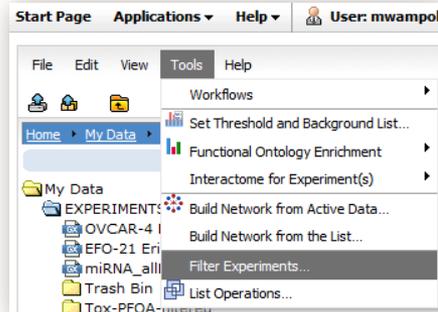
| Export | | | | | | |
|-------------------------------------|--|---|--------------|--------------|------------|------|
| <input type="checkbox"/> | Case Group | Control Group | Species | Gene Overlap | p-Value ↑ | View |
| <input type="checkbox"/> | Ulcerative Colitis Colonic Mucosa, without Response to Infiximab Treatment, before Treatment | Normal Colonic Mucosa | Homo sapiens | 304/785 | 0 | |
| <input type="checkbox"/> | Ulcerative Colitis, Infiximab Treated, Resistant to Treatment | Normal Colon | Homo sapiens | 295/775 | 0 | |
| <input type="checkbox"/> | Active Ulcerative Colitis, Azathioprine Treatment | Normal Colon | Homo sapiens | 284/570 | 0 | |
| <input type="checkbox"/> | Crohn Disease Colonic Mucosa, without Response to Infiximab Treatment, before Treatment | Normal Colonic Mucosa | Homo sapiens | 280/711 | 0 | |
| <input type="checkbox"/> | Active Ulcerative Colitis, Left-Sided Colitis | Normal Colon | Homo sapiens | 258/464 | 0 | |
| <input type="checkbox"/> | Active Ulcerative Colitis | Normal Colon | Homo sapiens | 252/450 | 0 | |
| <input type="checkbox"/> | Colorectal Cancer Leukocytes (CD45+ EpCAM-) | Colorectal Cancer Stromal Cells (CD45- EpCAM-) | Homo sapiens | 276/3022 | 2.842e-162 | |
| <input checked="" type="checkbox"/> | Stage II Colorectal Cancer | Normal Adjacent Colon to Stage II Colorectal Cancer | Homo sapiens | 163/667 | 7.15e-162 | |
| <input type="checkbox"/> | Anaplastic Thyroid Carcinoma | Nodular Goiter | Homo sapiens | 235/2065 | 4.854e-157 | |

- Lots of similar gene signatures with other ulcerative colitis datasets.
- To see what genes are similar between Stage II colorectal cancer and ulcerative colitis, begin by exporting the CRC data to your metacore account.

EXPORT RESULTS IN EXCEL FOR ANALYSIS OUTSIDE OF METACORE

Filter dataset

Compare Experiments Workflow



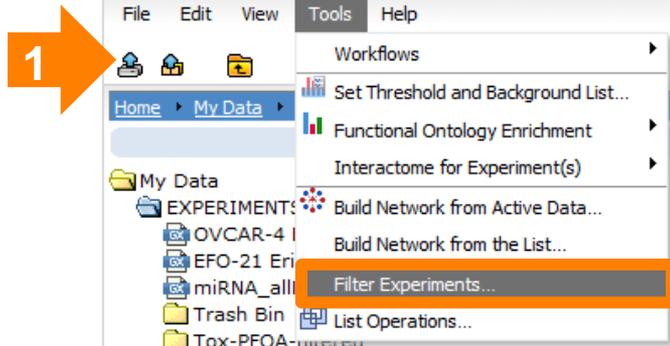
Data Analysis Workflows

A set of simple step-by-step wizards for analysis of your data.

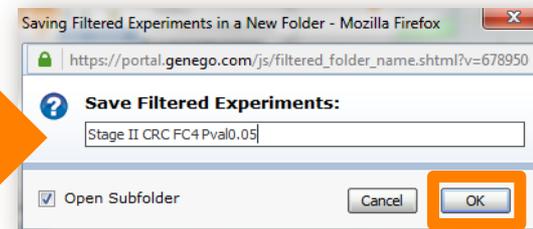
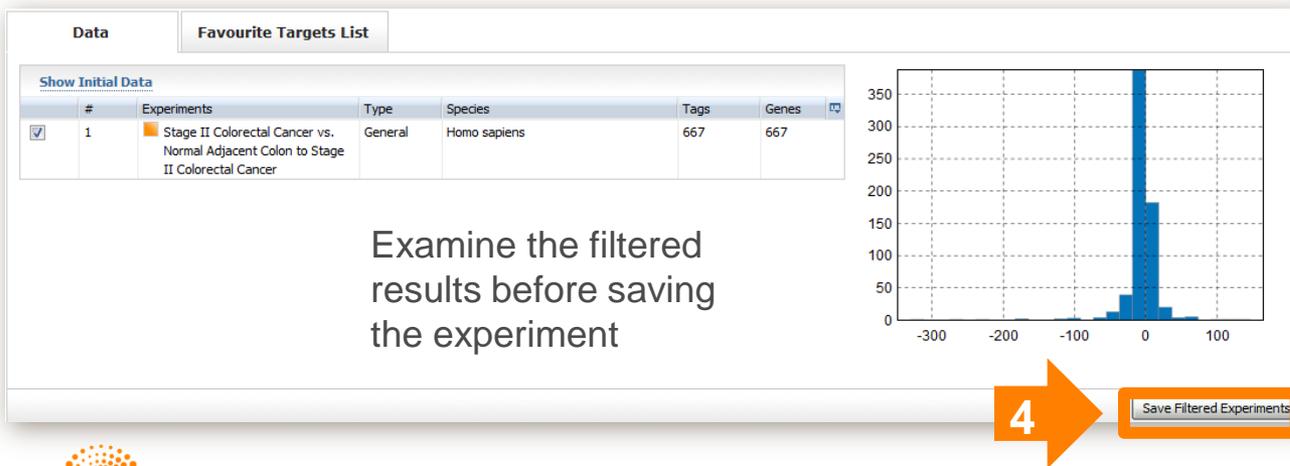
- Enrichment Analysis
- Analyze Single Experiment
- Compare Experiments
- Compare Compounds
- Toxicity Analysis
- Biomarker Assessment
- Interactome Analysis

- Question:
 - What pathways are disrupted by both ulcerative colitis and colorectal cancer expression data?

FILTER DATASET



Set your filtering thresholds and click apply



Choose a name for the folder and click 'OK'

ACTIVATE DATASETS AND RUN COMPARE EXPERIMENTS WORKFLOW

1

| Home > Active Data | | | |
|----------------------------------|------|--------|---|
| Name | Type | | |
| [...] Active Data | | | |
| Ulcerative Colitis Intestine ... | GX | 01/28/ | ✓ |
| Stage II Colorectal Cancer ... | GX | 01/28/ | ✓ |

2

Genomic Analysis Most Popular Questions Upload **Workflows & Reports** One-click Analysis Build Network

Data Analysis Workflows

A set of simple step-by-step wizards for analysis of your data.

- Enrichment Analysis
- Analyze Single Experiment
- Compare Experiments**
- Compare Compounds
- Toxicity Analysis
- Biomarker Assessment
- Interactome Analysis

WHAT PATHWAYS ARE DISRUPTED BY BOTH ULCERATIVE COLITIS AND COLORECTAL CANCER EXPRESSION DATA?

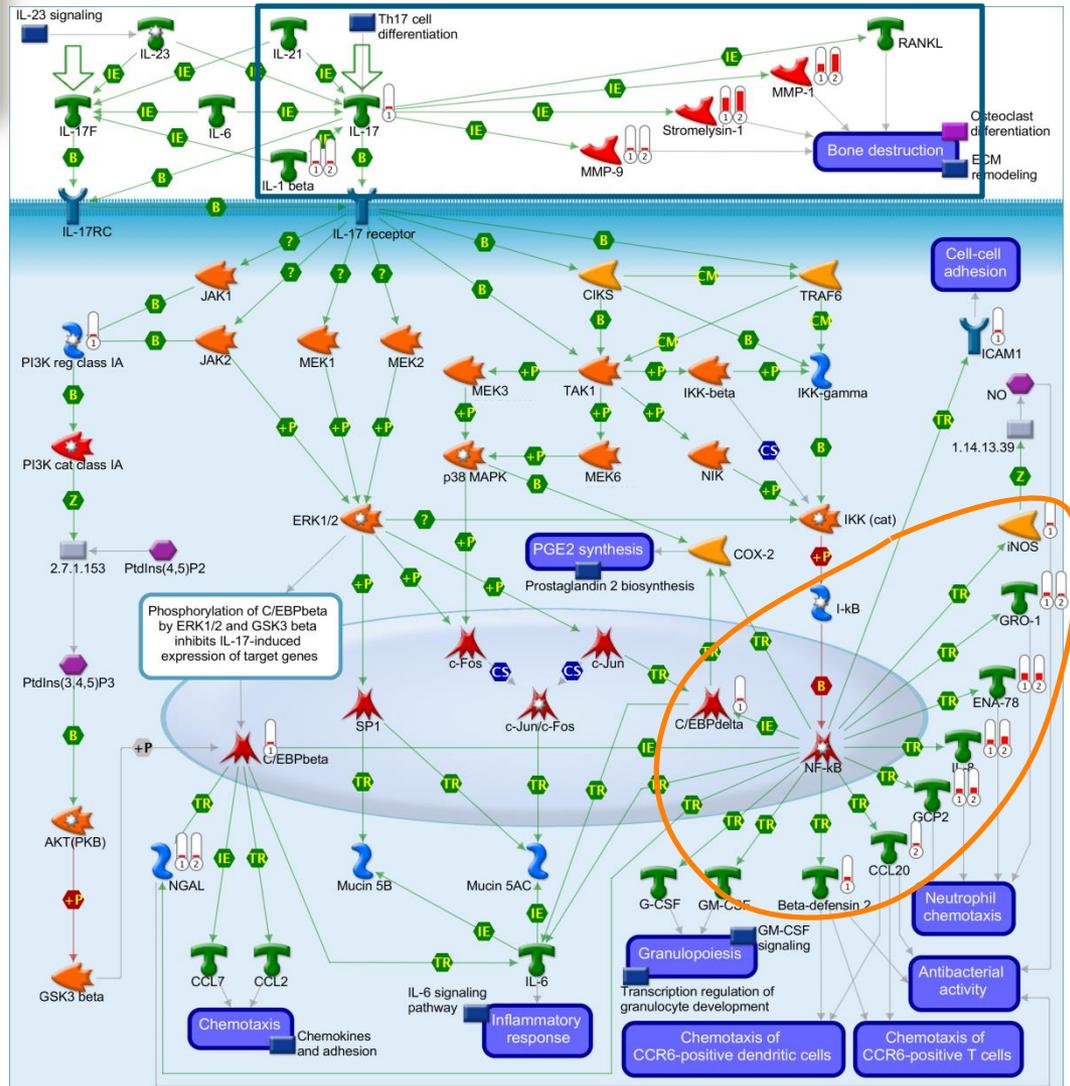
| Experiment name | Species | Network Objects |
|---|--------------|-----------------|
| Ulcerative Colitis Intestine vs. Normal Intestine | Homo sapiens | 772 |
| Stage II Colorectal Cancer vs. Normal Adjacent Colon to Stage II Colorectal Cancer_FF | Homo sapiens | 721 |

Cell migration, adhesion, and chemotaxis are processes common to both gene signatures

Increased expression of many matrix metalloproteinases could be leading to the extracellular matrix remodeling in these diseases.

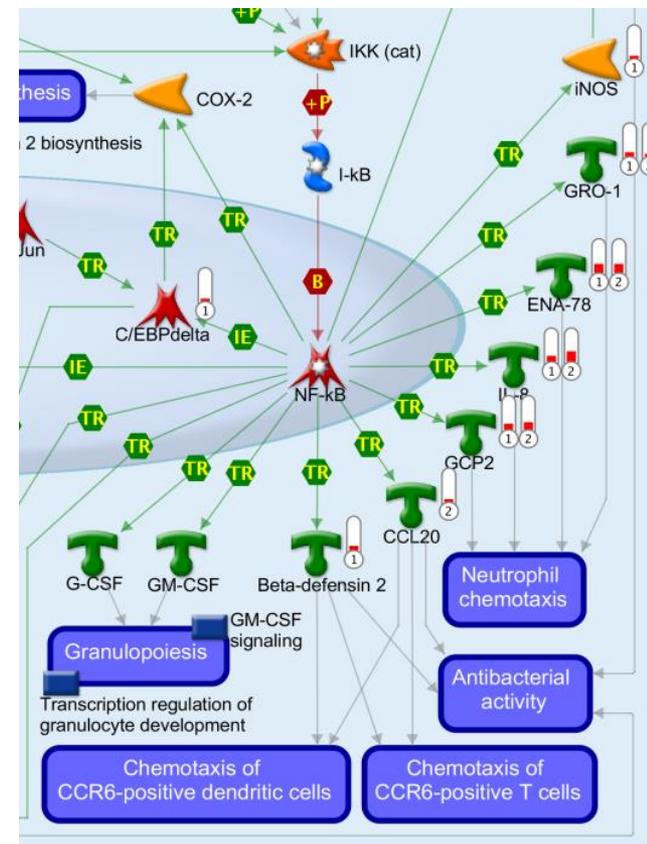
The common signature shares much in common with biomarkers from other gastrointestinal diseases.

Immune response IL-17 signaling pathways



SUMMARY

- The ulcerative colitis expression dataset was similar to other gastrointestinal diseases like Crohn's and colorectal cancer.
- The commonly expressed genes between UC and CRC point processes like cell migration and adhesion being impacted by both diseases.



NETWORK BUILDING

11 NETWORK ALGORITHMS

Purpose

Build sub-network list from seed nodes depending on which algorithm is used.

Add directionality to your network building

Find shortest directed path between transcription factors

Network built from seed nodes

Network expanding from seed nodes

Analyze network

Analyze network (transcription factors)

Analyze network (receptors)

Transcription regulation

Shortest paths

Trace pathways

Self regulation

Direct interactions

Auto expand

Expand by one interaction

Manual expand

Recommended size of starting list

Large – 300-600 recommended
> 2,000 will take time

Medium(small) –
< 50 seeds

Medium(large) –
< 100 seeds

Small – recommend
1-3 seeds

HOW TO USE THE DIRECT INTERACTIONS ALGORITHM TO BUILD A NETWORK USING COMPARE EXPERIMENTS RESULTS

Build network from
Compare
Experiment

Set network
building options



Network options

Choose building algorithm
Direct interactions

Use canonical pathways
(processing takes longer for large datasets)

Show additional options

Build network

- Questions:
 - How might the differentially expressed genes from one of these signatures be directly interacting?

BUILDING A NETWORK FROM COMPARE EXPERIMENTS RESULTS



Left click striped area

Select 'Direct interactions' algorithm



Network options

Choose building algorithm

Direct interactions

Use canonical pathways
(processing takes longer for large datasets)

[Show additional options](#)

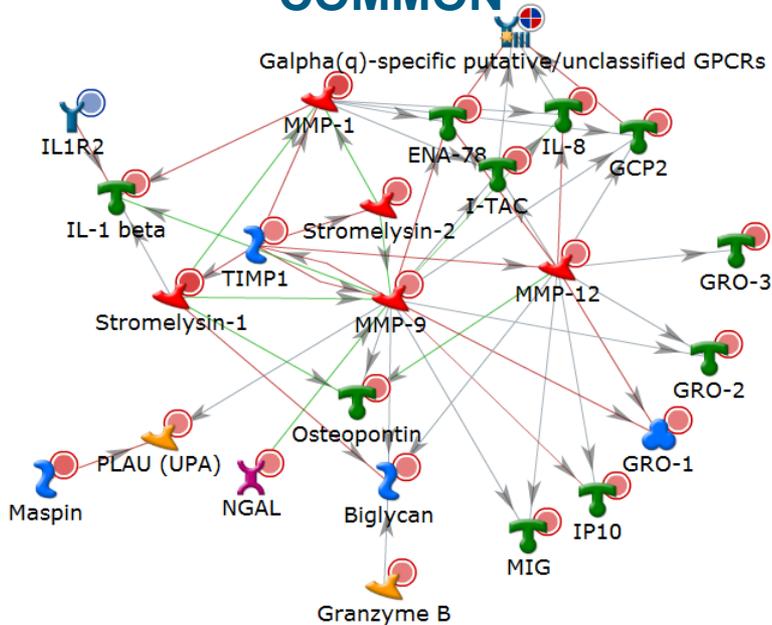
Build network



When finished click 'Build network'

WHAT DIFFERENTIALLY EXPRESSED GENES ARE DIRECTLY INTERACTING?

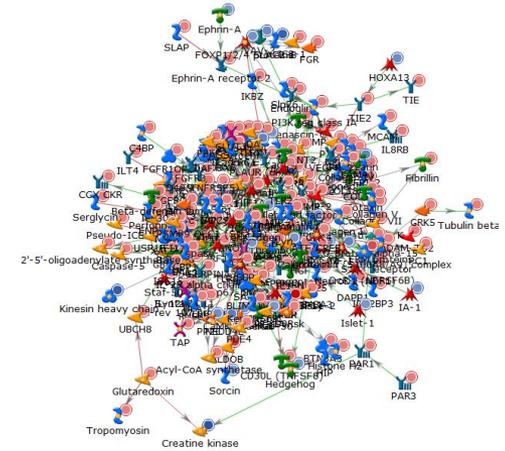
COMMON



Relationship with cell migration and chemotaxis as well as a strong connection with Crohn's disease and IBD

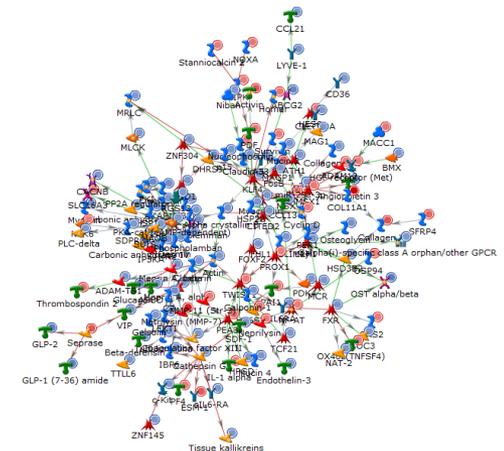
UNIQUE UC

Relationship with immune response and autoimmune diseases



UNIQUE CRC

Relationship with gastrointestinal diseases and cancers



WORKING WITH MIRNA DATA

Multi-omics analysis with miRNA & mRNA data

DATASET

Jernås et al. *BMC Immunology* 2013, **14**:32
<http://www.biomedcentral.com/1471-2172/14/32>



RESEARCH ARTICLE

Open Access

MicroRNA regulate immune pathways in T-cells in multiple sclerosis (MS)

Margareta Jernås^{1*}, Clas Malmeström², Markus Axelsson², Intawat Nookaew⁵, Hans Wadenvik³, Jan Lycke² and Bob Olsson⁴

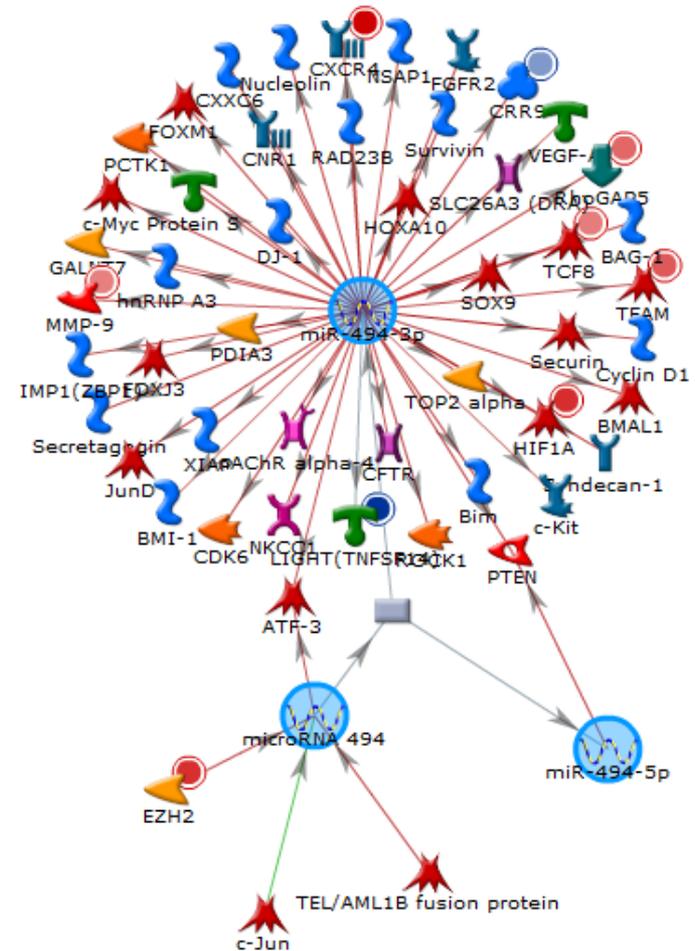
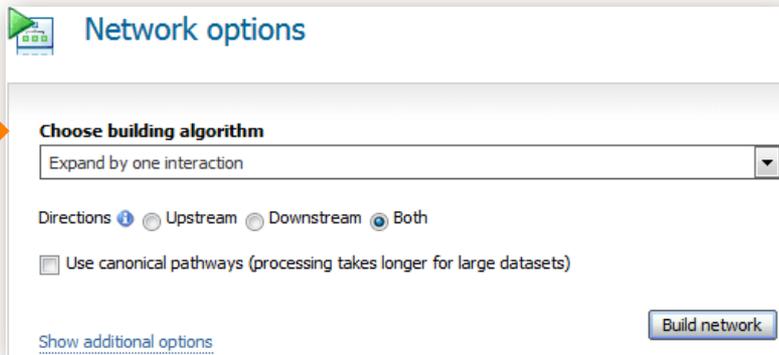
- GSE43591 – MicroRNA regulate immune pathways in T-cells in multiple sclerosis (MS) mRNA.
 - Affy/HG-U133_Plus_2
 - Fold change: ≤ -1.3 or ≥ 1.3
 - Multiple Sclerosis T-Lymphocytes vs. Normal T-Lymphocytes



UPLOADING MIRNA DATA

- Same procedure as gene expression, use Entrez ID or miRBase Accession ID (old style miRBase IDs are now under gene symbols)

I WANT TO BUILD A NETWORK OF ALL THE MRNA MIR-494 COULD BIND WITH

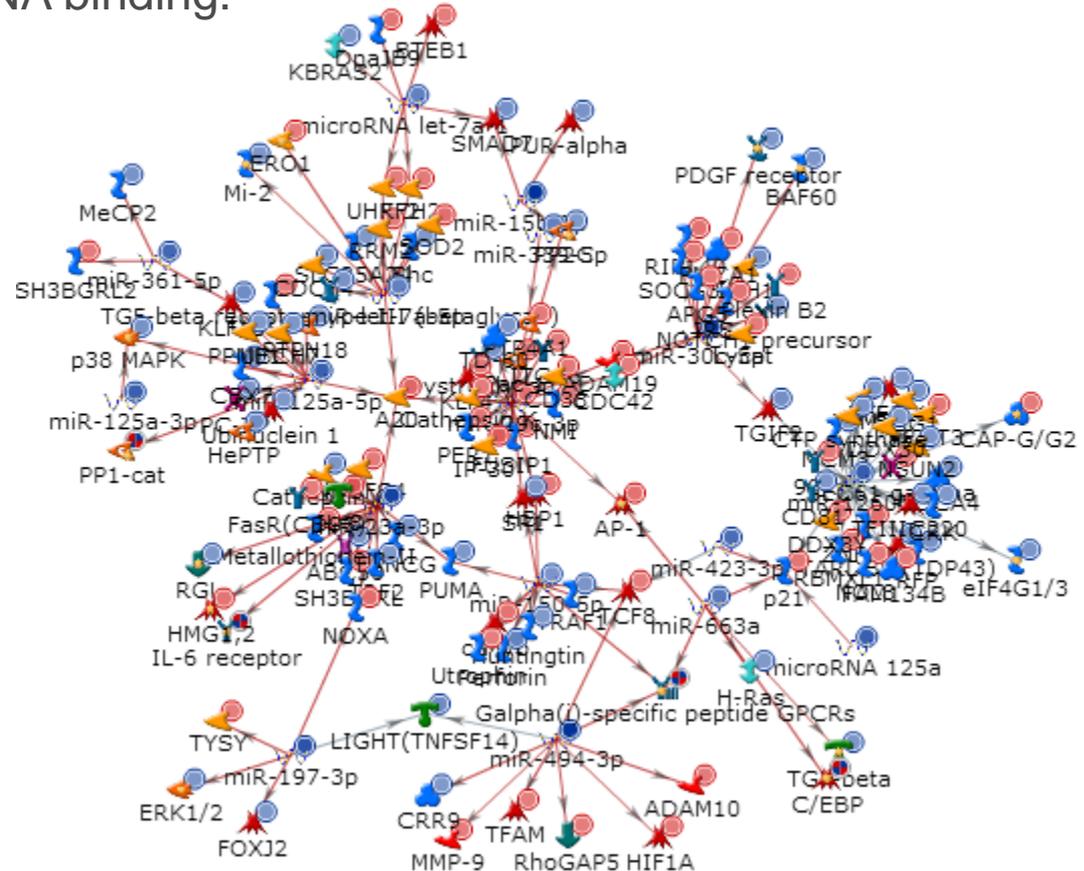


- Build a network using “expand by one interaction” algorithm for interactions with mir-494
- 8 mRNA involved potentially binding with mir-494-3p have a change in expression including: CXCR4 and MMP-9

WHAT IS THE RELATIONSHIP BETWEEN MIRNA AND MRNA EXPRESSION?

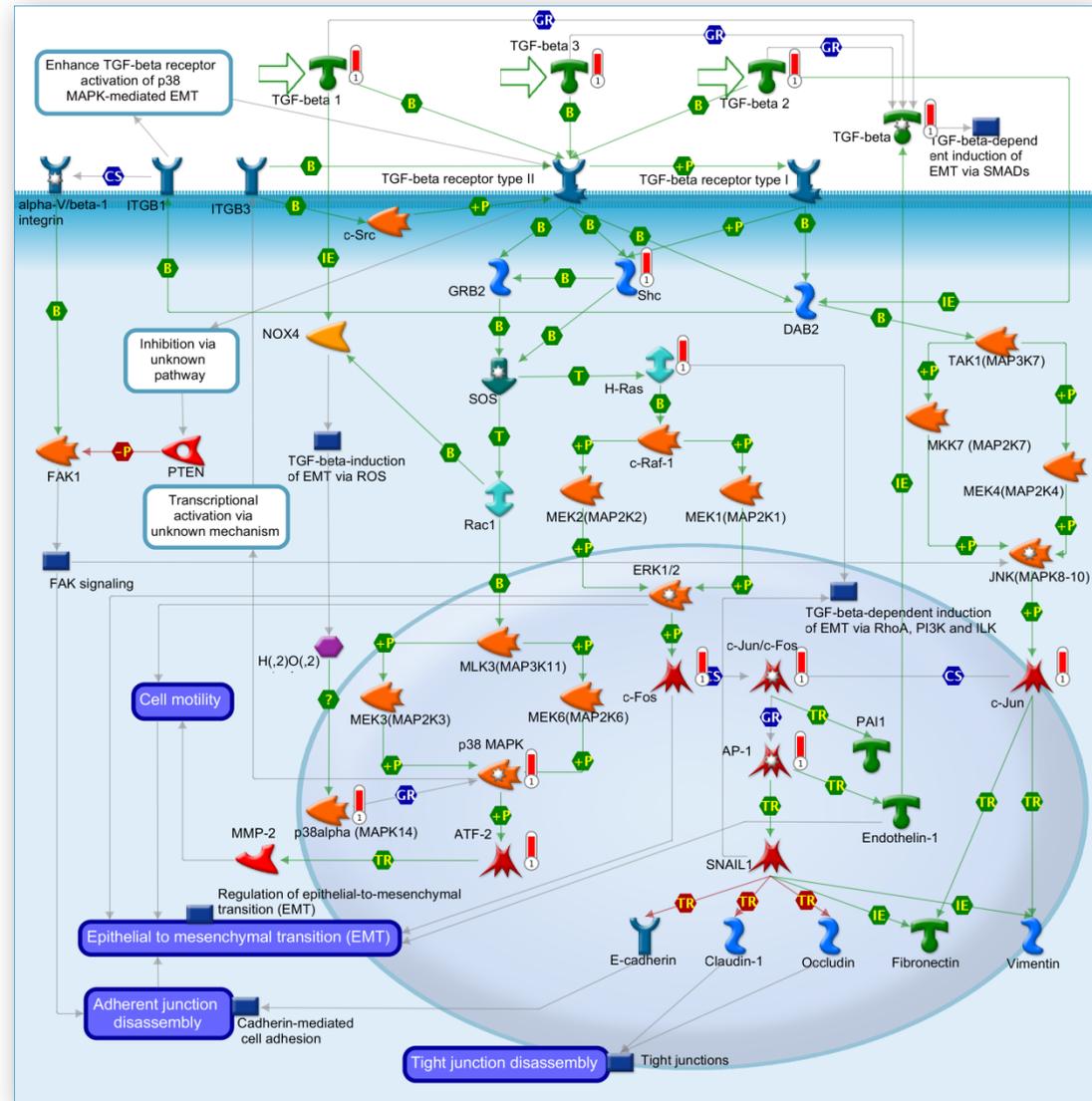
- Using the 'direct interaction' algorithm an interaction network between mRNA and miRNA expression can be built.
- Restrict interactions by using additional options to pre-filter the interactions for only miRNA binding.

- This network identifies potential miRNA binding to their mRNA targets based on literature.
- exported as an experiment to run enrichments



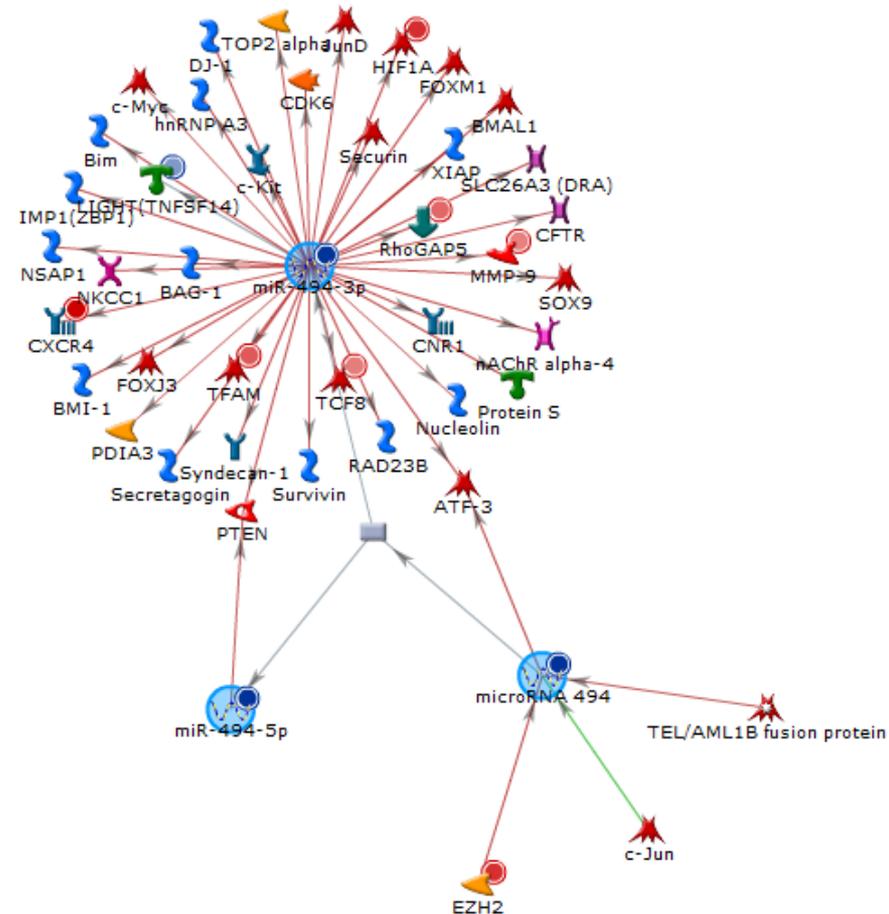
WHAT PATHWAYS ARE IMPACTED BY MRNA FROM THE INTERACTION NETWORK?

- mRNA from interaction network related to a number of immune response and development pathways.
- Interesting relationship between Multiple Sclerosis and mRNA interacting with miRNA.
- Could miRNA be impacting the expression of transcription factors related to AP-1 and its target MMP-9 and IL-8?



SUMMARY

- mir-494 has known interactions with MMP-9 and CXCR4.
- Building an miRNA binding network between mRNA and miRNA reveals a large interconnected network.
- mRNA from this network can play a role on immune response and development.
- Expression of MMP-9, IL-8, CXCR4, and transcription factors related to AP-1 may have relations with miRNA.



WORKING WITH METABOLITE DATA

Multi-omics analysis with
Metabolomics & mRNA data

LIVE DEMO: DATASETS

Gene Expression

- GSE26886 – Gene expression profiling of Barrett’s esophagus, adenocarcinoma, esophageal squamous epithelium and squamous cell carcinoma.
 - Affy/HG-U133_Plus_2
 - Fold change: ≤ -6 or ≥ 6 (P-value: ≤ 0.05)
 - Barrett Esophagus vs. Normal Esophagus
 - Esophageal Adenocarcinoma vs. Normal Esophagus

Metabolite Data

- Davis VW, Schiller DE, Eurich D, and Sawyer MB. (2012) Urinary metabolic signature of esophageal cancer and Barrett’s esophagus. World Journal of Surgical Oncology. 10:271.
 - Validated urine biomarkers using two statistical methods.
 - Fold change: -1 decrease or 1 increase
 - Barrett Esophagus vs. Control
 - Esophageal Adenocarcinoma vs. Control



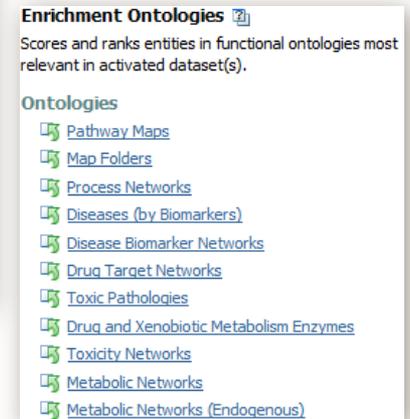
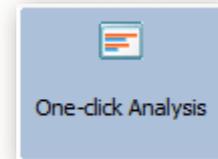
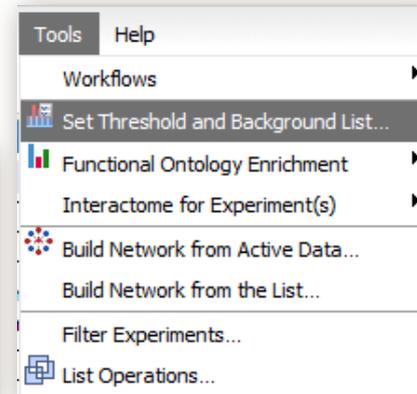
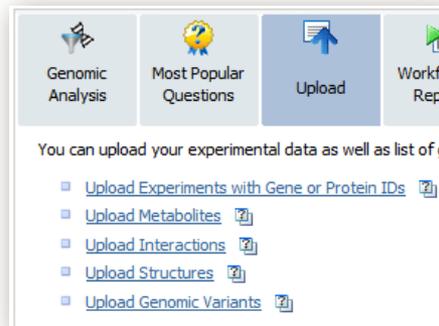
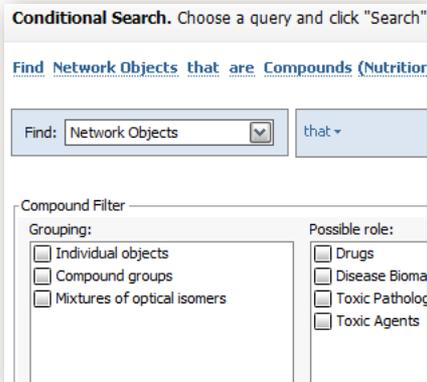
CREATE A CUSTOM BACKGROUND LIST OF COMPOUNDS AND RUN ENRICHMENT ANALYSIS ON METABOLOMIC DATA

Create list of compounds

Upload metabolites in MetaCore

Set Threshold/Background

Analyse Metabolic Networks



- Questions:

- What are the differences between the metabolites from Barrett's Esophagus and Esophageal Adenocarcinoma?
- Can overlaying transcriptomic data provide additional information on these differences?

USE ADVANCED SEARCH TO FIND AND SAVE A LIST OF COMPOUNDS

Search [Advanced Search](#)



Query 1 x Result x

Conditional Search. Choose a query and click "Search".

[Find Network Objects that are Compounds \(Nutritional or Endogenous or Mixed\)](#) Search

Find: Network Objects that are Com... + that

Compound Filter

| Grouping: | Possible role: | Category: |
|--|---|---|
| <input type="checkbox"/> Individual objects | <input type="checkbox"/> Drugs | <input checked="" type="checkbox"/> Nutritional |
| <input type="checkbox"/> Compound groups | <input type="checkbox"/> Disease Biomarkers | <input type="checkbox"/> Environmental |
| <input type="checkbox"/> Mixtures of optical isomers | <input type="checkbox"/> Toxic Pathology Biomarkers | <input checked="" type="checkbox"/> Endogenous |
| | <input type="checkbox"/> Toxic Agents | <input type="checkbox"/> Xenobiotic |
| | | <input type="checkbox"/> Metabolite of xenobiotic |
| | | <input checked="" type="checkbox"/> Mixed |



Query 1 x Result x

Query 1 Results x

[Find Network Objects that are Compounds \(Nutritional or Endogenous or Mixed\)](#)

[Export](#) [Build network](#)

| # | Icon | Name |
|----|------|---|
| 1 | | Dehydroalanine intracellular |
| 2 | | Phe-Leu extracellular region |
| 3 | | Pyrophosphate cytosol |
| 4 | | 26-Hydroxy-7-ketocholesterol intracellular |
| 5 | | Agmatine extracellular region |
| 6 | | Taurine intracellular |
| 7 | | Ile-Val-Tyr extracellular region |
| 8 | | 2E,9Z,12Z,15Z,18Z-tetracosapentaenoyl-CoA intracellular |
| 9 | | Tyramine extracellular region |
| 10 | | Ca(2+) mitochondrial matrix |
| 11 | | NAD(P)H intracellular |
| 12 | | Adipic acid mitochondrial matrix |
| 13 | | 12(S)-HETE extracellular region |

Result: 4753 (Only first 1000 entries are shown) page: 1/20



Export

Name: Background list of endogenous, nutritional, and mixed compounds

To: List [Show lists](#)

Genes of

Network objects

Human

Mouse

Rat

Through: Human (H. sapiens)

[Hide additional options](#)

Rows: With active data only

All rows

Current page

Selected rows

UPLOAD METABOLOMIC DATA INTO METACORE

1



Genomic Analysis Most Popular Questions **Upload** Workflows & Reports One-click Analysis

You can upload your experimental data as well as list of genes/proteins/metabolites.

- Upload Experiments with Gene or Protein IDs
- Upload Metabolites**
- Upload Interactions
- Upload Structures
- Upload Genomic Variants



Data Analysis Wizard

Step 1

Click "browse" to select file(s) to upload: **Next >>**

No file selected.

Data format

Warning: do not mix IDs in the same column.

Warning: Currently, Excel 2007 files are not supported. To upload your file, please save it as a text file with tab separated fields or an older Excel version.

Metabolic Parser recognizes the following metabolite identifiers:

- Chemical Name
- Formula
- Molecular Weight
- SMILES
- InChI
- CAS Number
- KeGG ID
- PubChem Compound ID
- Compound ID



Data Analysis Wizard (Metabolic parser)

Step 2

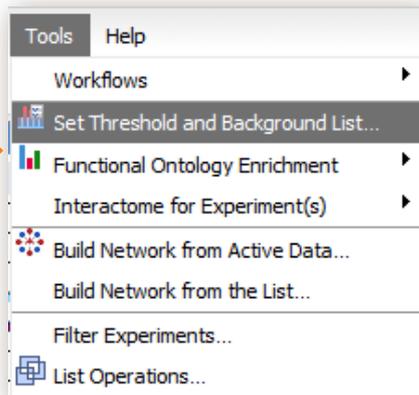
Only first 10 lines of your file are shown. Use horizontal scrolling if needed.
Use checkboxes against each row to specify table header lines

Specify the column types in your file:

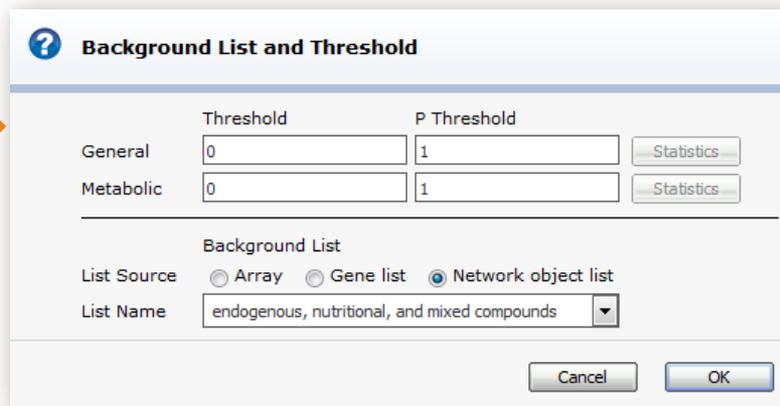
| File data | | | |
|--|--------------------------|-----------|---------|
| Experiments name prefix: Metabolite-data-BEvsC | | | |
| Type | Chemical Name | Intensity | P-value |
| Name | Name | intensity | p-value |
| <input checked="" type="checkbox"/> | Name | intensity | p-value |
| <input type="checkbox"/> | Urea | -1 | 0.01 |
| <input type="checkbox"/> | Acetate | -1 | 0.01 |
| <input type="checkbox"/> | Pantothenate | -1 | 0.05 |
| <input type="checkbox"/> | 3-Hydroxyisovaleric acid | -1 | 0.05 |
| <input type="checkbox"/> | Acetone | -1 | 0.01 |
| <input type="checkbox"/> | Formic acid | -1 | 0.01 |
| <input type="checkbox"/> | 2-hydroxyisobutyrate | -1 | 1 |
| <input type="checkbox"/> | Creatinine | -1 | 1 |
| <input type="checkbox"/> | Ethanolamine | -1 | 1 |

SET THRESHOLD/BACKGROUND AND RUN METABOLOMIC NETWORK (ENDOGENOUS) ANALYSIS

1



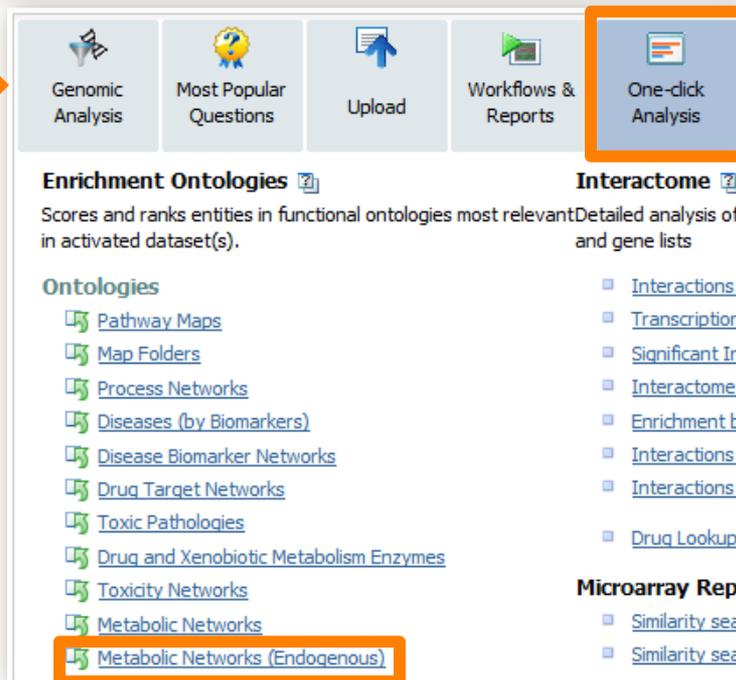
2



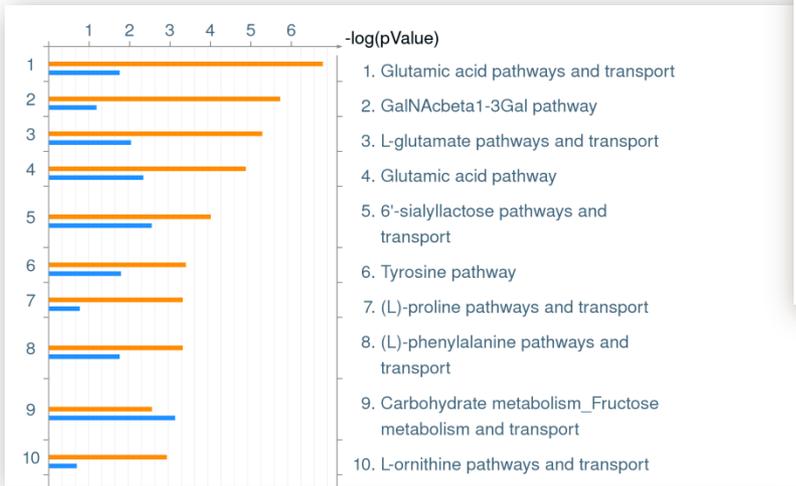
3

| Name | Type |
|--------------------|------|
| [..] Active Data | |
| BEvsC-metabolites | MX |
| EACvsC-metabolites | MX |

4

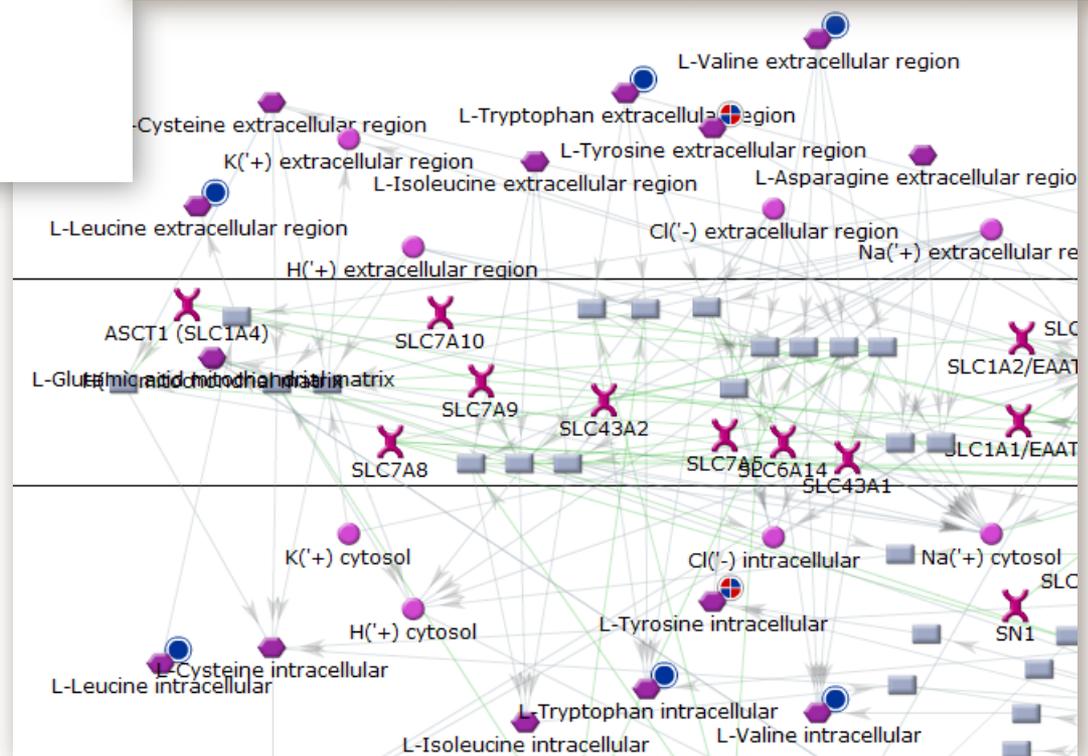


DIFFERENCES BETWEEN METABOLITES FROM BARRETT'S ESOPHAGUS AND ESOPHAGUL ADENOCARCINOMA



| Network Objects | # of Networks containing Network Object | Network Objects ranking | | |
|-----------------------------------|---|-------------------------|--------------|--------------|
| | | Overall | Metabolit... | Metabolit... |
| D-Glucose intracellular | 9 | 1 | 1 | |
| D-Glucose extracellular region | 9 | 1 | 1 | |
| L-Tryptophan intracellular | 8 | 2 | 2 | |
| L-Tryptophan extracellular region | 8 | 2 | 2 | |
| Urea intracellular | 8 | 2 | 2 | 1 |
| L-Tyrosine intracellular | 7 | 3 | 3 | 2 |
| Urea extracellular region | 6 | 4 | 4 | 3 |
| L-Tyrosine extracellular region | 5 | 5 | 5 | 4 |
| D-Sucrose extracellular region | 4 | 6 | | 5 |

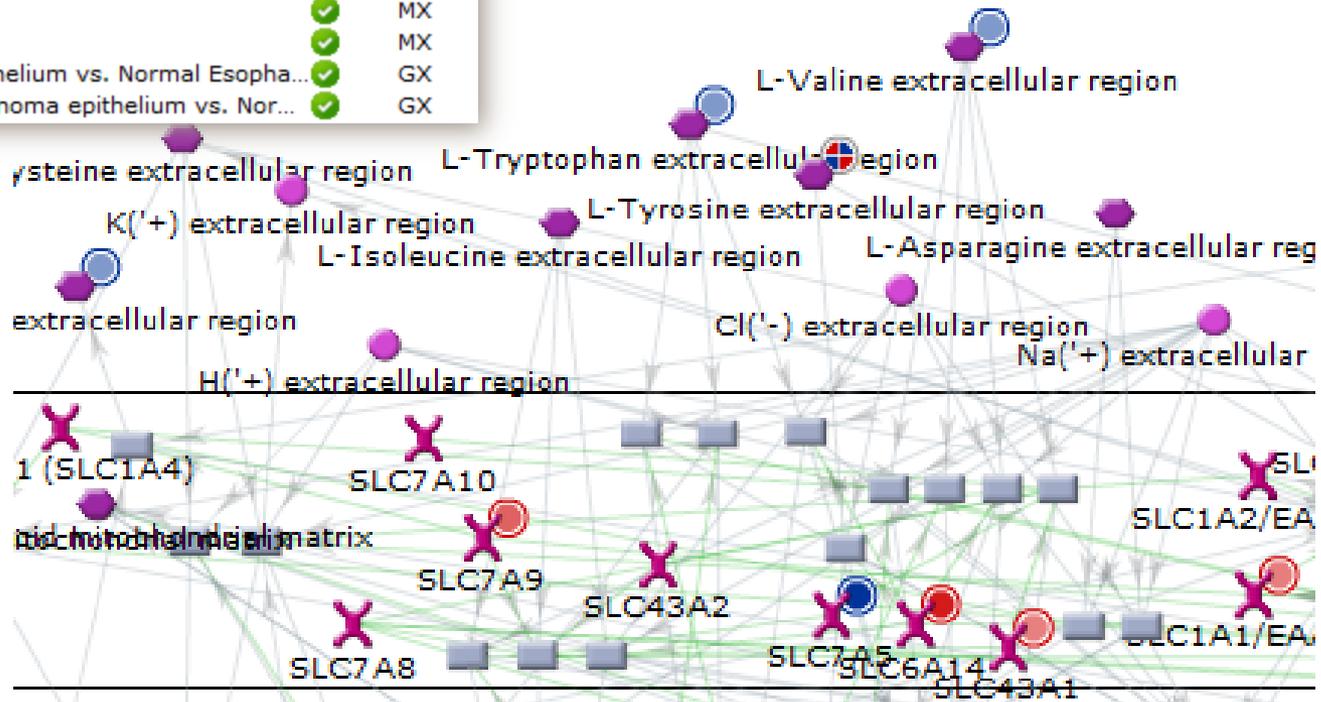
Enrichment analysis of Metabolomic Networks (Endogenous) can quickly identify metabolites impact on processes.



OVERLAYING EXPRESSION AND METABOLIC DATA ONTO METABOLIC PROCESSES

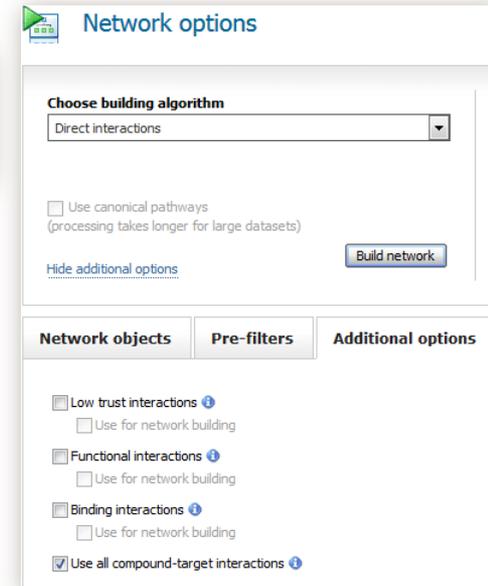
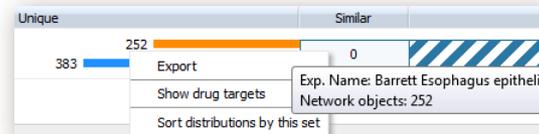
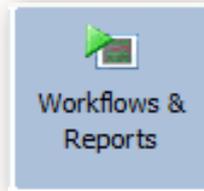
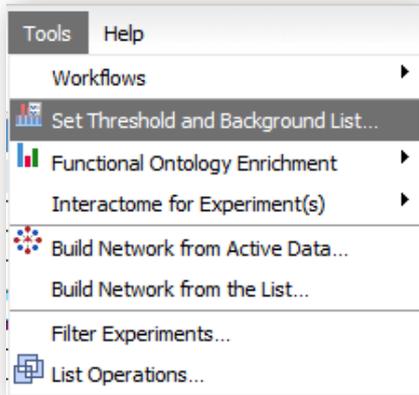
Home ▸ Active Data

| Name | Type |
|---|------|
| [...] Active Data | |
| BEvsC-metabolites | MX |
| EACvsC-metabolites | MX |
| Barrett Esophagus epithelium vs. Normal Esopha... | GX |
| Esophageal Adenocarcinoma epithelium vs. Nor... | GX |



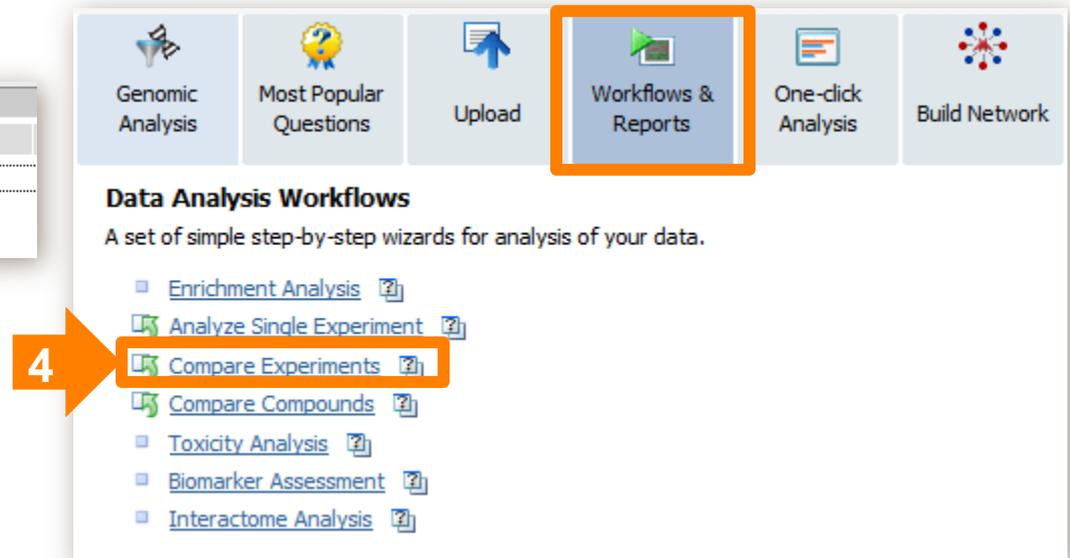
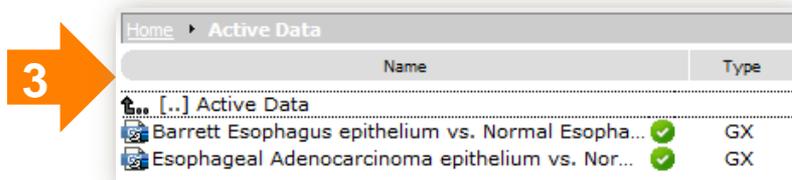
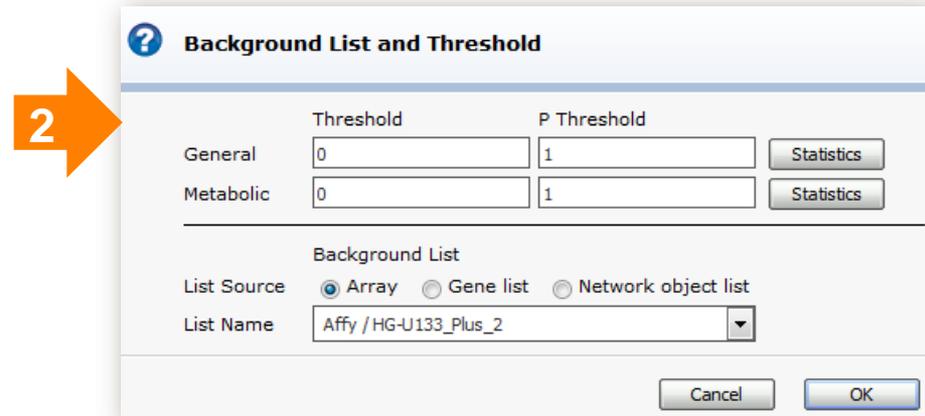
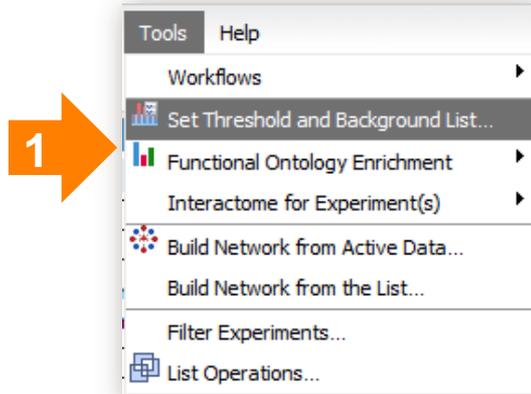
A number of channels are differentially expressed specifically in Barrett esophagus, but not esophageal adenocarcinoma.

BUILD A NETWORK USING METABOLOMIC AND TRANSCRIPTOMIC DATA



- Questions:
 - How are the differentially expressed genes common or unique to these two diseases related to the metabolomic data?

SET THRESHOLD/BACKGROUND AND RUN COMPARE EXPERIMENTS WORKFLOW



CAN DIFFERENCES IN GENE EXPRESSION HELP EXPLAIN THE METABOLITES?

| Experiment name | Species | Network Objects |
|---|--------------|-----------------|
| Barrett Esophagus epithelium vs. Normal Esophagus epithelium_FF | Homo sapiens | 933 |
| Esophageal Adenocarcinoma epithelium vs. Normal Esophagus epithelium_FF | Homo sapiens | 1064 |

Common gene expression related to remodeling and stomach/gastrointestinal diseases



▼ Pathway Maps

| # Maps | -log(pValue) | pValue | pValue ↑ | FDR | Rat |
|---|--------------|----------|-----------|----------|-------|
| 1 Cytoskeleton remodeling_Keratin filaments | 1.122e-10 | 1.000e+0 | 1.122e-10 | 1.000e+0 | 0/36 |
| | | 1.000e+0 | | 9.978e-8 | 14/36 |
| | | 1.000e+0 | | 1.000e+0 | 0/36 |
| | | 7.043e-2 | | 6.043e-1 | 3/36 |

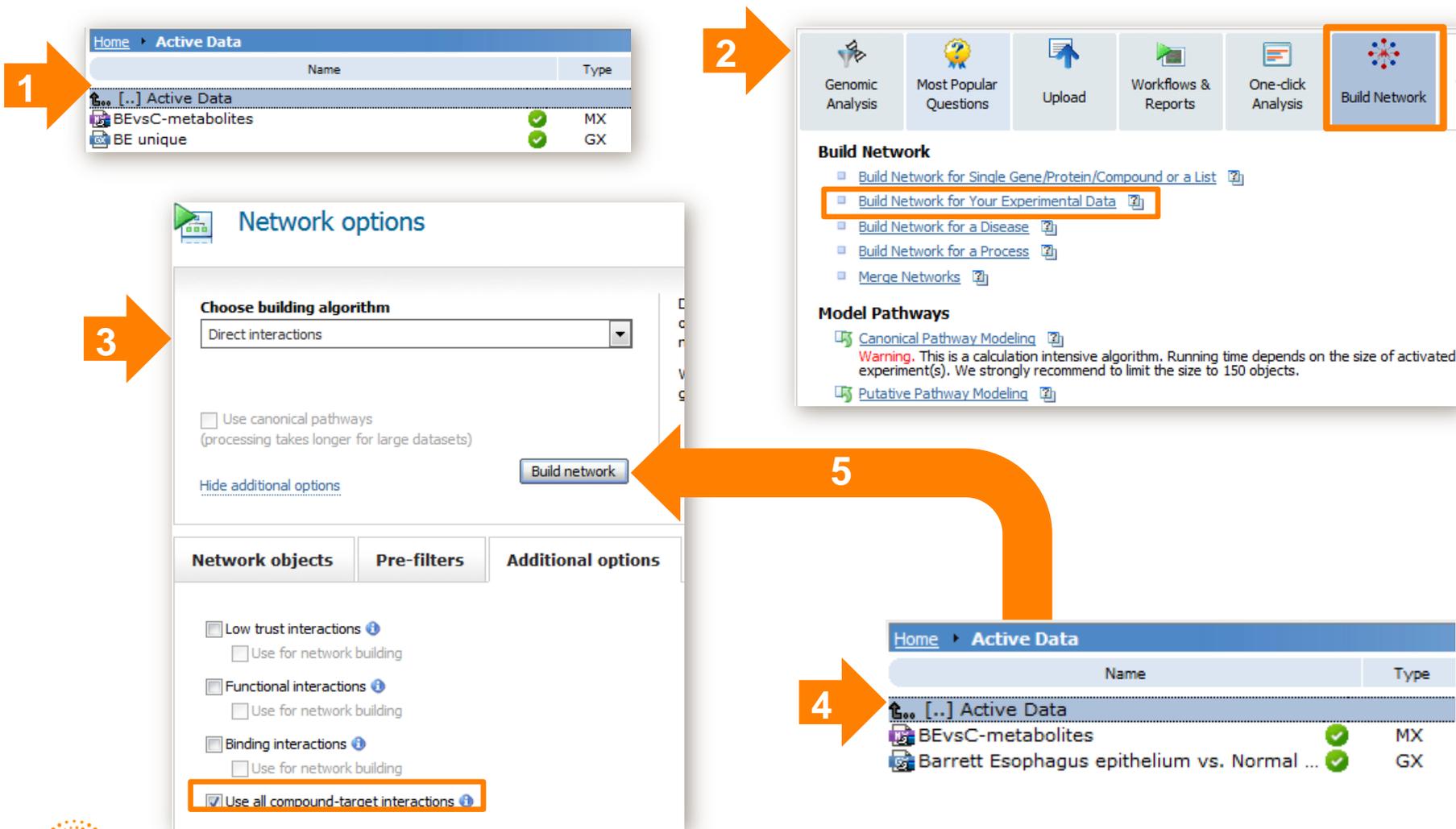
▼ Diseases (by Biomarkers)

| # Diseases | -log(pValue) | pValue | pValue ↑ | FDR | Rat |
|---------------------|--------------|-----------|-----------|-----------|----------|
| 1 Stomach Diseases | 1.720e-21 | 1.000e+0 | 1.720e-21 | 1.000e+0 | 0/3358 |
| | | 1.720e-21 | | 3.061e-18 | 221/3358 |
| | | 7.911e-9 | | 2.832e-6 | 83/3358 |
| | | 2.977e-14 | | 2.926e-12 | 128/3358 |
| 2 Stomach Neoplasms | 8.470e-21 | 1.000e+0 | 8.470e-21 | 1.000e+0 | 0/3311 |
| | | 8.470e-21 | | 7.539e-18 | 217/3311 |
| | | 4.020e-9 | | 2.159e-6 | 83/3311 |
| | | 9.978e-15 | | 1.159e-12 | 128/3311 |

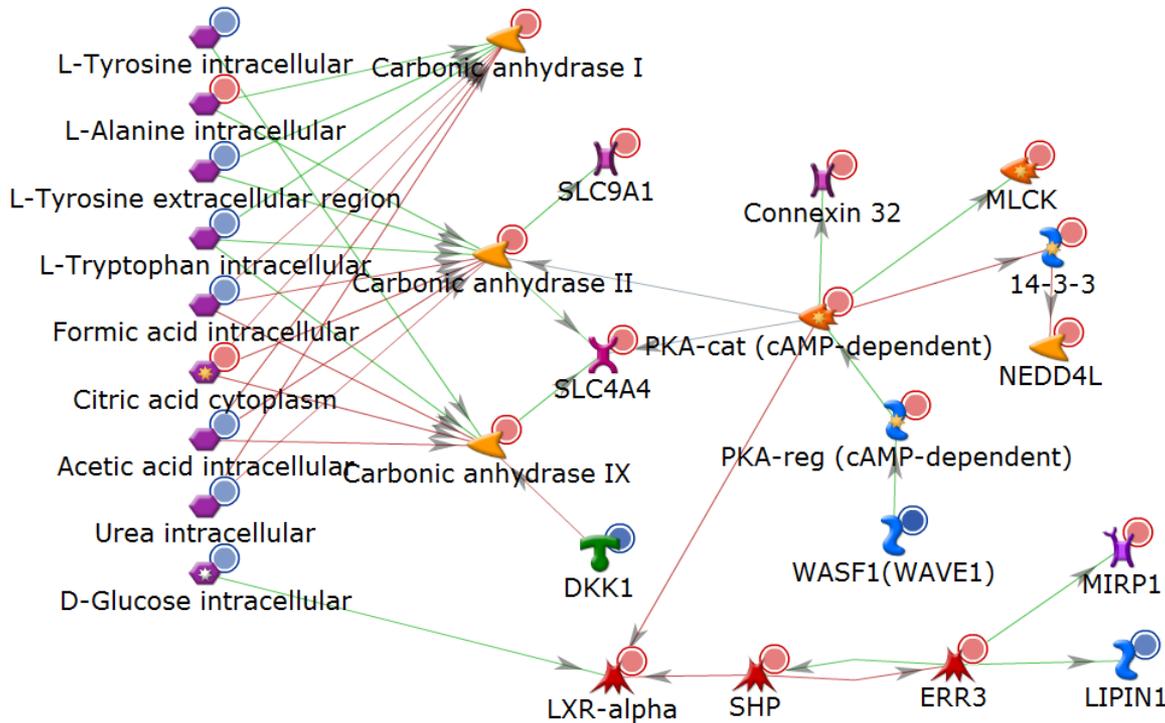
Exp. Name: Barrett Esophagus epithelium
Network objects: 252

Export the unique gene expression for Barrett's Esophagus as a new experiment to build a network with it

BUILDING A NETWORK USING METABOLOMIC AND TRANSCRIPTOMIC DATA



NETWORK OF UNIQUE GENE EXPRESSION AND METABOLITES FROM BARRETT'S ESOPHAGUS



Diseases

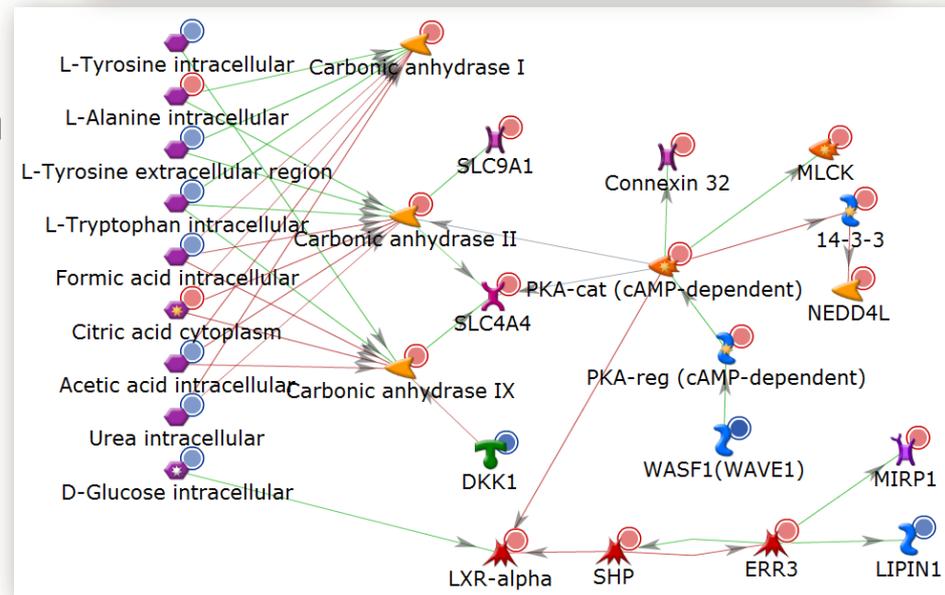
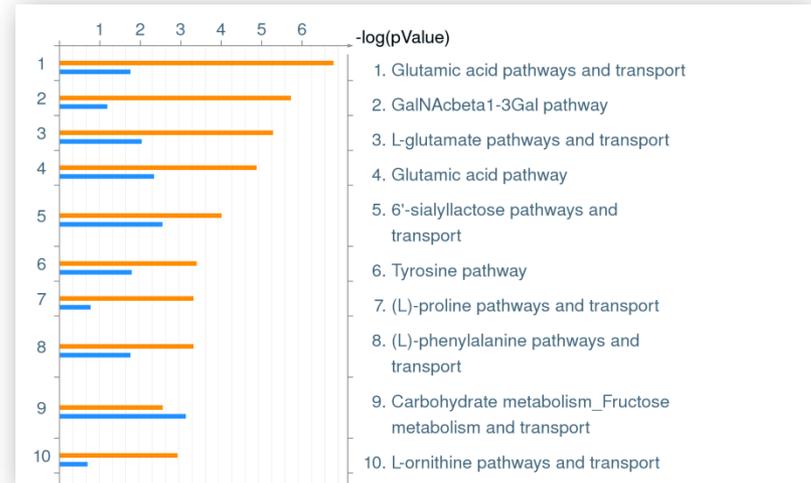
| Name | % | p-Value |
|--|---------|----------|
| Acidosis | 25.00% | 2.887e-7 |
| Acid-Base Imbalance | 25.00% | 3.852e-7 |
| Acidosis, Renal Tubular | 12.50% | 2.181e-5 |
| Pathological Conditions, Signs and ... | 68.75% | 2.530e-5 |
| Metabolic Diseases | 56.25% | 3.550e-5 |
| Bone Resorption | 18.75% | 6.484e-5 |
| Digestive System Diseases | 100.00% | 7.098e-5 |
| Nutritional and Metabolic Diseases | 56.25% | 8.921e-5 |

GO Processes

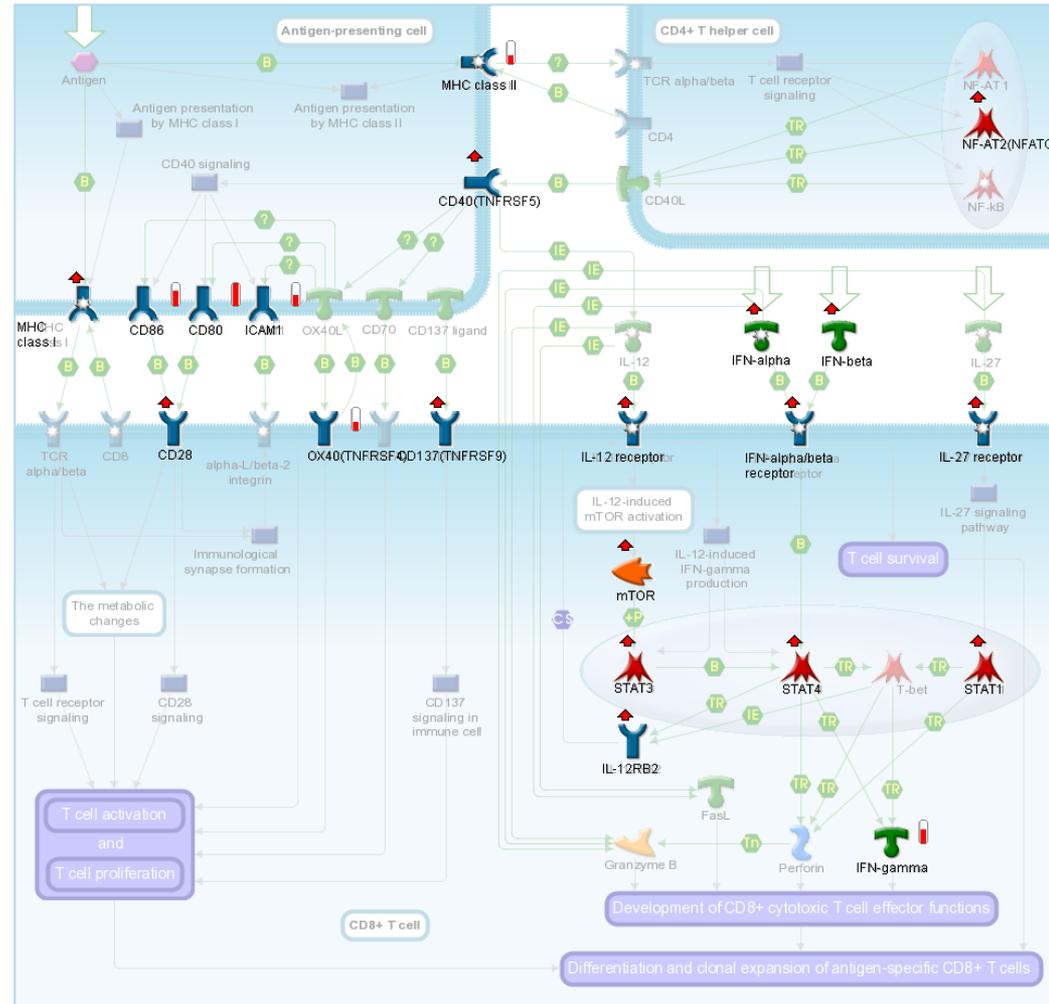
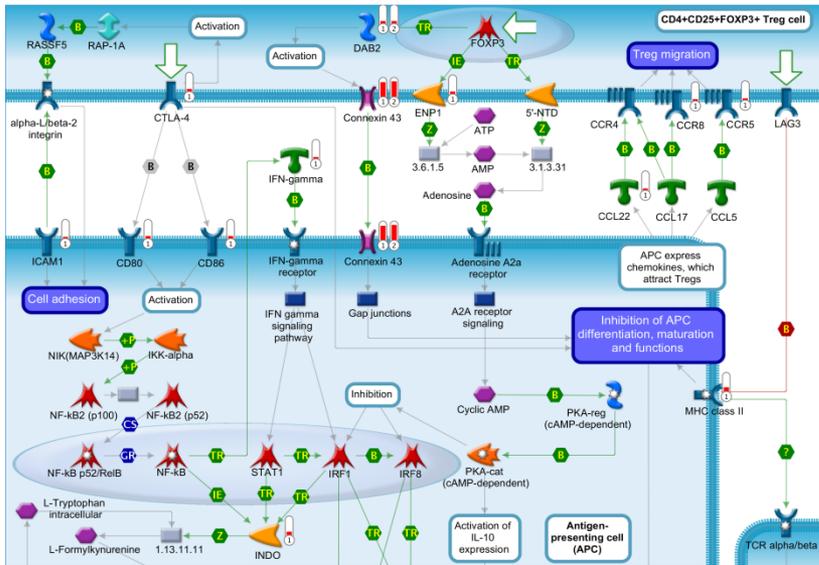
| Name | % | p-Value |
|--|--------|----------|
| bicarbonate transport | 25.00% | 1.252e-8 |
| one-carbon metabolic process | 18.75% | 2.269e-6 |
| regulation of transcription from RN... | 56.25% | 7.966e-6 |
| ion transport | 50.00% | 8.808e-6 |
| regulation of intracellular pH | 18.75% | 1.425e-5 |
| regulation of cellular pH | 18.75% | 1.711e-5 |
| organic anion transport | 31.25% | 2.300e-5 |
| regulation of pH | 18.75% | 4.241e-5 |

SUMMARY

- Barrett's esophagus metabolites show significant changes in glutamic acid pathways.
- Overlaying expression shows expression changes of solute carriers specifically for Barrett's Esophagus.
- Some genes uniquely expressed by Barrett's esophagus are key in regulating acid/base balance and might be modulated by the metabolites.

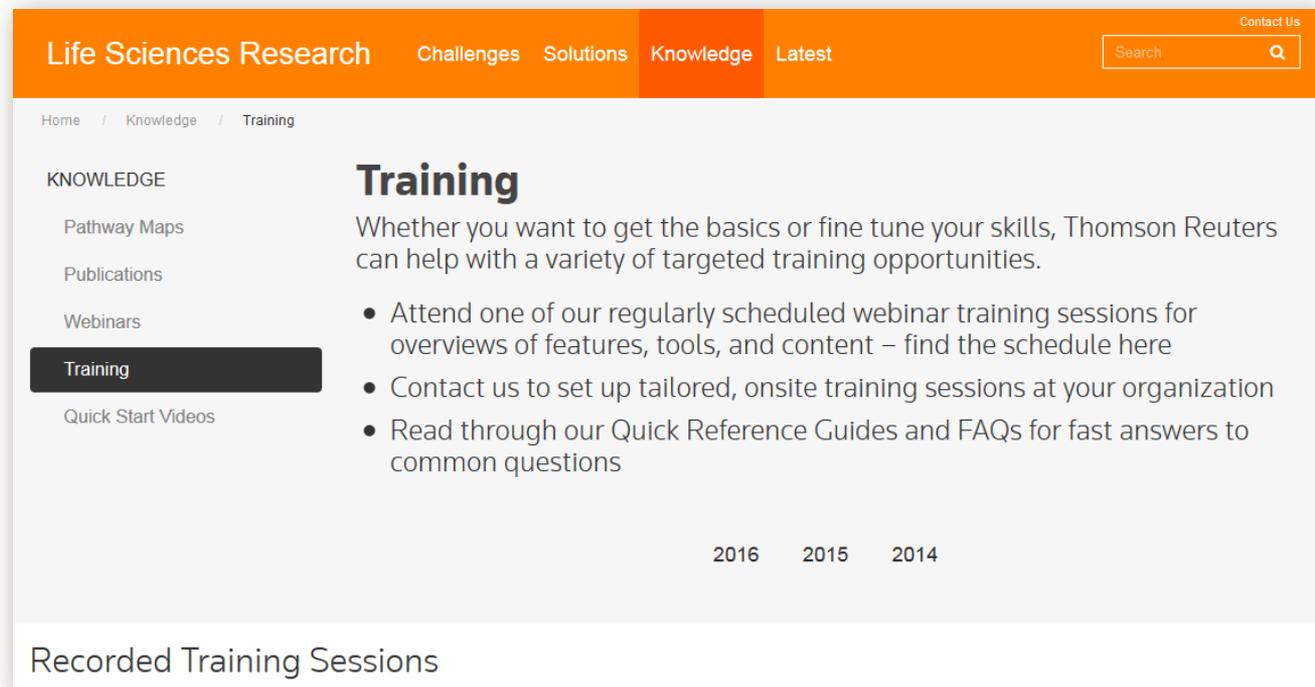


ANY QUESTIONS?



METACORE LIVE WEBINARS

- Follow Matthew Wampole on LinkedIn for information on the next Webinar 
- You can find recordings of previously held sessions at <http://lsresearch.thomsonreuters.com/knowledge/training-videos>



The screenshot shows the Thomson Reuters Knowledge Training page. The top navigation bar includes 'Life Sciences Research', 'Challenges', 'Solutions', 'Knowledge', and 'Latest'. A search bar is located in the top right corner. The left sidebar lists 'KNOWLEDGE' categories: 'Pathway Maps', 'Publications', 'Webinars', 'Training' (highlighted), and 'Quick Start Videos'. The main content area features the heading 'Training' and a paragraph: 'Whether you want to get the basics or fine tune your skills, Thomson Reuters can help with a variety of targeted training opportunities.' Below this are three bullet points: 'Attend one of our regularly scheduled webinar training sessions for overviews of features, tools, and content – find the schedule here', 'Contact us to set up tailored, onsite training sessions at your organization', and 'Read through our Quick Reference Guides and FAQs for fast answers to common questions'. At the bottom of the main content area, there are filters for the years '2016', '2015', and '2014'. The footer of the page includes the Thomson Reuters logo and the text 'Recorded Training Sessions'.