



REUTERS/Jim Young

METACORE – MAKING THE MOST OUT OF YOUR OMICS DATA

Matthew Wampole, PhD. – Solution Scientist

matthew.wampole@thomsonreuters.com



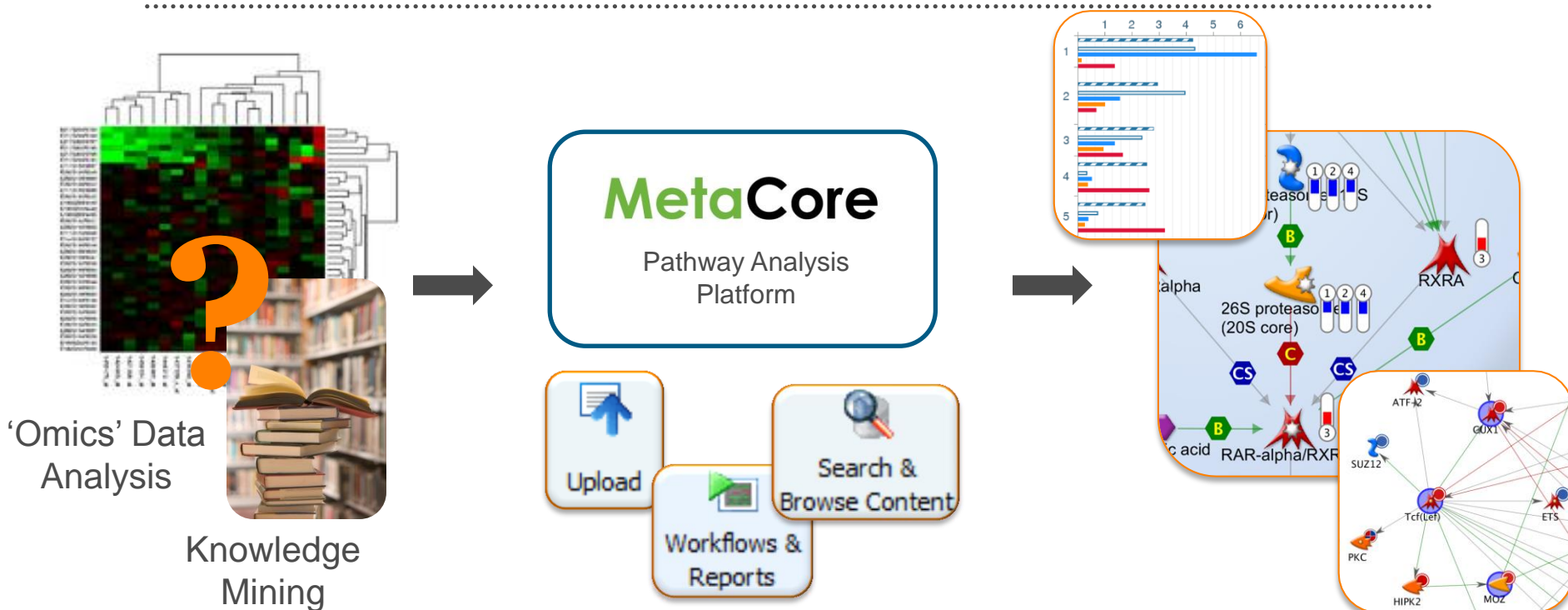
THOMSON REUTERS

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

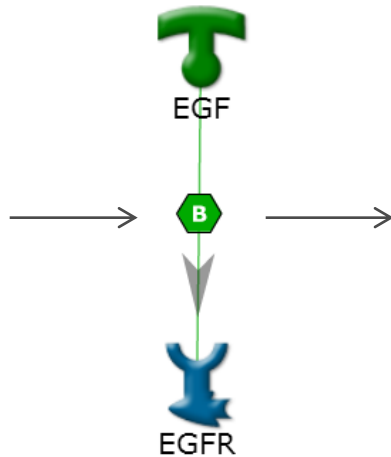
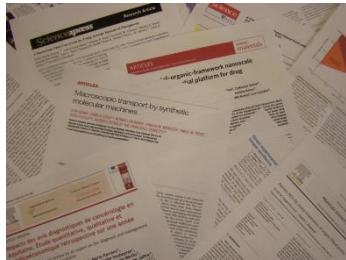


METACORE: YOUR GPS IN PATHWAY ANALYSIS



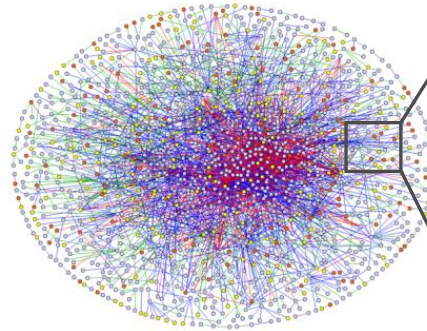
- Gain molecular understanding of disease
- Analyze and understand experimental findings (Omics data) in the context of validated biological pathways.
- Generate and confirm hypotheses for novel biomarkers, targets, mechanisms of action

FROM PEER REVIEWED ARTICLES TO SIGNALING PATHWAYS

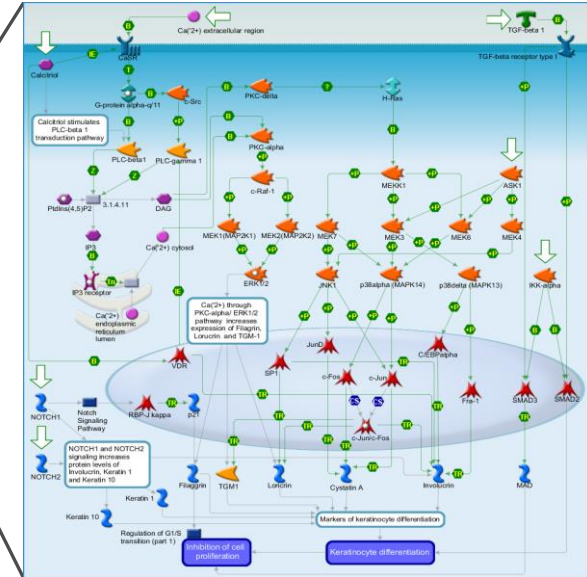


PUBLICATIONS
(195 for EGF-EGFR
interaction)

**MOLECULAR
INTERACTION**



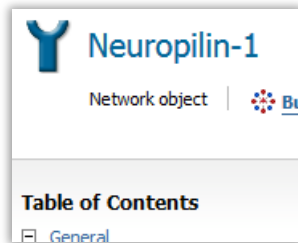
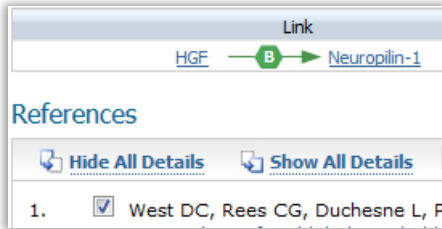
GLOBAL NETWORK:
~ 1,600,000
molecular interactions



**~ 3,000 canonical and
disease signaling pathways**

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

When you click



What you see

Icon of network object

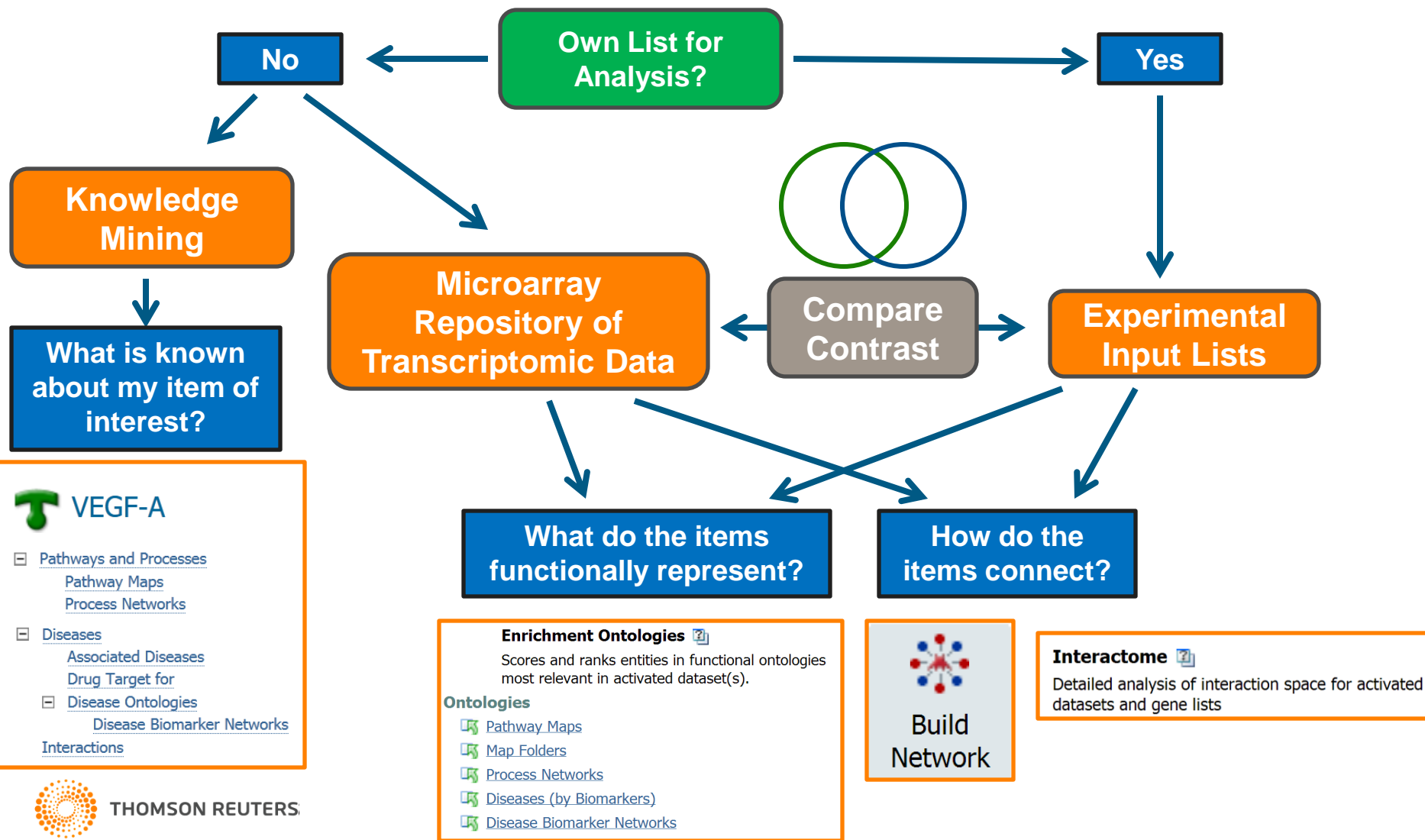
Effect
-activating
-inhibiting

Mechanism

-B=binding

Directionality

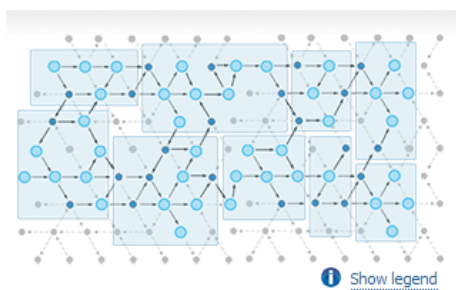
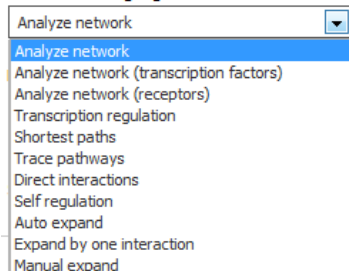
WAYS TO APPROACH METACORE



FLEXIBILITY IN DATA ANALYSIS TOOLS

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

Choose building algorithm



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

THOMSON REUTERS
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

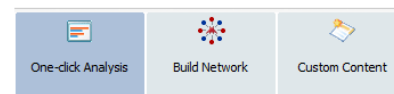
31
map folders

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		
2	Cell cycle_Role of APC in cell cycle regulation	1.785E-9	7.218E-5	1.353E-12		
3	Cell cycle_Initiation of mitosis	2.073E-5	6.316E-8	1.497E-10		
4	Immune response_ETV3 affect on CSF1-promoted macrophage differentiation	1.114E-3	1.769E-6	4.305E-9		

But also One-Click analysis for instant answers



Enrichment Ontologies

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](#)

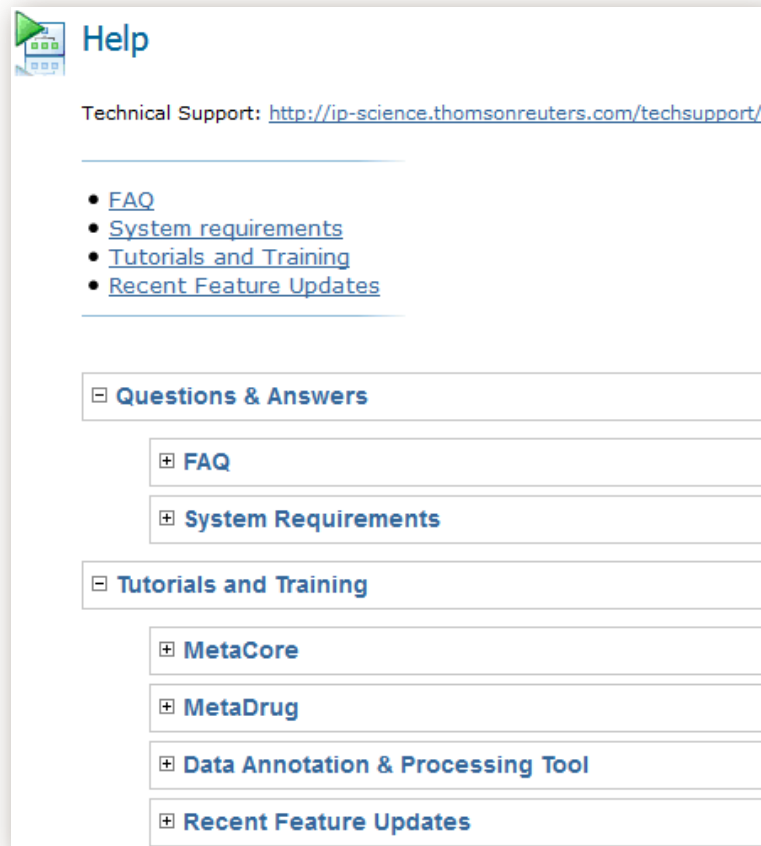
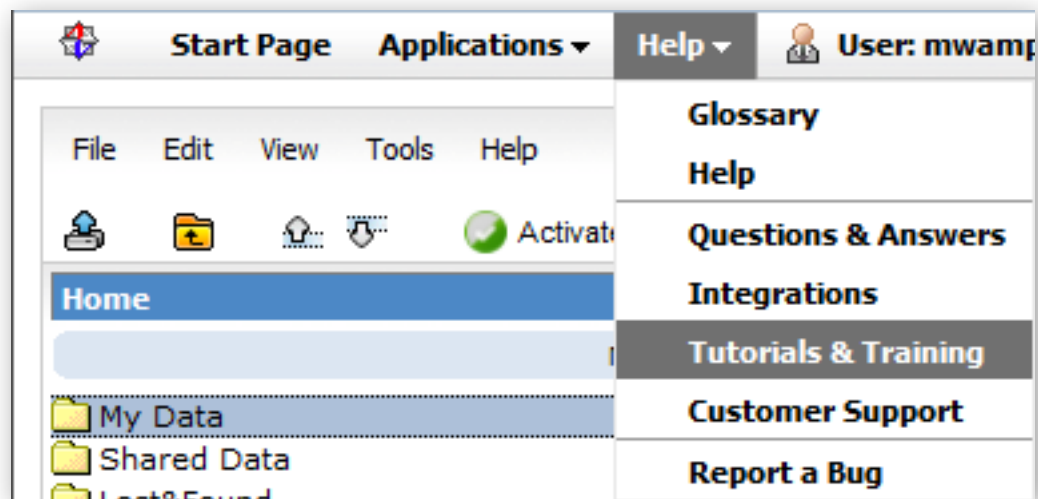
Microarray Repository

- [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!



LOGIN TO METACORE

- Go to portal.genego.com



HOME | SUPPORT | TRAINING | ABOUT US

BIOWORLD TODAY

TOMORROW'S NEWS - EVERY DAY.

The issues influencing the future of biopharma. Delivered to you every business day.

SIGN UP FOR YOUR
FREE TRIAL TODAY



“Something that I do with *MetaCore™* in one afternoon now, would have taken a week before.”

DR. CHARLES LECELLIER,
PRINCIPAL INVESTIGATOR,
IGMM

THOMSON REUTERS SYSTEMS BIOLOGY SOLUTIONS

YOUR GPS IN PATHWAY ANALYSIS

Whether you want to reduce the risk in your OMICs analysis, realize the potential of your biomarkers, or establish a target's mechanism of action, Thomson Reuters has the right **solution** for you.

METACORE™

High quality biological systems content in context, giving you essential data and analytical tools to accelerate your scientific research.

METAMINER PARTNERSHIPS

A series of industry-academy partnerships on systems biology of common human diseases and stem cells, led by Thomson Reuters.

METADRUG™

A leading systems pharmacology solution that incorporates extensive manually curated information on biological effects of small molecule compounds.

LOGIN

Username

Password

☐ Remember Me

LOGIN

[Forgot your password?](#)

© 2014 THOMSON REUTERS

[PRIVACY & COOKIES](#)

[DATA USAGE](#)

[TERMS OF USE](#)

[COPYRIGHT](#)

[CONTACT US](#)



THOMSON REUTERS

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".

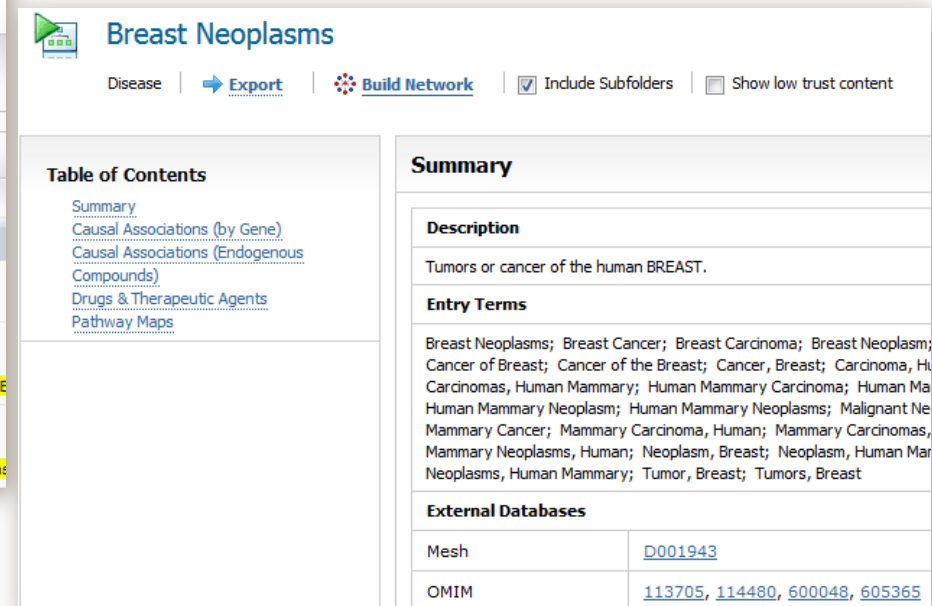
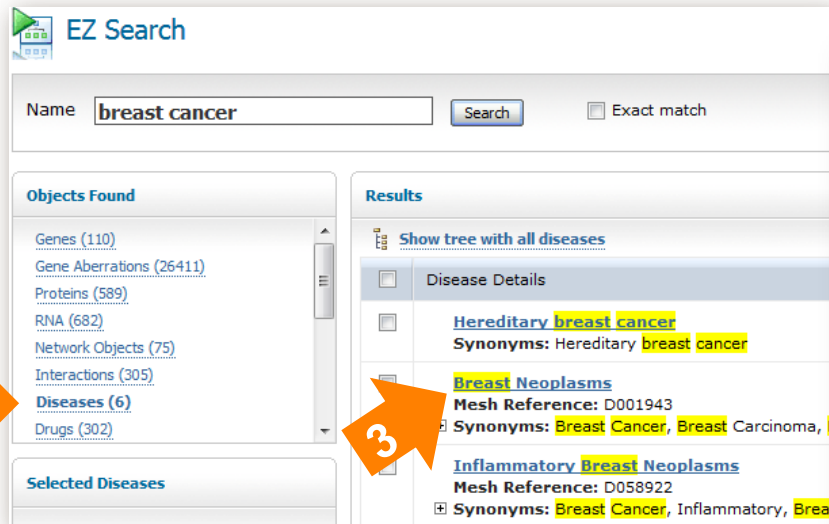
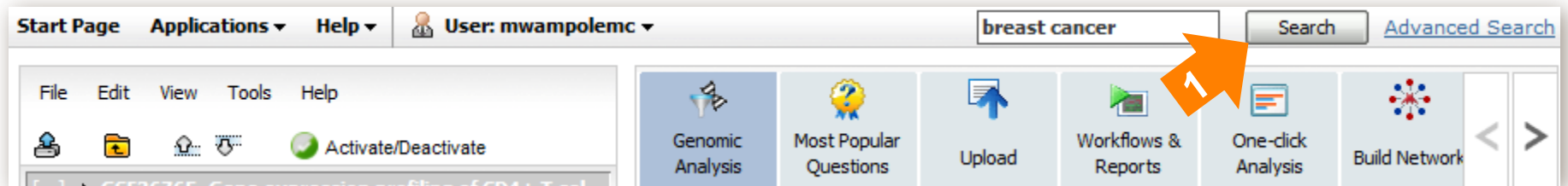
Find Alterations and Aberrations (RNA Level) with increased level or
with decreased level that are associated with Diseases Breast Neoplasms ...
with increased level or with decreased level and are associated with
Diseases Melanoma ...

Find:

that

- 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



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

Causal Associations (by Gene)

Result pages: 1 * 6 7 8 9 10 * 168 (Showing results 141 to 160 of 3344)

#	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

Search [Advanced 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 ...

Search

Find: Alterations and Aberrati...

that

are associated with

Diseases

Breast Neo...

+ that

☐ Include Subfold...

and

are associated with

Diseases

Melanoma

+ that

☐ Include Subfold...

Conversion "are associated with"

Abundance:

☒ Up

☒ Down

☐ Indifferent

Activity/Gain/Loss of Functions:

☐ Up

☐ Down

☐ Indifferent

☐ Unknown

Subcellular localization change:

From:

any

To:

any

#	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;I Ductal;Endor Breast;Menir
31	VEGFC	VEGFC_(HUMAN)_transcript	Mature RNA	indifferent;down;u	down;up	Glioblastoma Acute;Neuro Carcinoma, F



THOMSON REUTERS

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

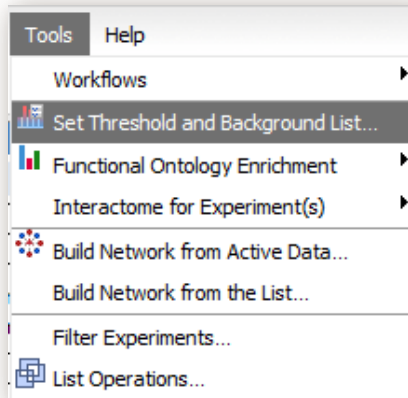
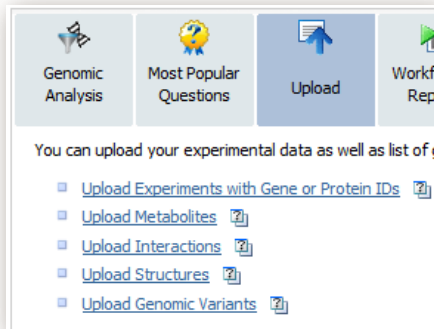
Upload
dataset into
MetaCore

Set
Threshold/
Background

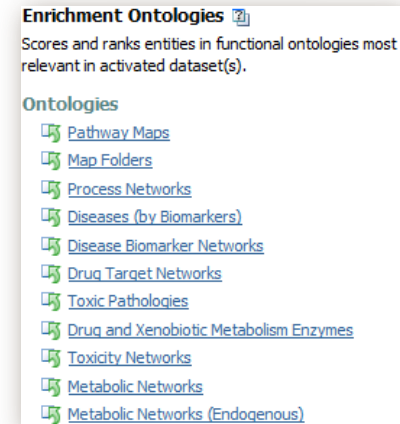
Analyse
Map
Folders



Upload



One-click Analysis



- 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

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	Name	Fold-change	P-value
<input checked="" type="checkbox"/> Affymetrix tag IDs (expression)	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

4

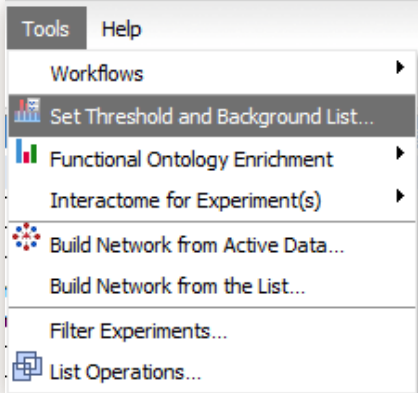
Data Analysis Wizard (General parser)

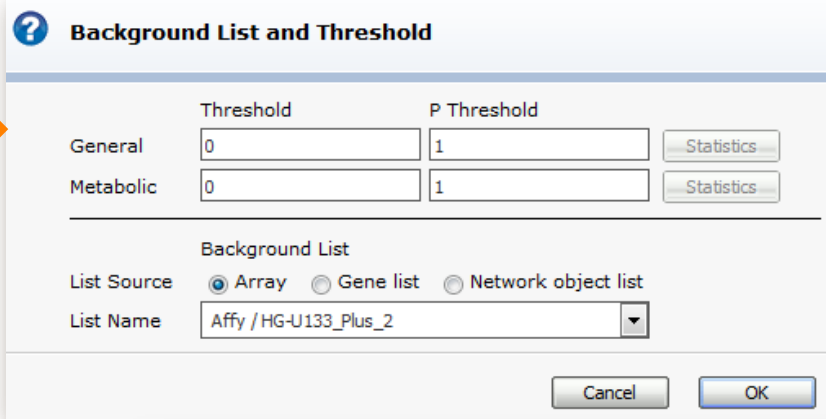
Step 3

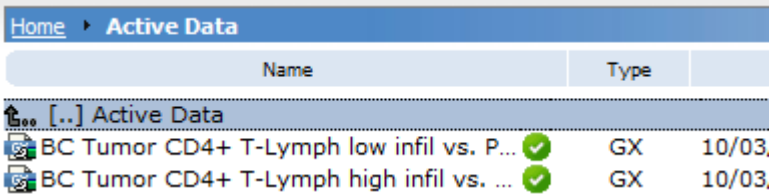
Species

Choose species: Homo sapiens

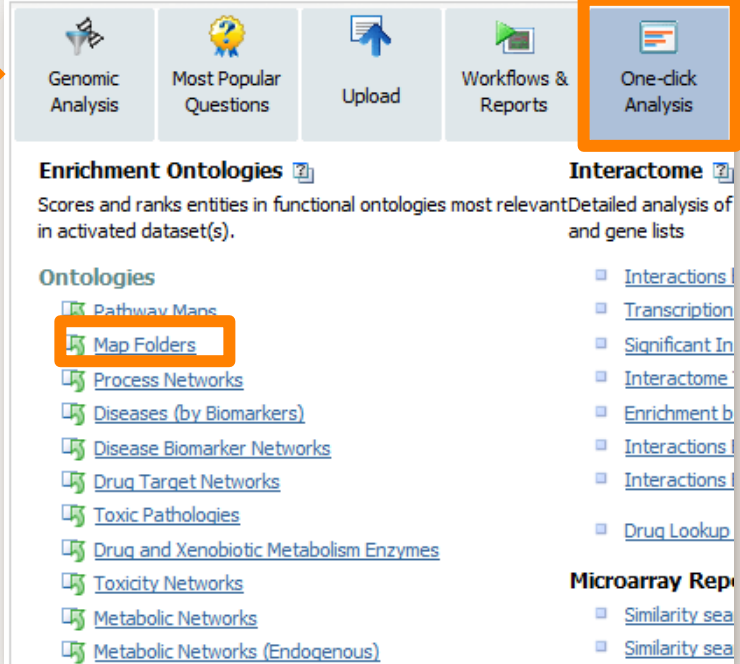
SET THRESHOLD/BACKGROUND AND RUN MAP FOLDER ANALYSIS

1 

2 

3 

Name	Type	
[...] Active Data		
BC Tumor CD4+ T-Lymph low infil vs. P...	GX	10/03
BC Tumor CD4+ T-Lymph high infil vs. ...	GX	10/03

4 

Enrichment Ontologies

Scores and ranks entities in functional ontologies most relevant in activated dataset(s).

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

Detailed analysis of and gene lists

- Interactions
- Transcription
- Significant In
- Interactome
- Enrichment b
- Interactions
- Interactions
- Drug Lookup

Microarray Rep

- Similarity sea
- Similarity sea

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?

<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

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

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

#	Map folders	0	2	4	6	8	10	-log(pValue)	pValue	min(pValue) ↑	FDR	Ratio
1	Systemic Lupus Erythematosus							1.311e-13	1.311e-13	8.127e-12	130/1267	
								2.068e-6		1.165e-5	115/1267	
2	Dermatitis, Allergic Contact							3.586e-13	3.586e-13	1.112e-11	107/958	
								7.333e-5		2.842e-4	87/958	
3	Neurofibromatosis							3.317e-9	7.715e-12	3.427e-8	110/1145	
								7.715e-12		4.783e-10	123/1145	
4	Immune system response							5.494e-11	5.494e-11	1.135e-9	113/1117	
								2.849e-5		1.359e-4	100/1117	

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

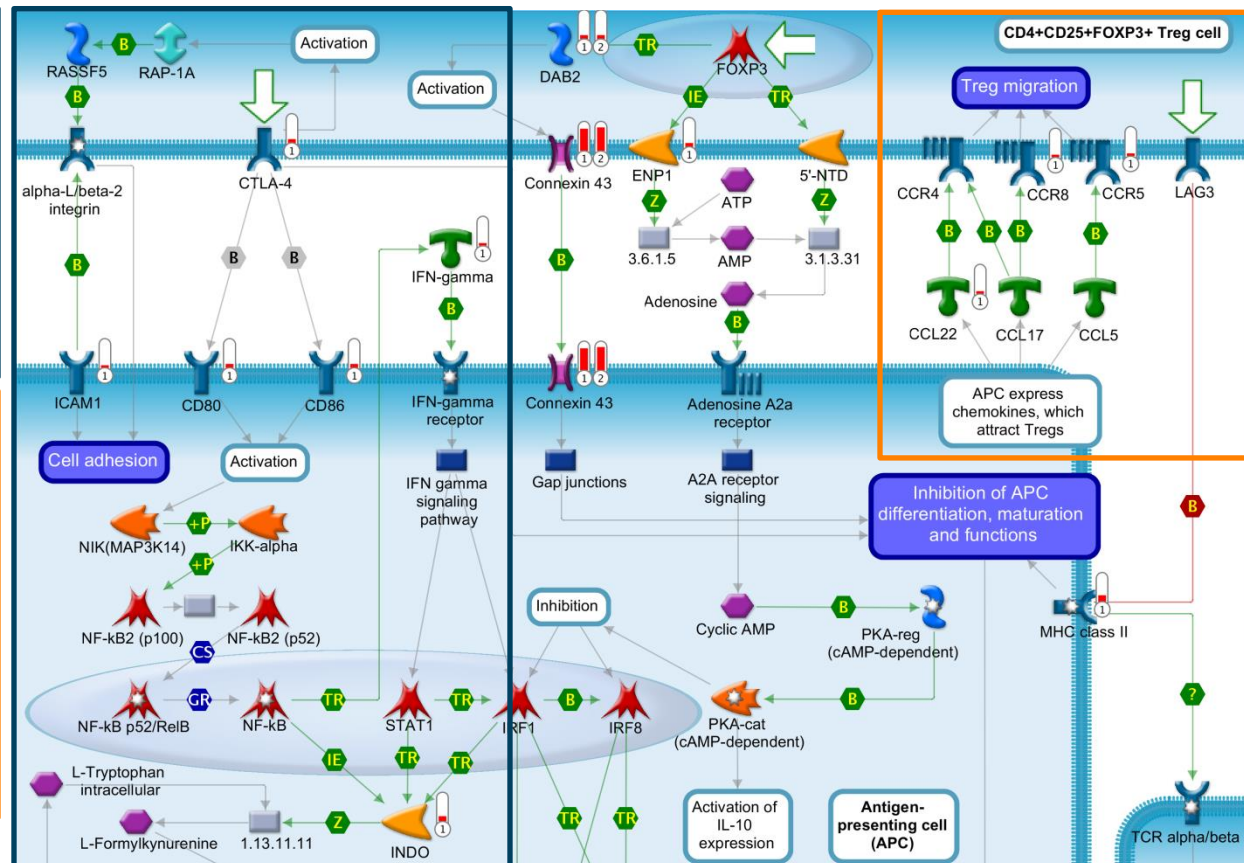
ARE THERE PARTICULAR PATHWAYS SHOWING A DIFFERENCE BETWEEN HIGH AND LOW INFILTRATING T-LYMPHOCYTES?

<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

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.

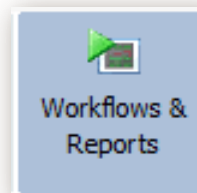
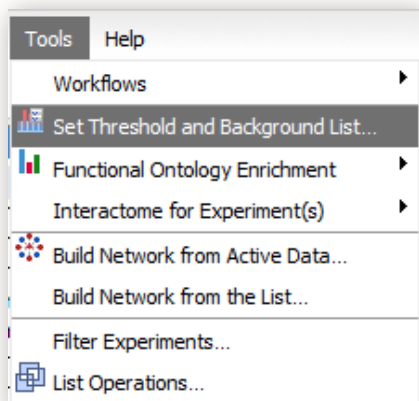
Increased expression of receptors (CCR8 & CCR5) and ligand (CCL22) for T_{reg} migration is seen in high infiltrating T-lymphocytes.



COMPARING TWO DATASETS WITH COMPARE EXPERIMENTS

Set Threshold/
Background

Compare Experiments
Workflow



Data Analysis Workflows

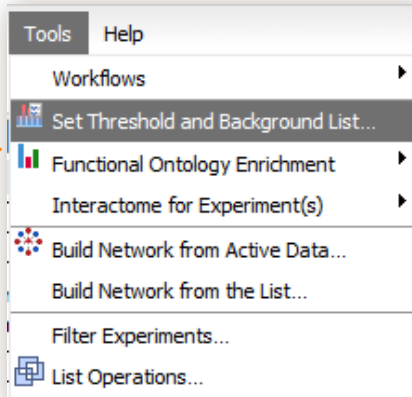
A set of simple step-by-step wizards for analysis of your data.

- [Enrichment Analysis](#)
- [Analyze Single Experiment](#)
- [Compare Experiments](#)
- [Compare Compounds](#)
- [Toxicity Analysis](#)
- [Biomarker Assessment](#)
- [Interactome Analysis](#)

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

SET THRESHOLD/BACKGROUND AND RUN COMPARE EXPERIMENTS WORKFLOW

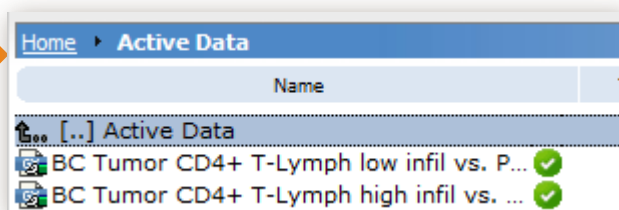
1



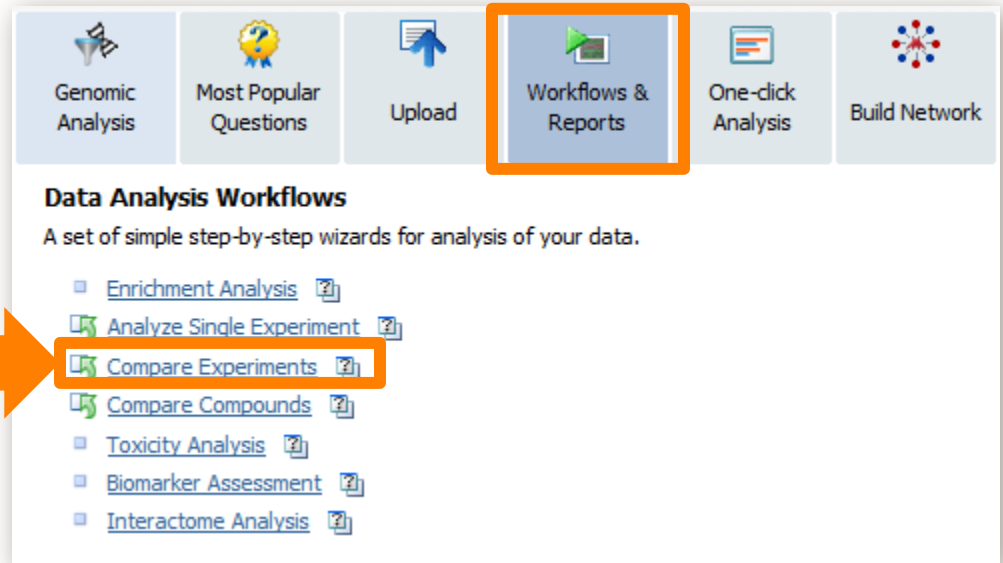
2

The 'Background List and Threshold' dialog box is shown. It has two sections: 'Threshold' and 'Background List'. The 'Threshold' section has two rows: 'General' and 'Metabolic', each with a 'Threshold' input field (set to 0) and a 'P Threshold' input field (set to 1). The 'Background List' section has a 'List Source' section with radio buttons for 'Array' (selected), 'Gene list', and 'Network object list'. Below it is a 'List Name' dropdown menu showing 'Affy / HG-U133_Plus_2'. There are 'Cancel' and 'OK' buttons at the bottom right.

3

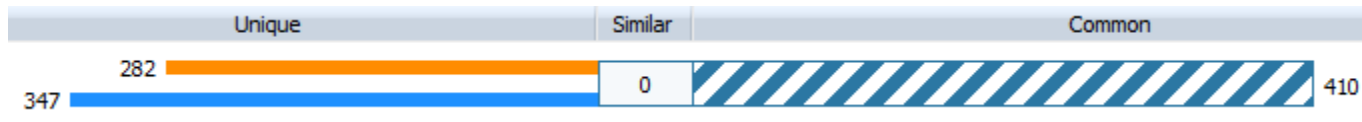


4

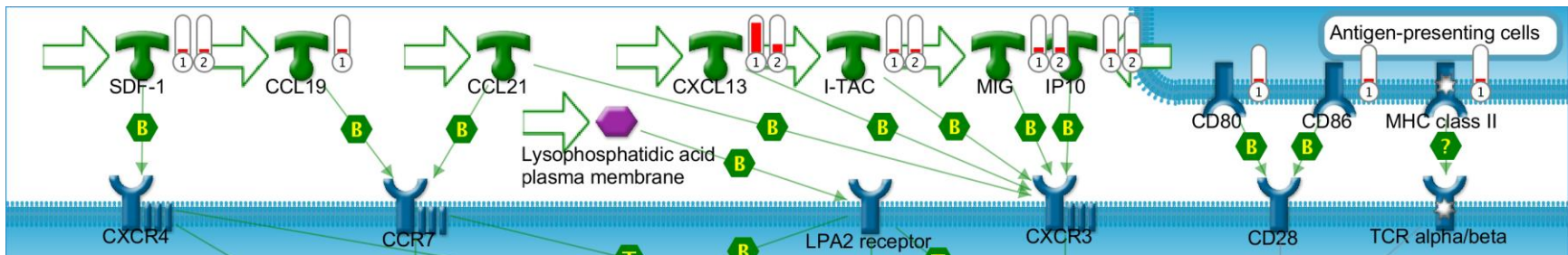


WHAT PATHWAYS ARE COMMONLY AFFECTED BY HIGH AND LOW INFILTRATING T-LYMPHOCYTES?

<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



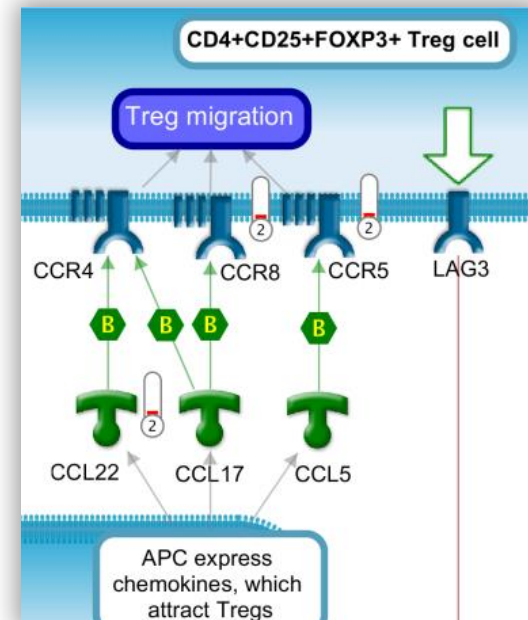
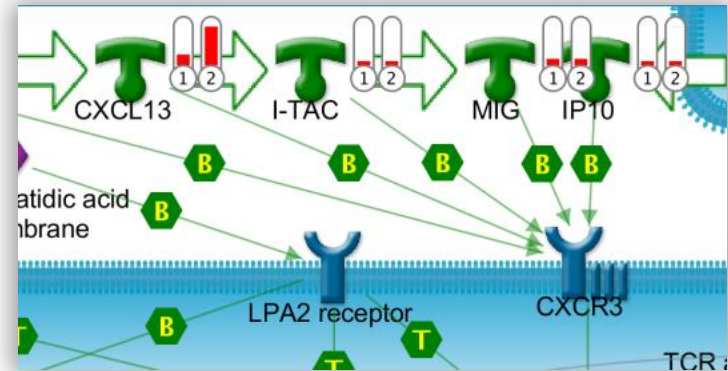
Chemotaxis Leukocyte chemotaxis



- 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

- **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
 - 30-45 min – Using the Microarray repository for gene comparisons against public data
 - 45-60 min – Building Networks with MetaCore
 - 30-45 min – Multi-omics analysis with miRNA & mRNA data
 - 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.

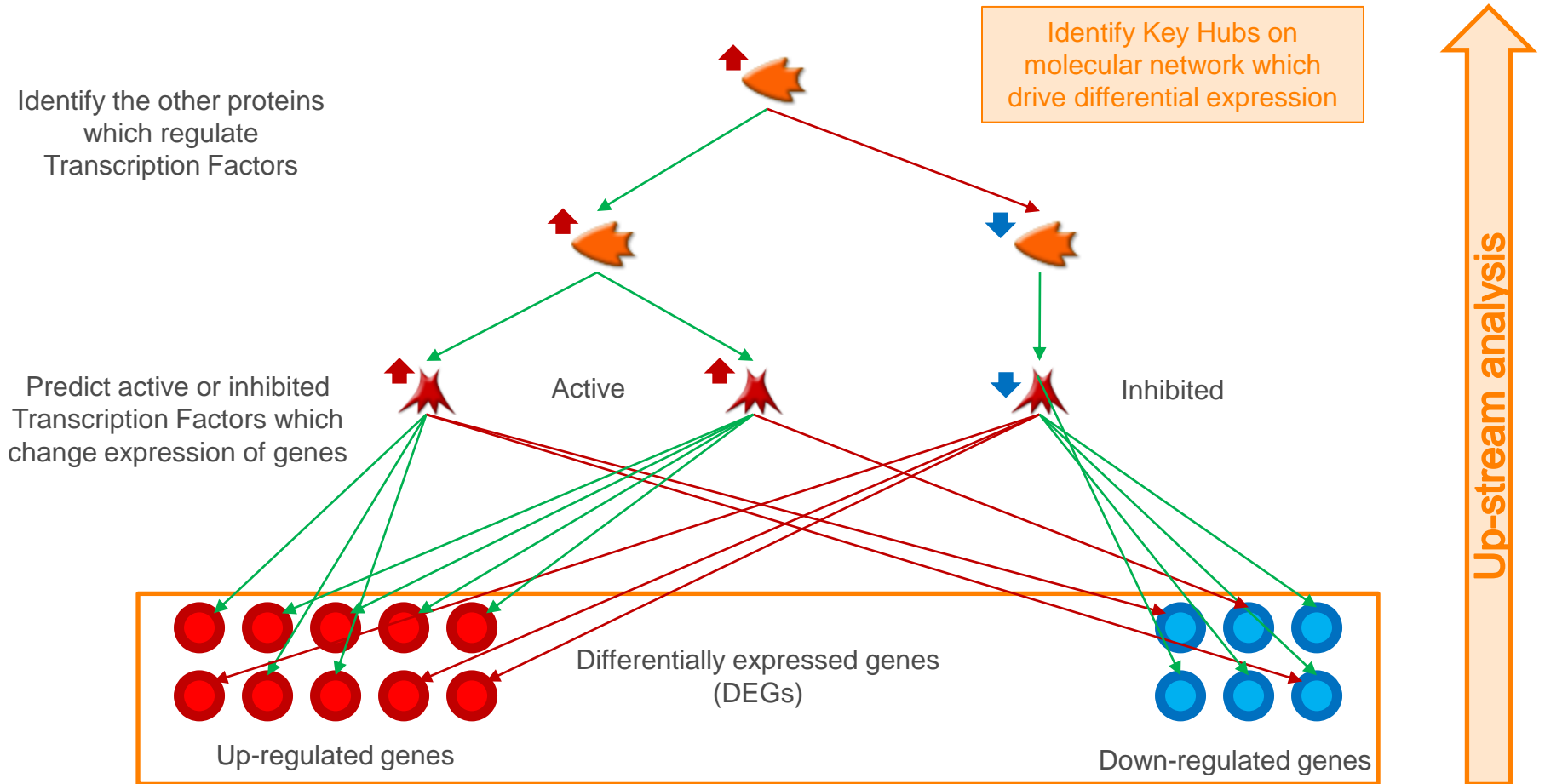
One-Click Analysis

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


(Optional)


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

Analysis Settings

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

SYNERGY ENRICHMENT RESULTS

P-value threshold

KEY HUBS ALGORITHM

Causal Reasoning

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

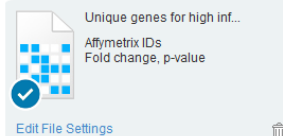
WELCOME TO KEY PATHWAY ADVISOR

NEW ANALYSIS

1 File Upload

2 Analysis Settings

3 Run Analysis



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

3 Next

2

DRAG AND DROP YOUR GENE LIST/EXPRESSION FILE HERE ⓘ

or

Select file to upload

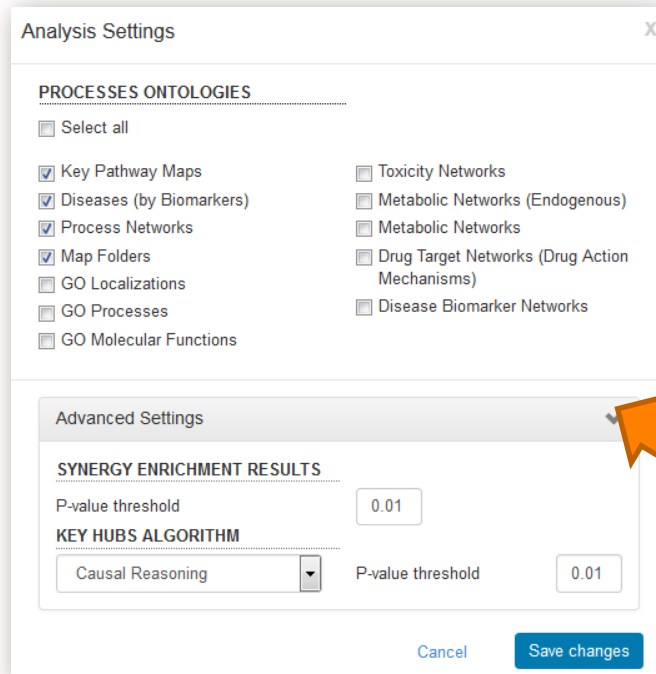
Click here to find additional information on uploading data



THOMSON REUTERS

ANALYSIS SETTINGS

Include additional ontologies for enrichment



Analysis Settings

PROCESSES ONTOLOGIES

☐ Select all

<input checked="" type="checkbox"/> Key Pathway Maps	<input type="checkbox"/> Toxicity Networks
<input checked="" type="checkbox"/> Diseases (by Biomarkers)	<input type="checkbox"/> Metabolic Networks (Endogenous)
<input checked="" type="checkbox"/> Process Networks	<input type="checkbox"/> Metabolic Networks
<input checked="" type="checkbox"/> Map Folders	<input type="checkbox"/> Drug Target Networks (Drug Action Mechanisms)
<input type="checkbox"/> GO Localizations	<input type="checkbox"/> Disease Biomarker Networks
<input type="checkbox"/> GO Processes	
<input type="checkbox"/> GO Molecular Functions	

Advanced Settings

SYNERGY ENRICHMENT RESULTS

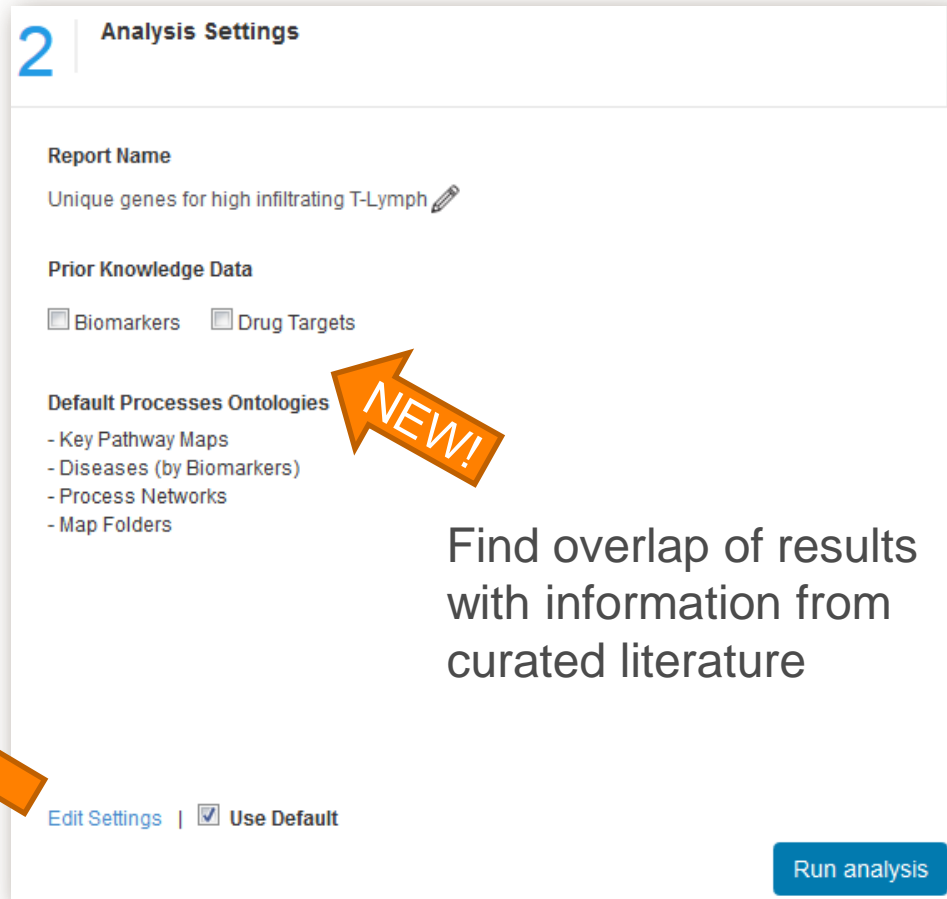
P-value threshold

KEY HUBS ALGORITHM

Causal Reasoning


P-value threshold

[Cancel](#) [Save changes](#)



2 Analysis Settings

Report Name

Unique genes for high infiltrating T-Lymph 

Prior Knowledge Data

☐ Biomarkers ☐ Drug Targets

Default Processes Ontologies

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

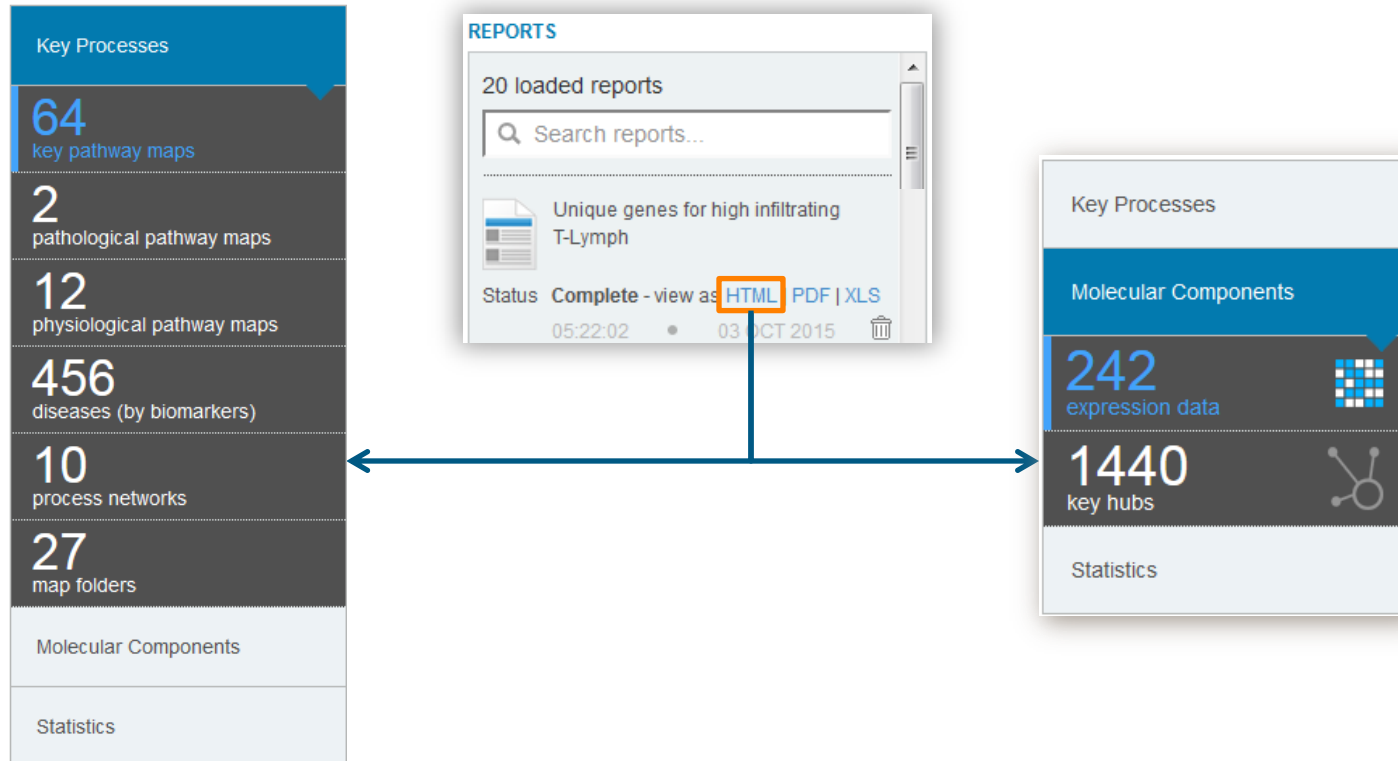
[Edit Settings](#) | ☒ Use Default

[Run analysis](#)

NEW!

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 checked="" type="checkbox"/> grouped <input 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



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

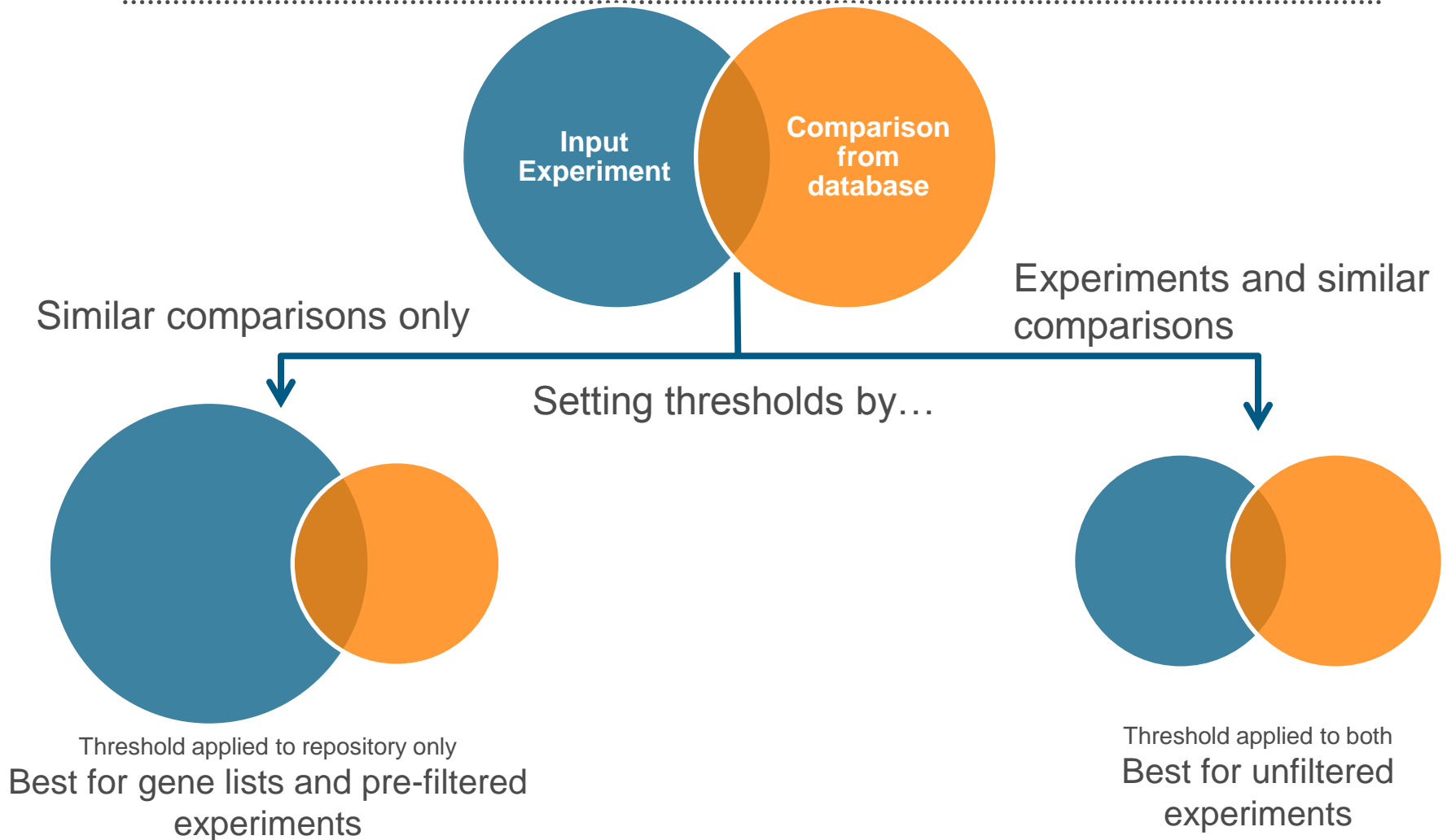
Indicates key hub is also a DEG

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



One-click Analysis

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 !\[\]\(223f1a84e0bc2cacb9c165f716817dcc_img.jpg\)](#)

Microarray Repository

- [Similarity search by Genes !\[\]\(e548a391c65118ac2476924cdb5db38c_img.jpg\)](#)
- [Similarity search by Functional Descriptors !\[\]\(6fc1fda334fce799e3b50f6cf68d70a8_img.jpg\)](#)

▼ Similar comparisons to experiments

Export

<input type="checkbox"/> Case Group	Control Group
<input type="checkbox"/> Ulcerative Colitis Colonic Mucosa, without Response to Infliximab Treatment, before Treatment	Normal Colonic Mucosa
<input type="checkbox"/> Ulcerative Colitis, Infliximab 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 Infliximab Treatment, before Treatment	Normal Colonic Mucosa

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



THOMSON REUTERS

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

Ω: Add/Remove

Home

Name	Type	Date
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	<input type="radio"/> up <input type="radio"/> down <input checked="" type="radio"/> 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

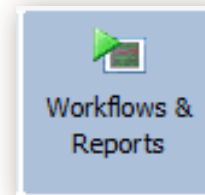
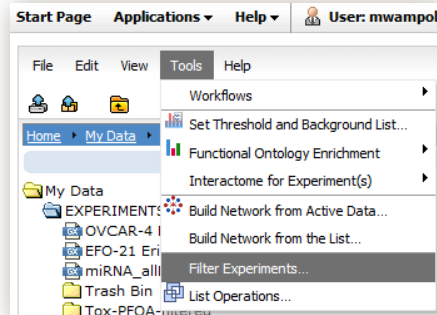
Export						
<input type="checkbox"/>	Case Group	Control Group	Species	Gene Overlap	p-Value ↑	View
<input type="checkbox"/>	Ulcerative Colitis Colonic Mucosa, without Response to Infiximab Treatment, before Treatment	Normal Colonic Mucosa	Homo sapiens	304/785	0	
<input type="checkbox"/>	Ulcerative Colitis, 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

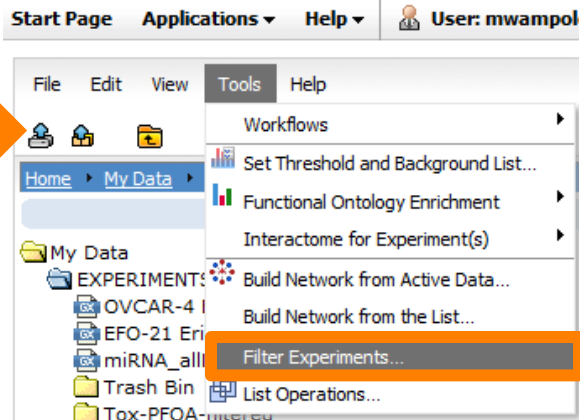
A set of simple step-by-step wizards for analysis of your data.

- [Enrichment Analysis](#)
- [Analyze Single Experiment](#)
- [Compare Experiments](#)
- [Compare Compounds](#)
- [Toxicity Analysis](#)
- [Biomarker Assessment](#)
- [Interactome Analysis](#)

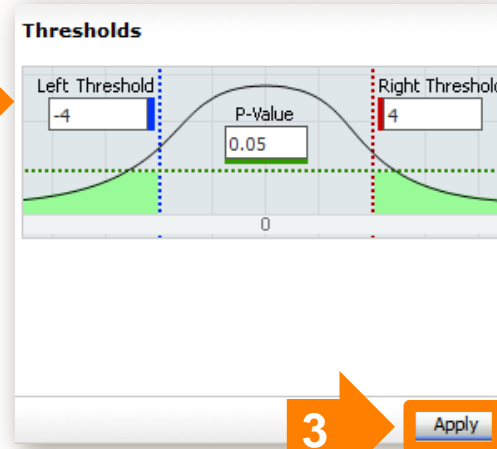
- Question:
 - What pathways are disrupted by both ulcerative colitis and colorectal cancer expression data?

FILTER DATASET

1



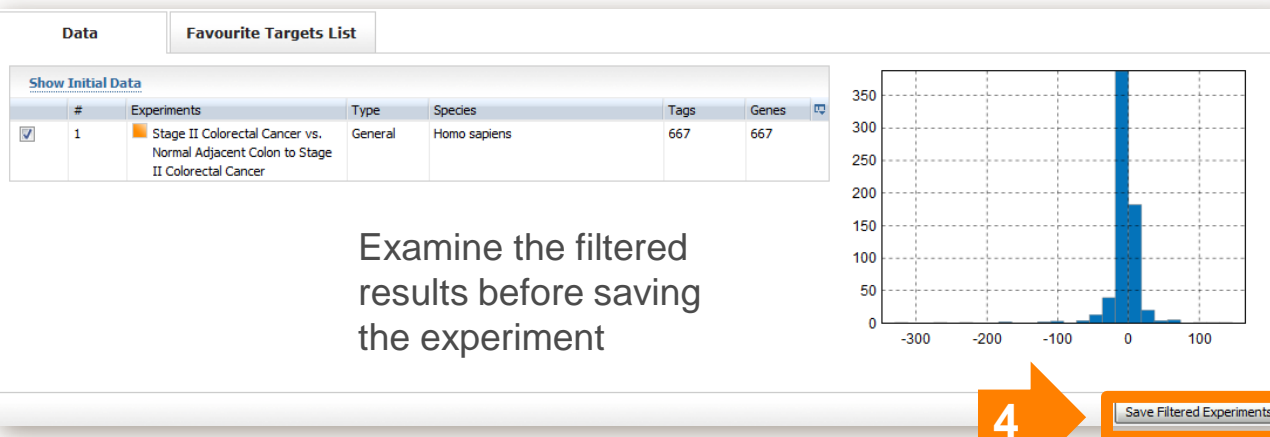
2



Set your filtering thresholds and click apply

3

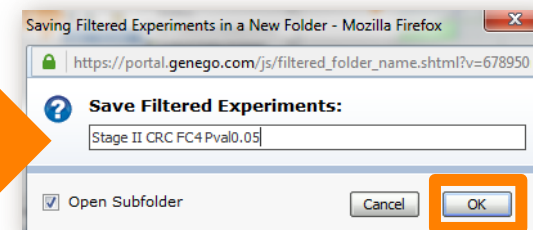
Examine the filtered results before saving the experiment



4

Save Filtered Experiments

5



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?

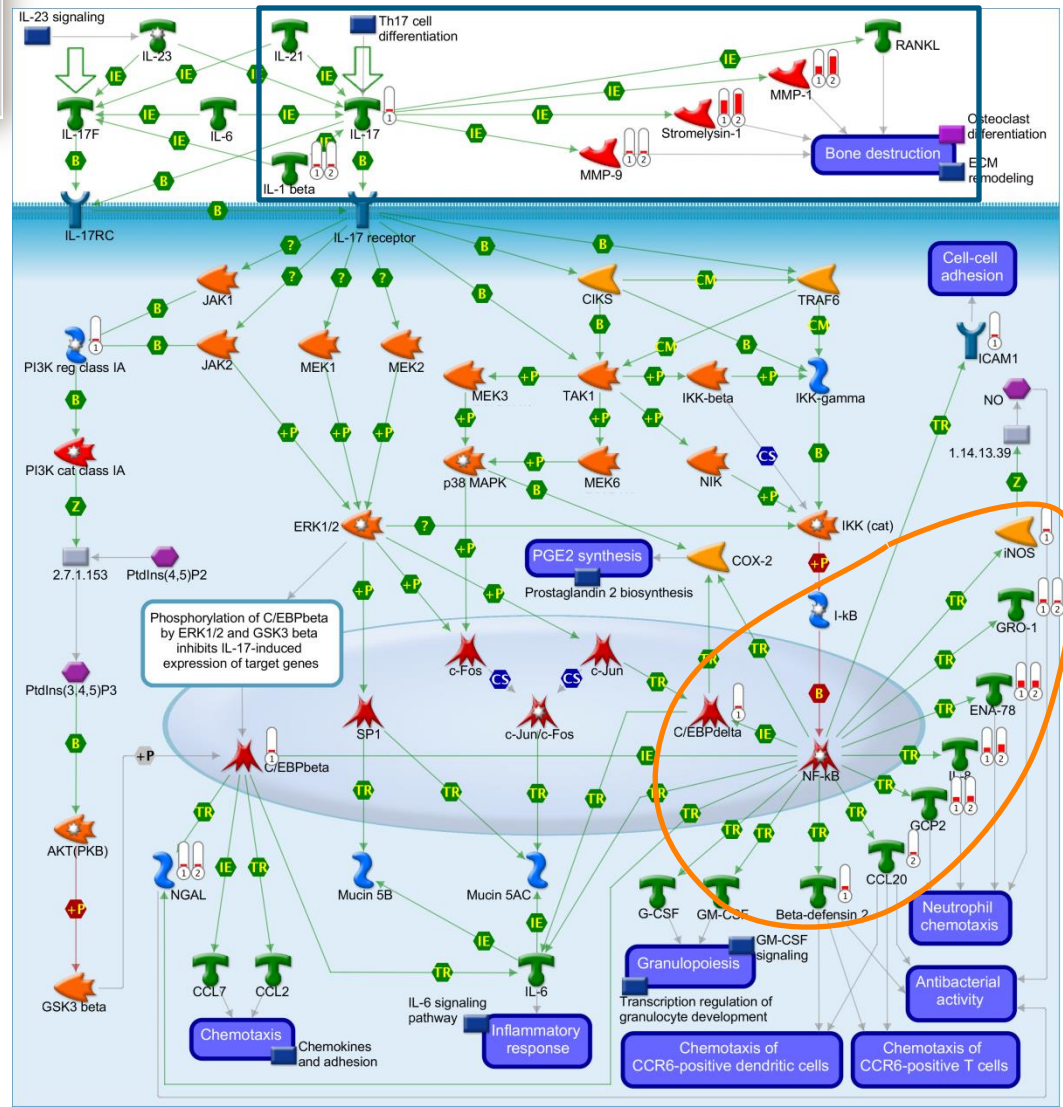
Experiment name	Species	Network Objects
Ulcerative Colitis Intestine vs. Normal Intestine	Homo sapiens	772
Stage II Colorectal Cancer vs. Normal Adjacent Colon to Stage II Colorectal Cancer_FF	Homo sapiens	721

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.

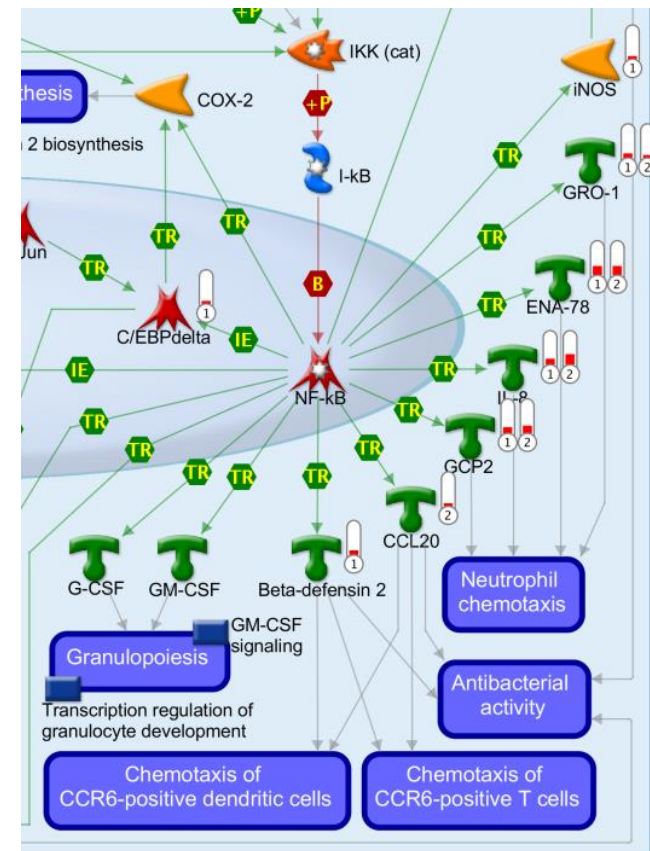
The common signature shares much in common with biomarkers from other gastrointestinal diseases.

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

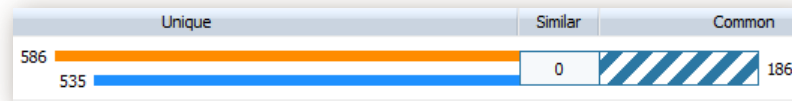
Medium(large) –
< 100 seeds

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

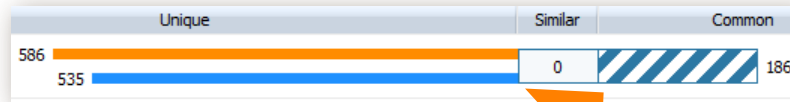
☐ Use canonical pathways
(processing takes longer for large datasets)

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

2

Network options

Choose building algorithm

Direct interactions

☐ Use canonical pathways
(processing takes longer for large datasets)

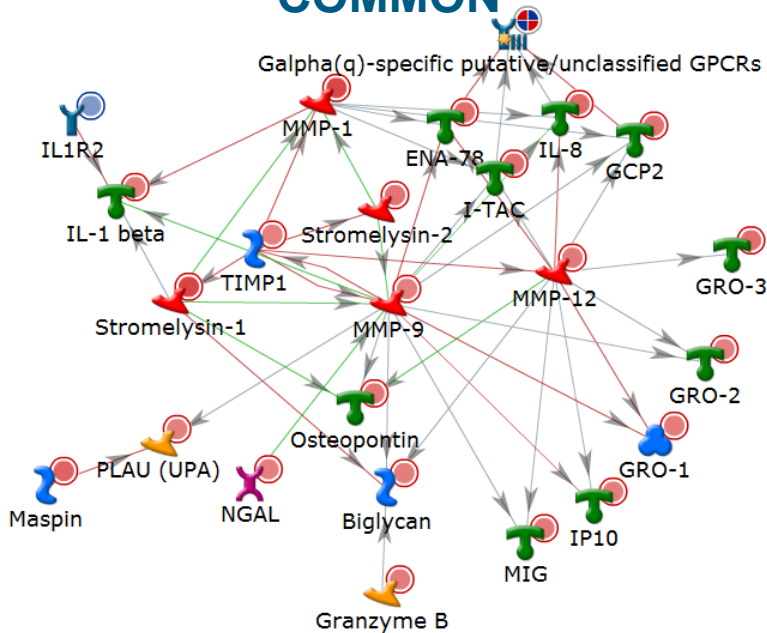
[Show additional options](#)

Build network

3

When finished click
'Build network'

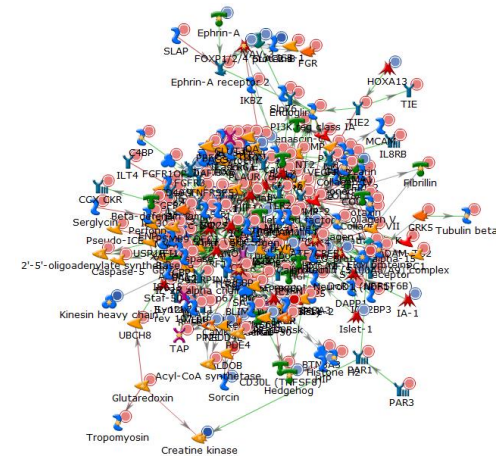




Relationship with cell migration and chemotaxis as well as a strong connection with Crohn's disease and IBD

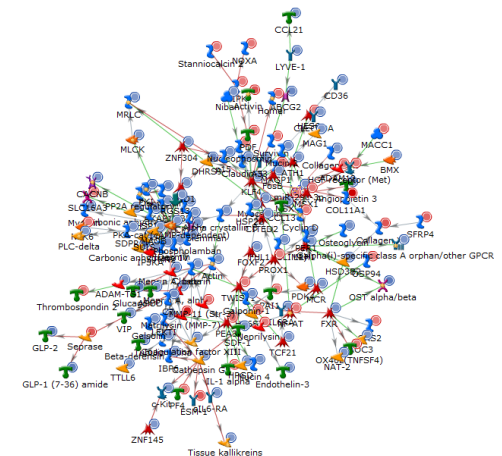
UNIQUE UC

Relationship with immune response and autoimmune diseases



UNIQUE CRC

Relationship with gastrointestinal diseases and cancers



THOMSON REUTERS

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



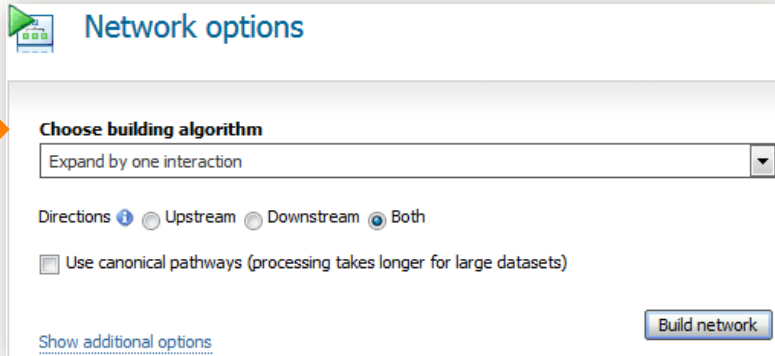
THOMSON REUTERS

UPLOADING MIRNA DATA

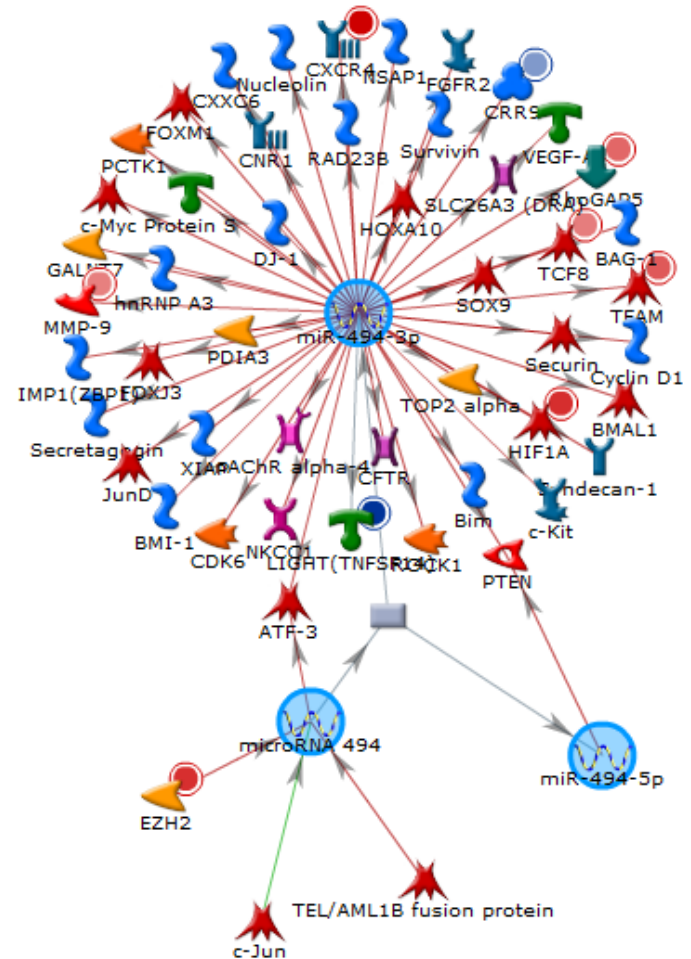
- Same procedure as gene expression, use Entrez ID or miRBase Accession ID (old style miRBase IDs are now under gene symbols)



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



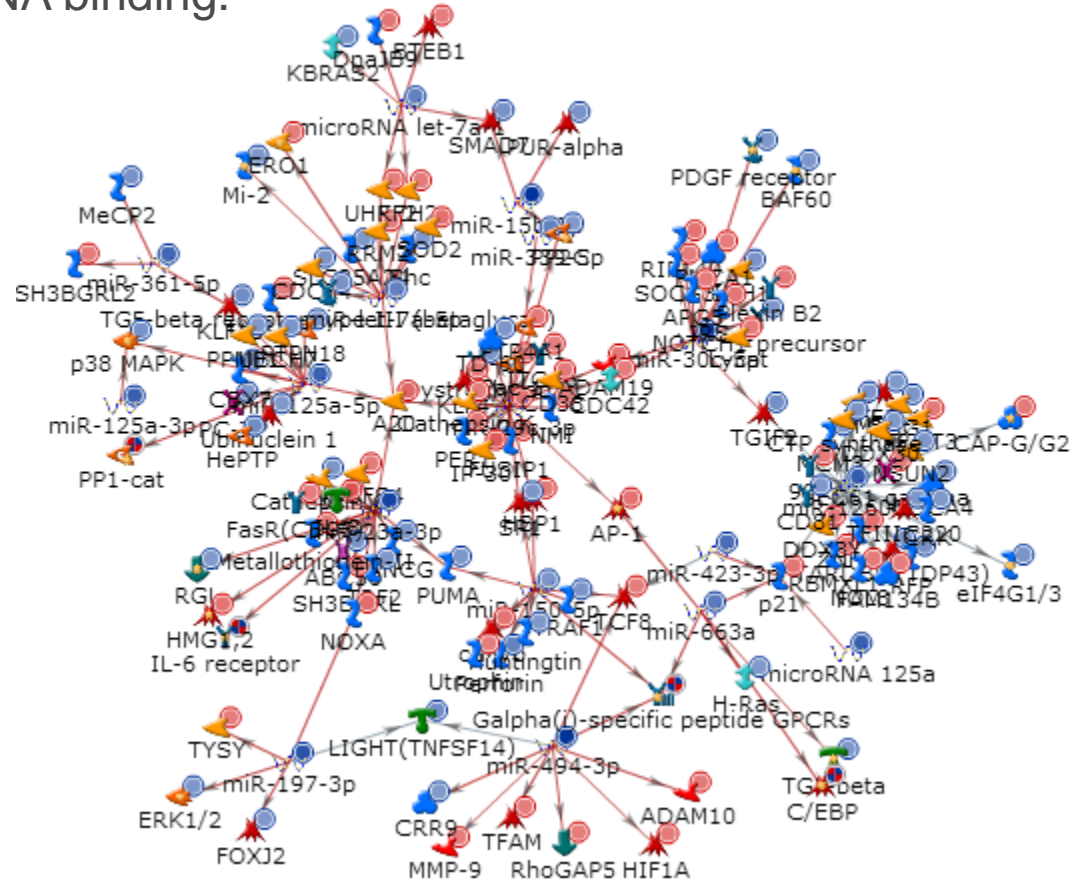
- Build a network using “expand by one interaction” algorithm for interactions with mir-494
- 8 mRNA involved potentially binding with mir-494-3p have a change in expression including: CXCR4 and MMP-9



WHAT IS THE RELATIONSHIP BETWEEN MIRNA AND MRNA EXPRESSION?

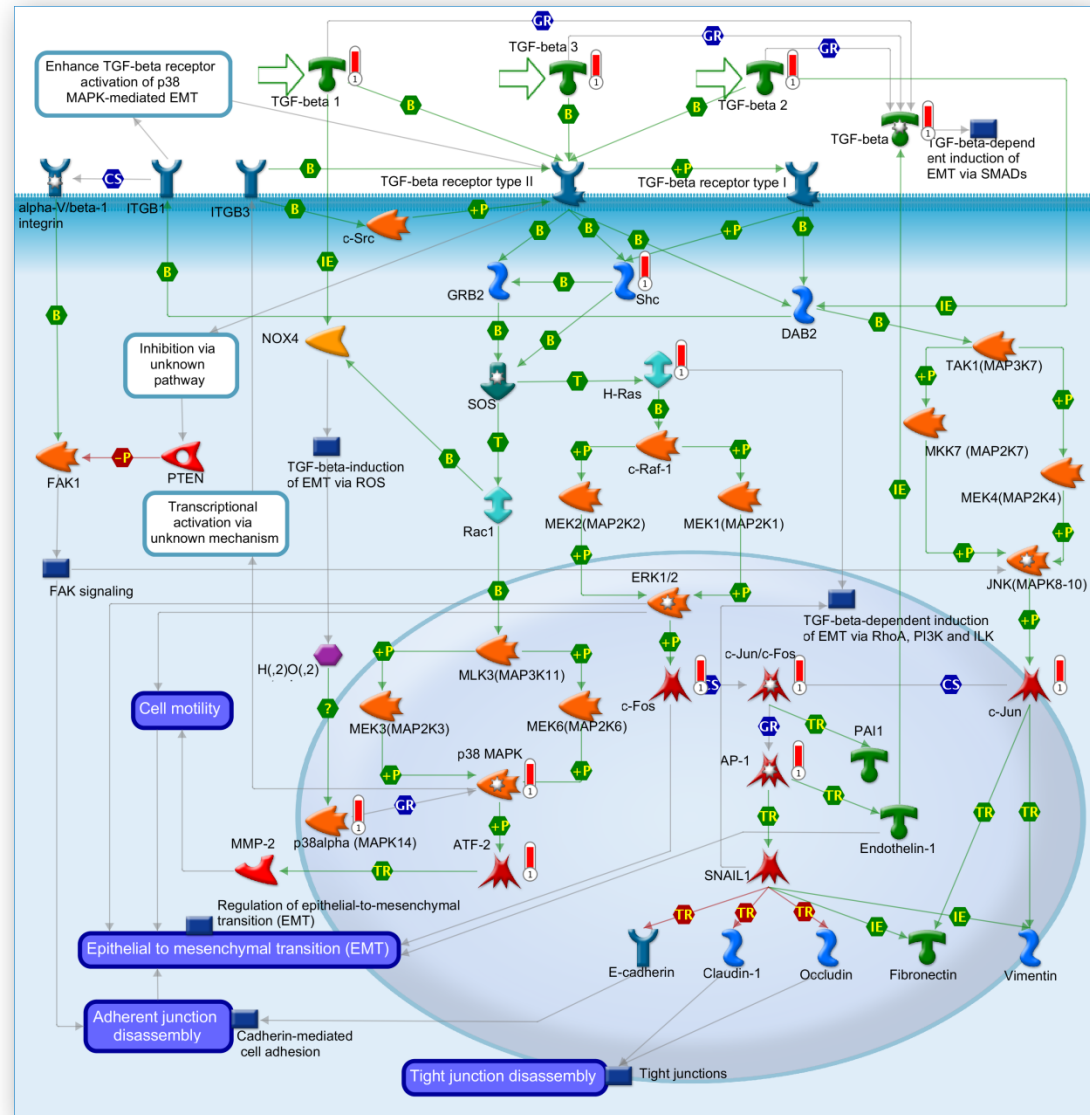
- Using the 'direct interaction' algorithm an interaction network between mRNA and miRNA expression can be built.
- Restrict interactions by using additional options to pre-filter the interactions for only miRNA binding.

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



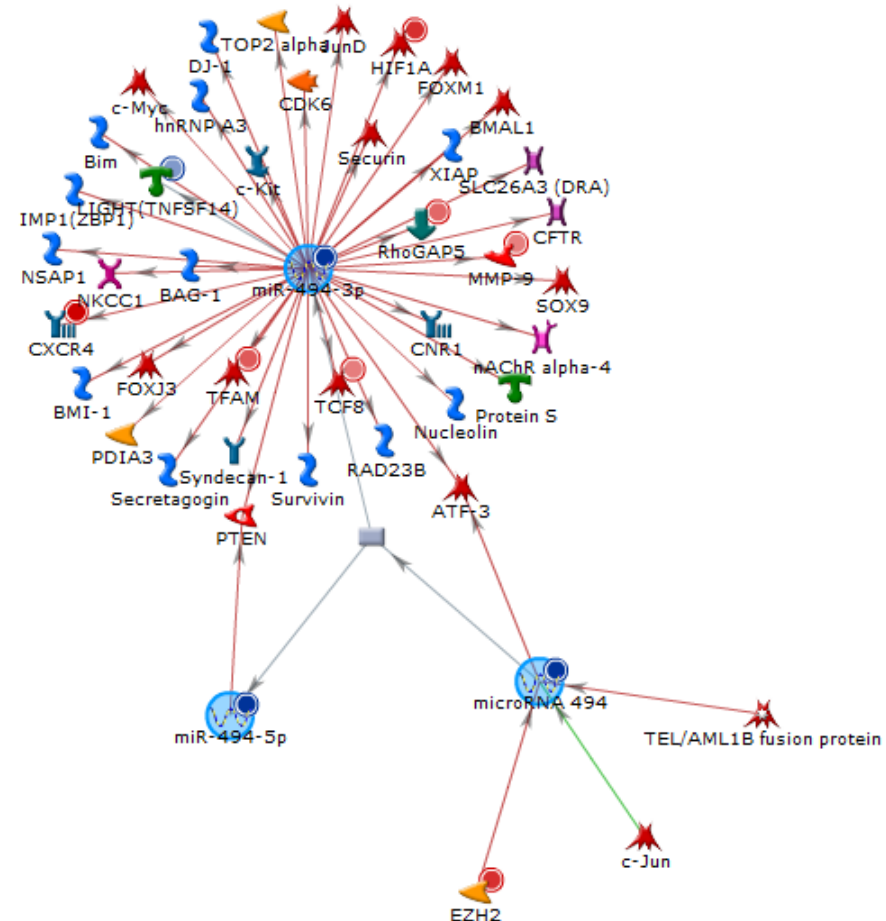
WHAT PATHWAYS ARE IMPACTED BY MRNA FROM THE INTERACTION NETWORK?

- 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

The screenshot displays the MetaCore web interface with several key components:

- Conditional Search:** A search bar with the text "Find Network Objects that are Compounds (Nutrition)" and a dropdown menu set to "Network Objects".
- Compound Filter:** A section with "Grouping:" and "Possible role:" filters. Under "Grouping", options include "Individual objects", "Compound groups", and "Mixtures of optical isomers". Under "Possible role:", options include "Drugs", "Disease Biomarkers", "Toxic Pathologies", and "Toxic Agents".
- Upload Button:** A blue button with an upward arrow icon labeled "Upload".
- Tools Menu:** A dropdown menu with options: "Workflows", "Set Threshold and Background List...", "Functional Ontology Enrichment", "Interactome for Experiment(s)", "Build Network from Active Data...", "Build Network from the List...", "Filter Experiments...", and "List Operations...".
- Enrichment Ontologies:** A section titled "Enrichment Ontologies" with a description: "Scores and ranks entities in functional ontologies most relevant in activated dataset(s)". It lists various 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", and "Metabolic Networks (Endogenous)".

- 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

1

2

3

4

Query 1 x Result x

Search Advanced Search

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...

Compound Filter

Grouping:

- ☐ Individual objects
- ☐ Compound groups
- ☐ Mixtures of optical isomers

Possible role:

- ☐ Drugs
- ☐ Disease Biomarkers
- ☐ Toxic Pathology Biomarkers
- ☐ Toxic Agents

Category:

- ☒ Nutritional
- ☐ Environmental
- ☒ Endogenous
- ☐ Xenobiotic
- ☐ Metabolite of xenobiotic
- ☒ 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: ☒ All rows ☐ With active data only


☐ Current page

☐ Selected rows

THOMSON REUTERS

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:

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

3

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

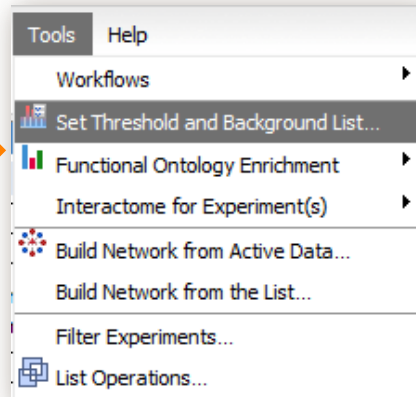
Experiments name prefix: Metabolite-data-BEvsC

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

The screenshot shows the 'Background List and Threshold' dialog box. It has two sections: 'General' and 'Metabolic'. Each section has a 'Threshold' and a 'P Threshold' input field, both set to 0. There are 'Statistics' buttons next to each. Below these is the 'Background List' section, which has a 'List Source' section with radio buttons for 'Array', 'Gene list', and 'Network object list' (selected). There is also a 'List Name' dropdown menu with the text 'endogenous, nutritional, and mixed compounds'. At the bottom are 'Cancel' and 'OK' buttons.

4

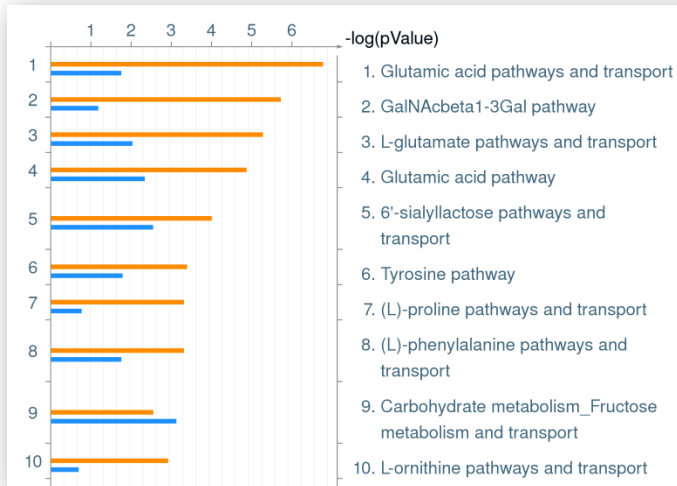
The screenshot shows the 'One-click Analysis' interface. It has a top navigation bar with icons for 'Genomic Analysis', 'Most Popular Questions', 'Upload', 'Workflows & Reports', and 'One-click Analysis' (highlighted with an orange box). Below the navigation bar are two main sections: 'Enrichment Ontologies' and 'Interactome'. The 'Enrichment Ontologies' section has a list of links: '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', and 'Metabolic Networks (Endogenous)' (highlighted with an orange box). The 'Interactome' section has a list of links: 'Interactions', 'Transcription', 'Significant In', 'Interactome', 'Enrichment b', 'Interactions', 'Interactions', and 'Drug Lookup'. At the bottom right, there is a 'Microarray Rep' section with links for 'Similarity sea' and 'Similarity sea'.

3













The screenshot shows the 'Active Data' table. It has a header with 'Name' and 'Type'. Below the header are two rows of data: 'BEVsC-metabolites' and 'EACVsC-metabolites'. Both rows have a green checkmark in the 'Type' column and are marked with 'MX' in the 'Name' column.

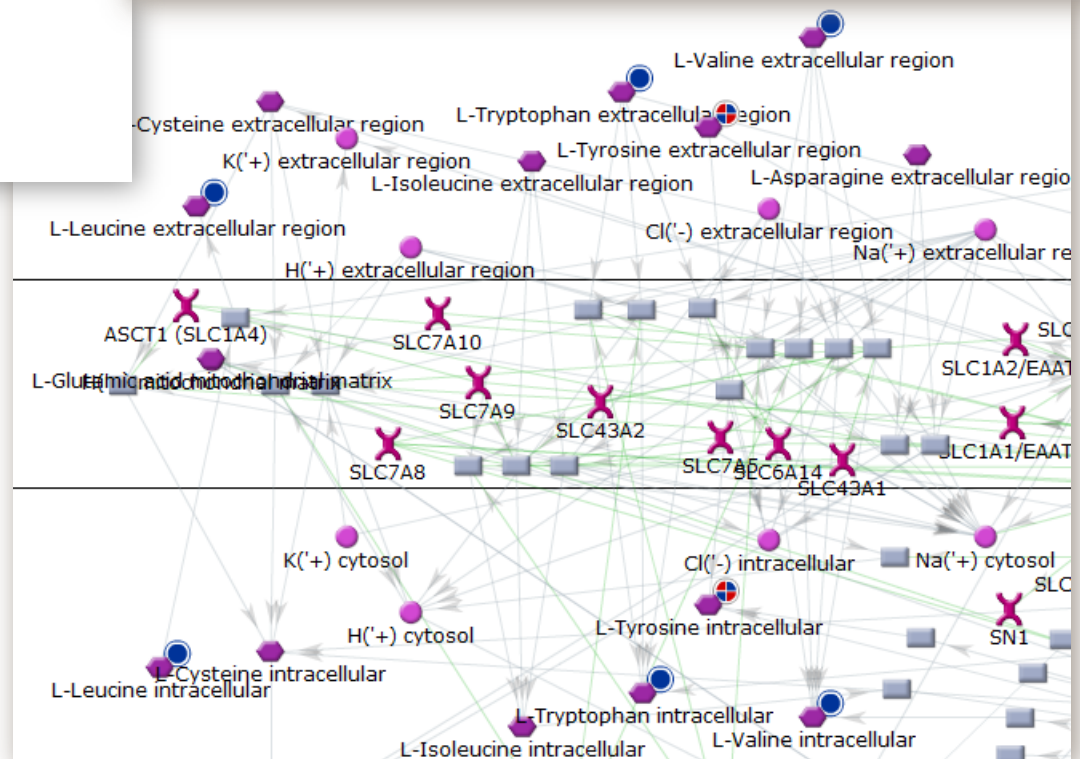
Name	Type
BEVsC-metabolites	MX
EACVsC-metabolites	MX

.....

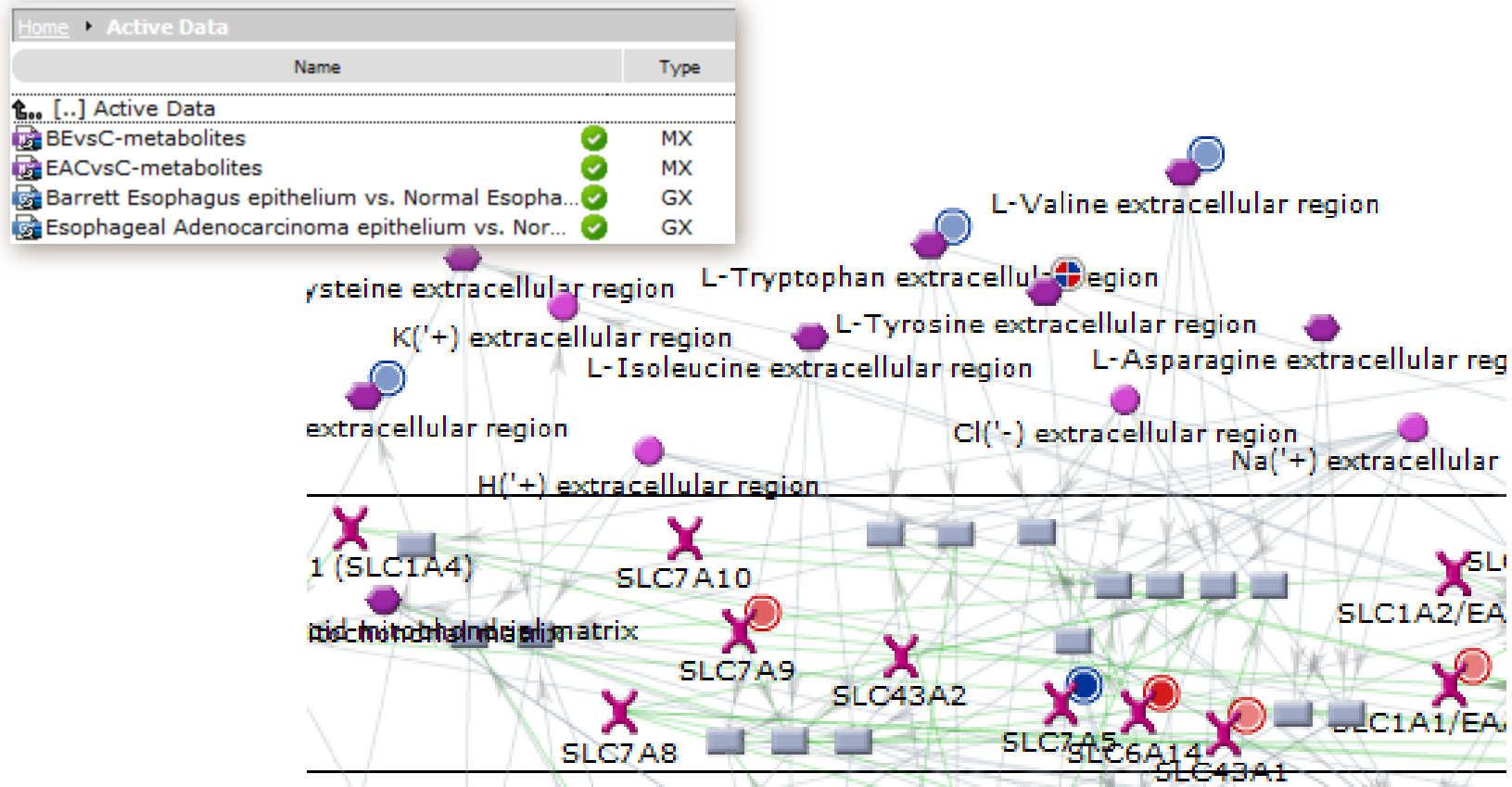


Enrichment analysis of Metabolomic Networks (Endogenous) can quickly identify metabolites impact on processes.

	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



OVERLAYING EXPRESSION AND METABOLIC DATA ONTO METABOLIC PROCESSES



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



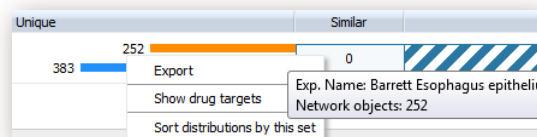
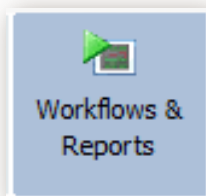
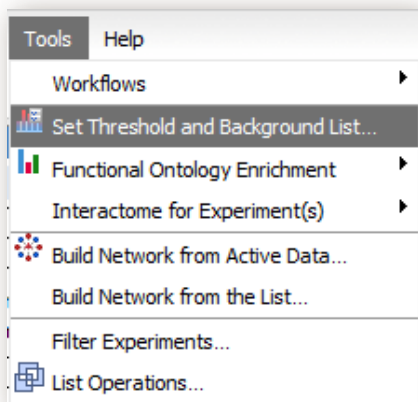
BUILD A NETWORK USING METABOLOMIC AND TRANSCRIPTOMIC DATA

Set
Threshold/
Background

Compare
Experiments
Workflow

Export
unique
network
objects

Build Direct
Interaction
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

Export

Name: BE unique

To: Experiments

Genes of

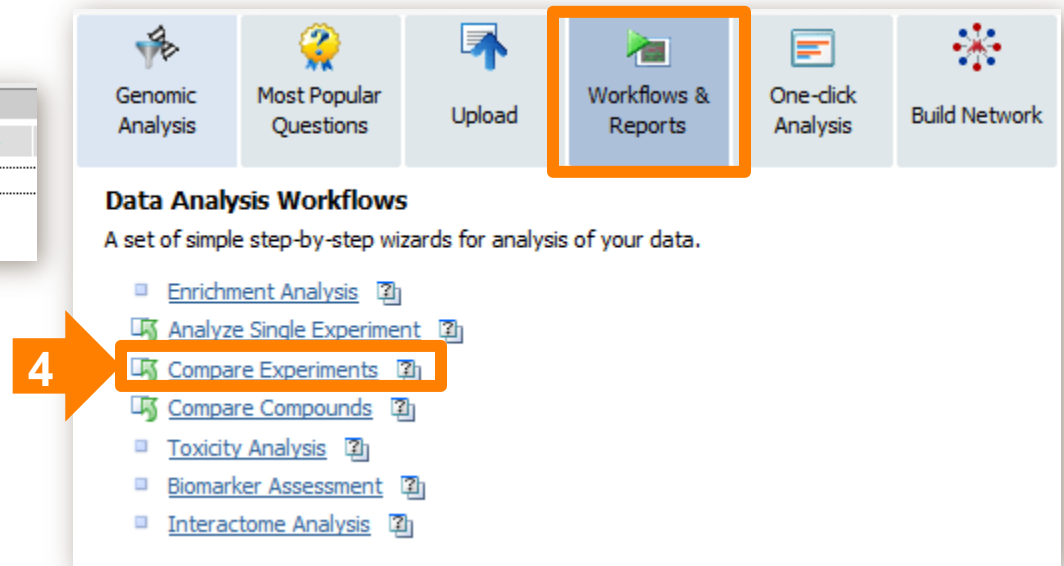
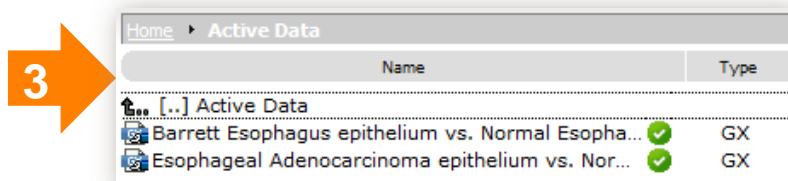
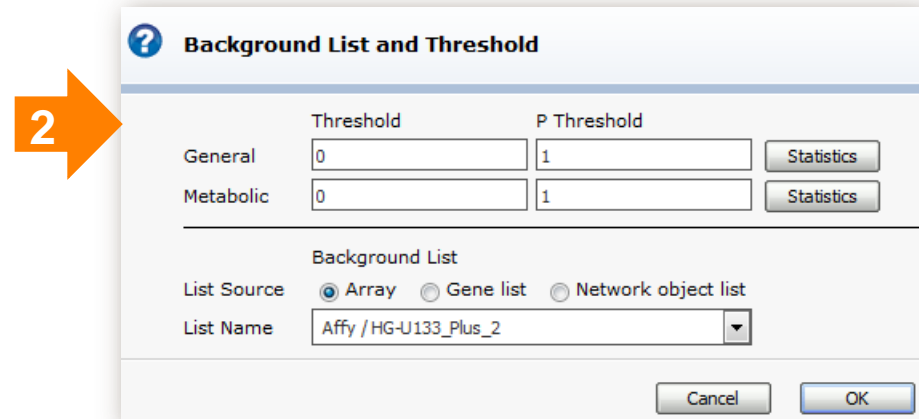
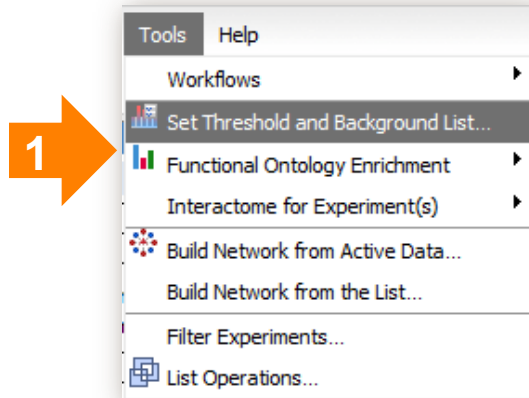
Homo sapiens

The 'Network options' dialog box is shown. It has a 'Choose building algorithm' dropdown set to 'Direct interactions'. There are checkboxes for 'Use canonical pathways', 'Use all compound-target interactions', and others. A 'Build network' button is at the bottom right.

- 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

Unique	Similar	Common
383	252	681

Common gene expression related to remodeling and stomach/gastrointestinal diseases

▼ Pathway Maps

<div>Export</div>		<div>Export to image</div>		Sorting method: <div>Particular maps</div>						Total results: 10		
	#	Maps	0	2	4	6	8	-log(pValue)	pValue	pValue ↑	FDR	Rat
	1	Cytoskeleton remodeling, Keratin filaments	<div><div></div></div>					1.000e+0	1.122e-10	1.000e+0	0/36	
			<div><div></div></div>					1.122e-10		9.978e-8	14/36	
			<div><div></div></div>					1.000e+0		1.000e+0	0/36	
			<div><div></div></div>					7.043e-2		6.043e-1	3/36	

▼ Diseases (by Biomarkers)

<div><div>Export</div><div>Export to image</div></div>		Sorting method: <div>Particular diseases</div>										Total results: 10			
	# Diseases	0	2.5	5	7.5	10	12.5	15	17.5	20	-log(pValue)	pValue	pValue ↑	FDR	Ra
	1 Stomach Diseases	<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div>										1.000e+0	1.720e-21	1.000e+0	0/3358
		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div>										1.720e-21		3.061e-18	221/3358
		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div>										7.911e-9		2.832e-6	83/3358
		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div>										2.977e-14		2.926e-12	128/3358
	2 Stomach Neoplasms	<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div>										1.000e+0	8.470e-21	1.000e+0	0/3311
		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div>										8.470e-21		7.539e-18	217/3311
		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div>										4.020e-9		2.159e-6	83/3311
		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div>										9.978e-15		1.159e-12	128/3311

Unique	Similar
383	252
Export	0
Show drug targets	
Sort distributions by this set	

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

1

Home ▸ Active Data

Name	Type
[...] Active Data	
BEvsC-metabolites	MX
BE unique	GX

2

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

Build Network

- ☐ Build Network for Single Gene/Protein/Compound or a List
- ☒ Build Network for Your Experimental Data
- ☐ Build Network for a Disease
- ☐ Build Network for a Process
- ☐ Merge Networks

Model Pathways

- ☒ Canonical Pathway Modeling
- ☒ Putative Pathway Modeling

3

Network options

Choose building algorithm

Direct interactions

☐ Use canonical pathways
(processing takes longer for large datasets)

[Hide additional options](#)

Build network

Network objects **Pre-filters** **Additional options**

☐ Low trust interactions

☐ Use for network building

☐ Functional interactions

☐ Use for network building

☐ Binding interactions

☐ Use for network building

☒ Use all compound-target interactions

4

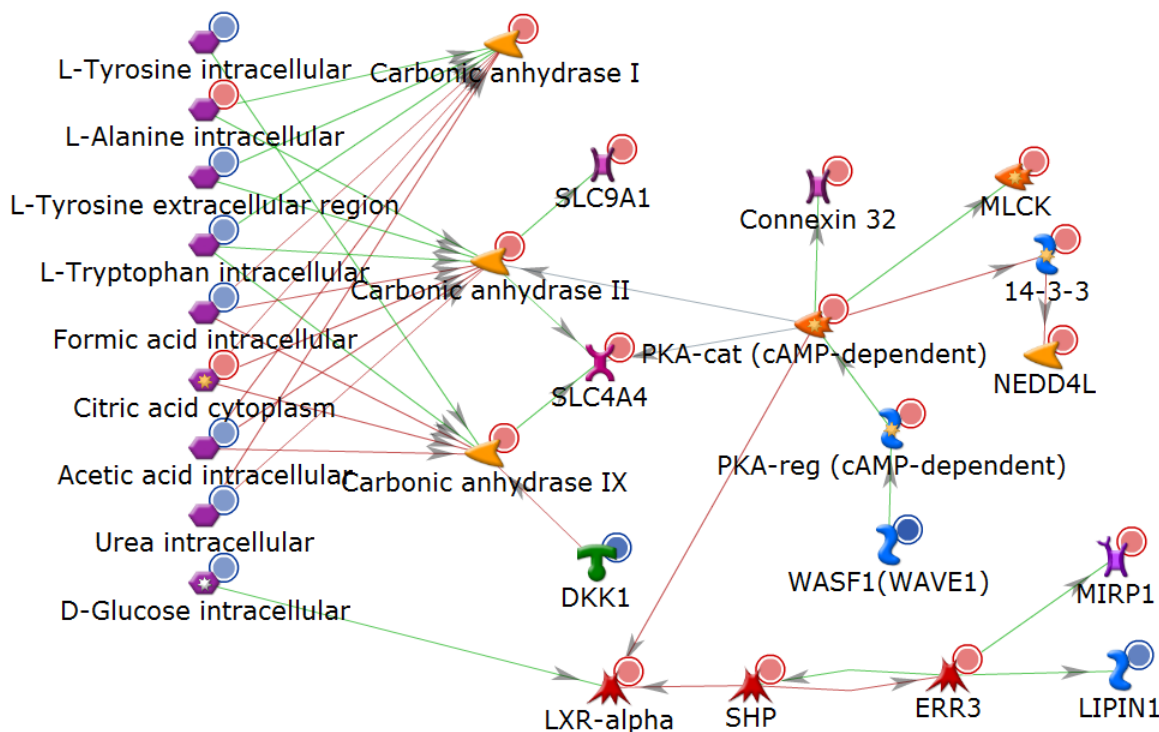
Home ▸ Active Data

Name	Type
[...] Active Data	
BEvsC-metabolites	MX
Barrett Esophagus epithelium vs. Normal ...	GX

5



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



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

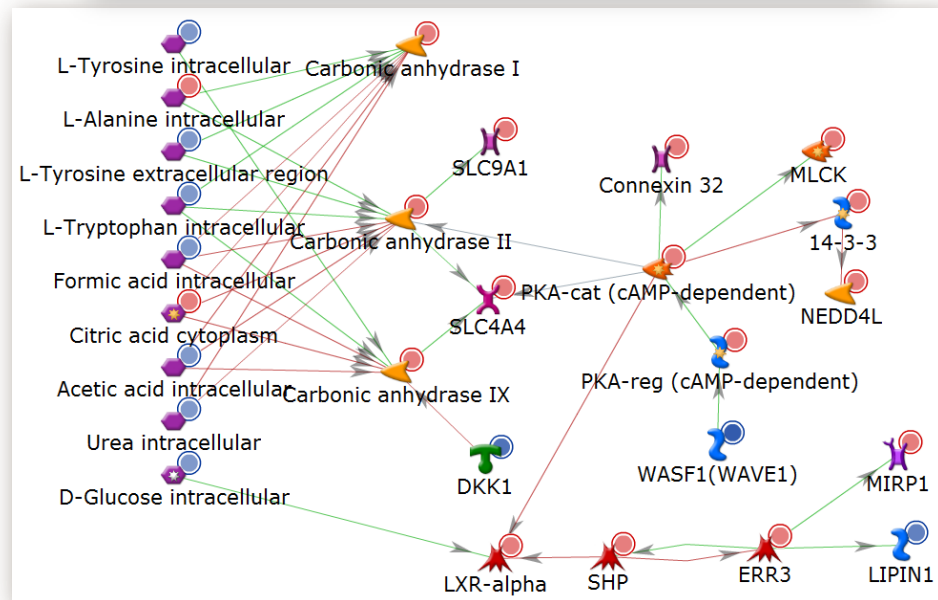
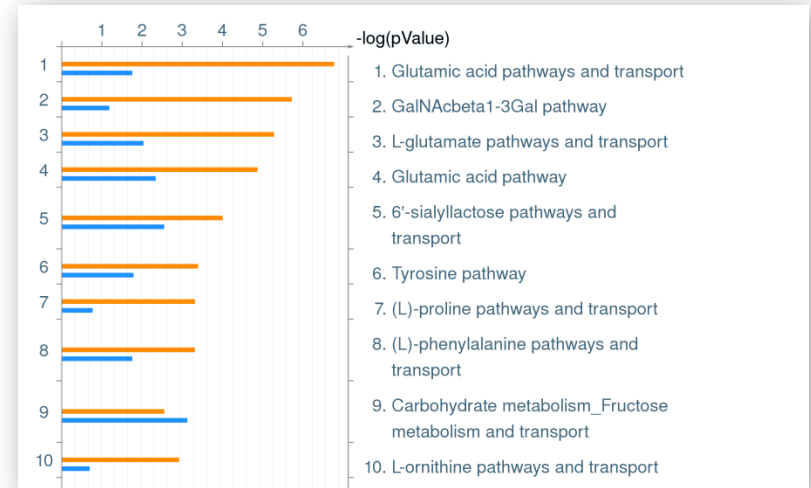
GO Processes

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

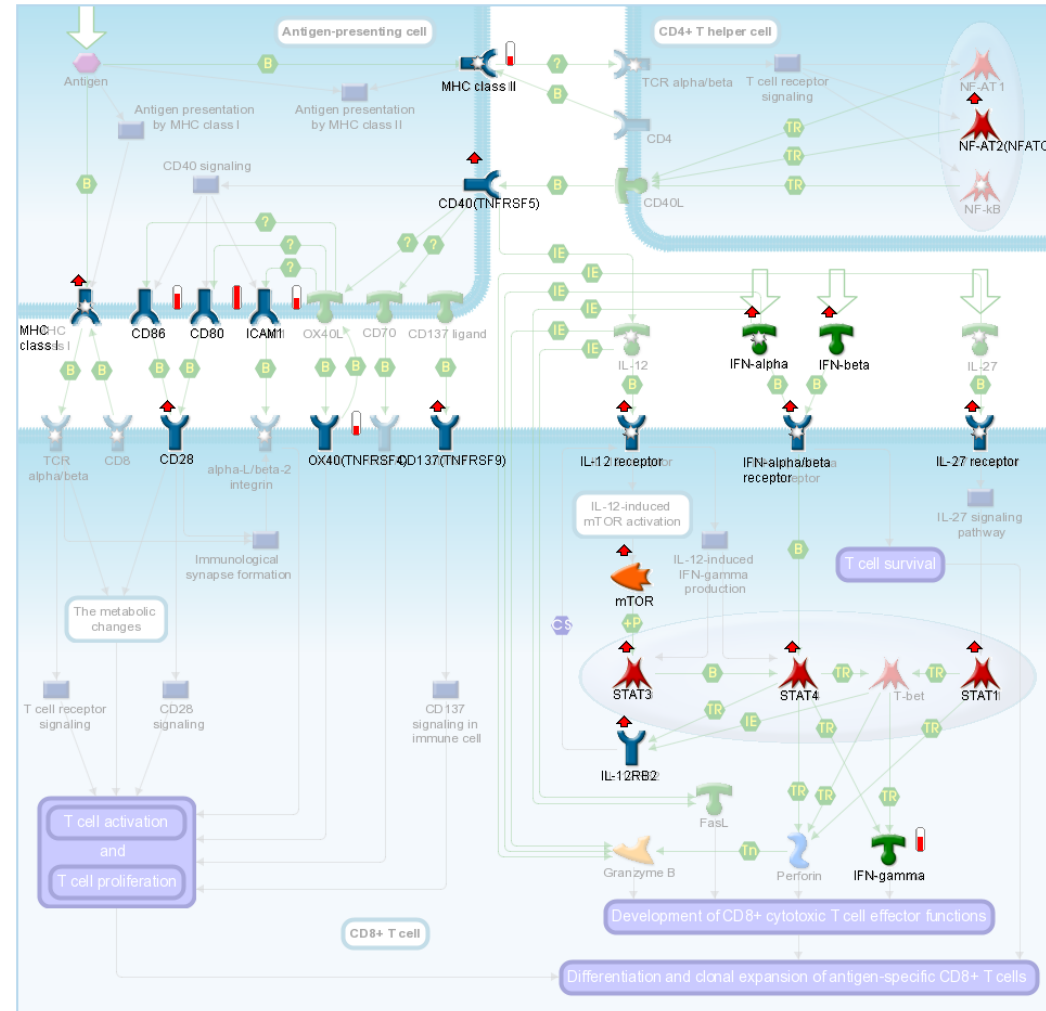
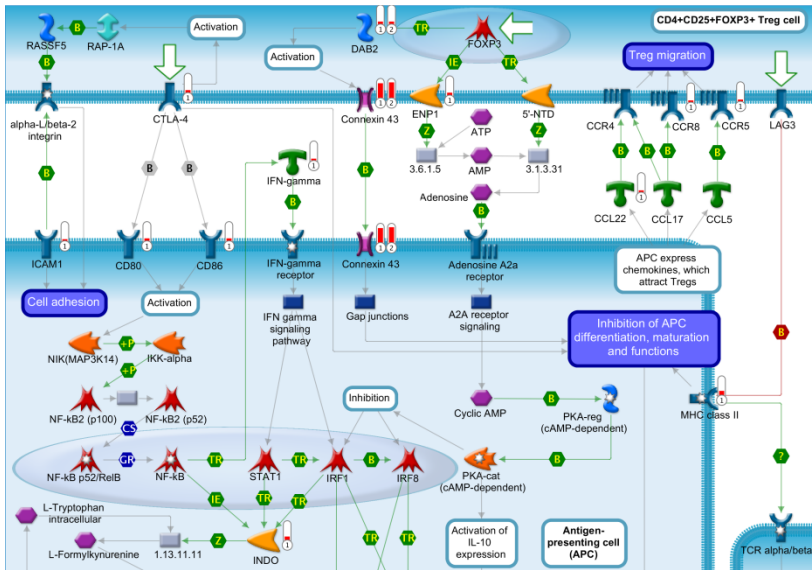


SUMMARY


- 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.

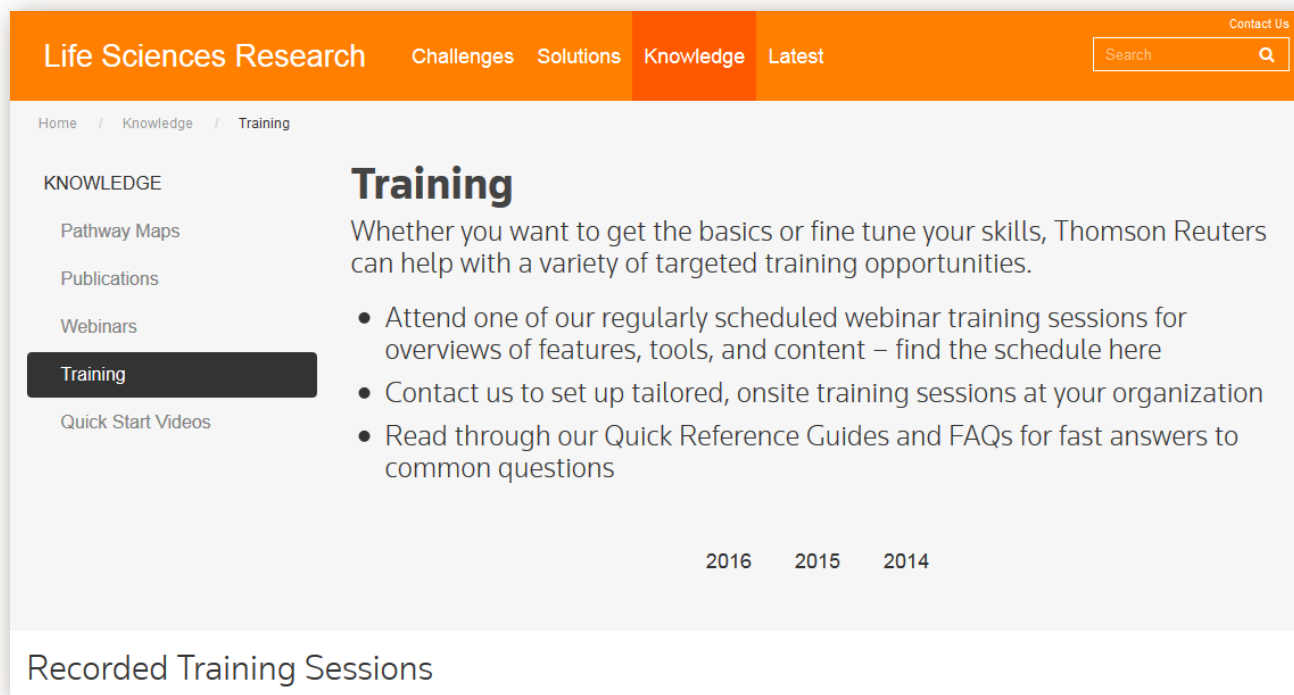


ANY QUESTIONS?



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 Life Sciences Research website. The top navigation bar is orange with links for Life Sciences Research, Challenges, Solutions, Knowledge (highlighted), and Latest. A search bar and a Contact Us link are on the right. Below the navigation bar, a breadcrumb trail shows Home / Knowledge / Training. On the left, a KNOWLEDGE sidebar lists Pathway Maps, Publications, Webinars, Training (highlighted), and Quick Start Videos. The main content area is titled 'Training' and includes a description: '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 is a bulleted list of three items: attending regularly scheduled webinar training sessions, contacting for tailored onsite training, and reading Quick Reference Guides and FAQs. At the bottom of the main content area are the years 2016, 2015, and 2014. The footer features the Thomson Reuters logo and the text 'Recorded Training Sessions'.

Life Sciences Research Challenges Solutions Knowledge Latest [Contact Us](#)

Home / Knowledge / Training

KNOWLEDGE

- Pathway Maps
- Publications
- Webinars
- Training**
- Quick Start Videos

Training

Whether you want to get the basics or fine tune your skills, Thomson Reuters can help with a variety of targeted training opportunities.

- 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
- Read through our Quick Reference Guides and FAQs for fast answers to common questions

2016 2015 2014

THOMSON REUTERS

Recorded Training Sessions