OICR
Ontario Institute for Cancer Research

EMBL-EBI

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Linking Biological Pathways and Networks to Disease

Robin Haw
7th September 2014
BioNetVisA Workshop/ECCB'14

www.reactome.org

International Cancer Genome Consortium

Ontario

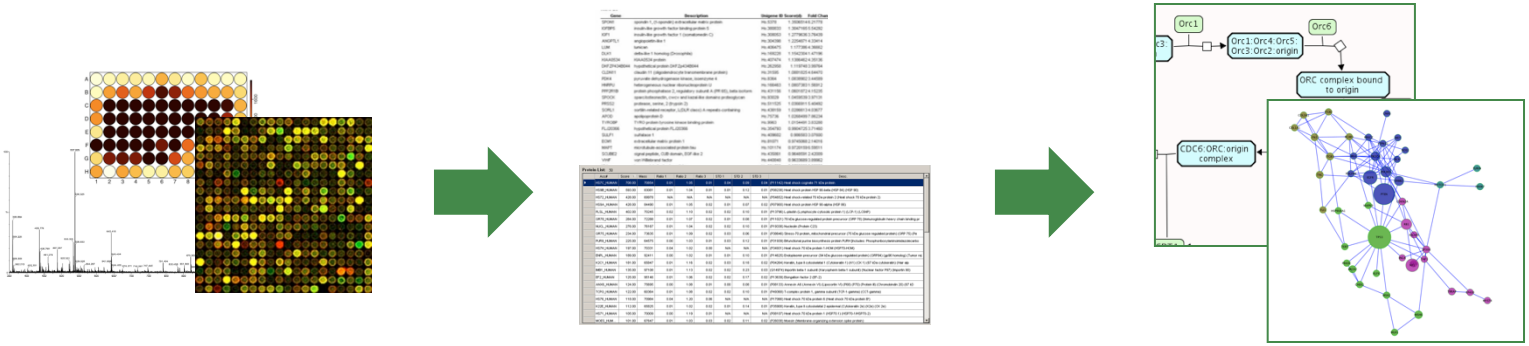
Ministry of Research and Innovation

National Human Genome Research Institute

NATIONAL INSTITUTES OF HEALTH

What is Reactome?

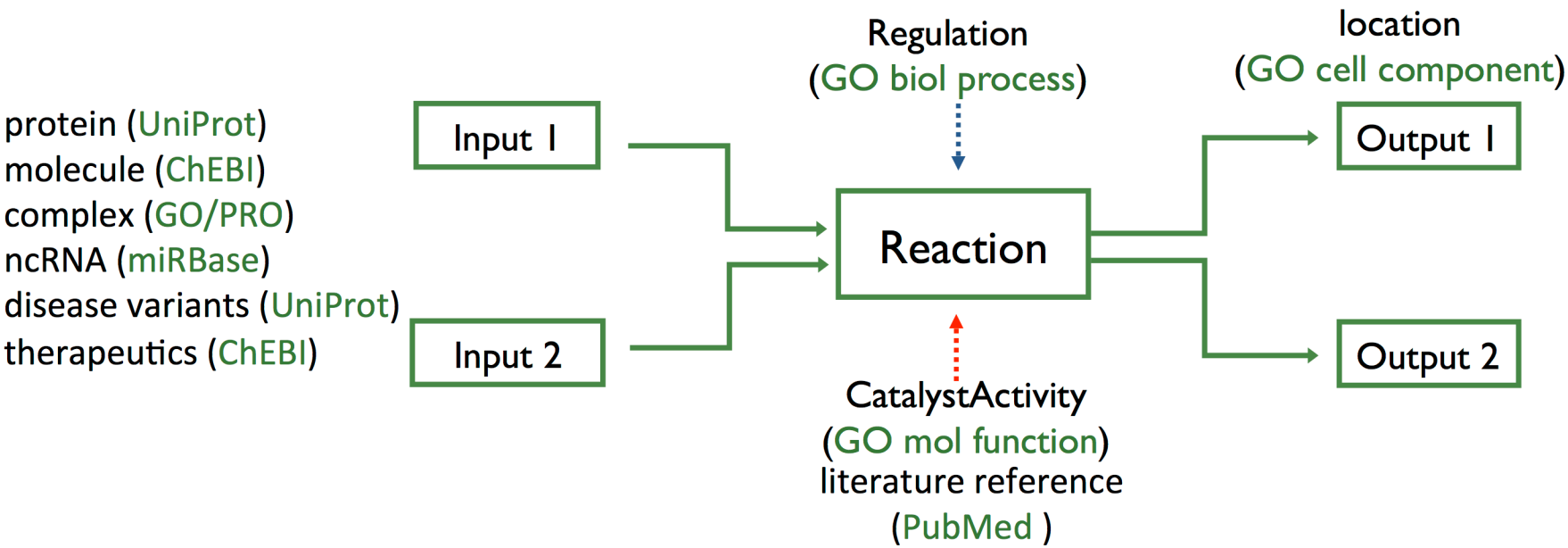
- Open source and open access pathway database
  - 1500+ pathway modules encompassing many areas of human biology
  - Expert authored, manually curated and peer-reviewed.
  - Every pathway is traceable to primary literature.
- Extensively cross-referenced to external bioinformatics databases.
- Computationally inferred pathways for 19 model organisms.
- Provides tools and datasets for browsing and visualizing pathway data.



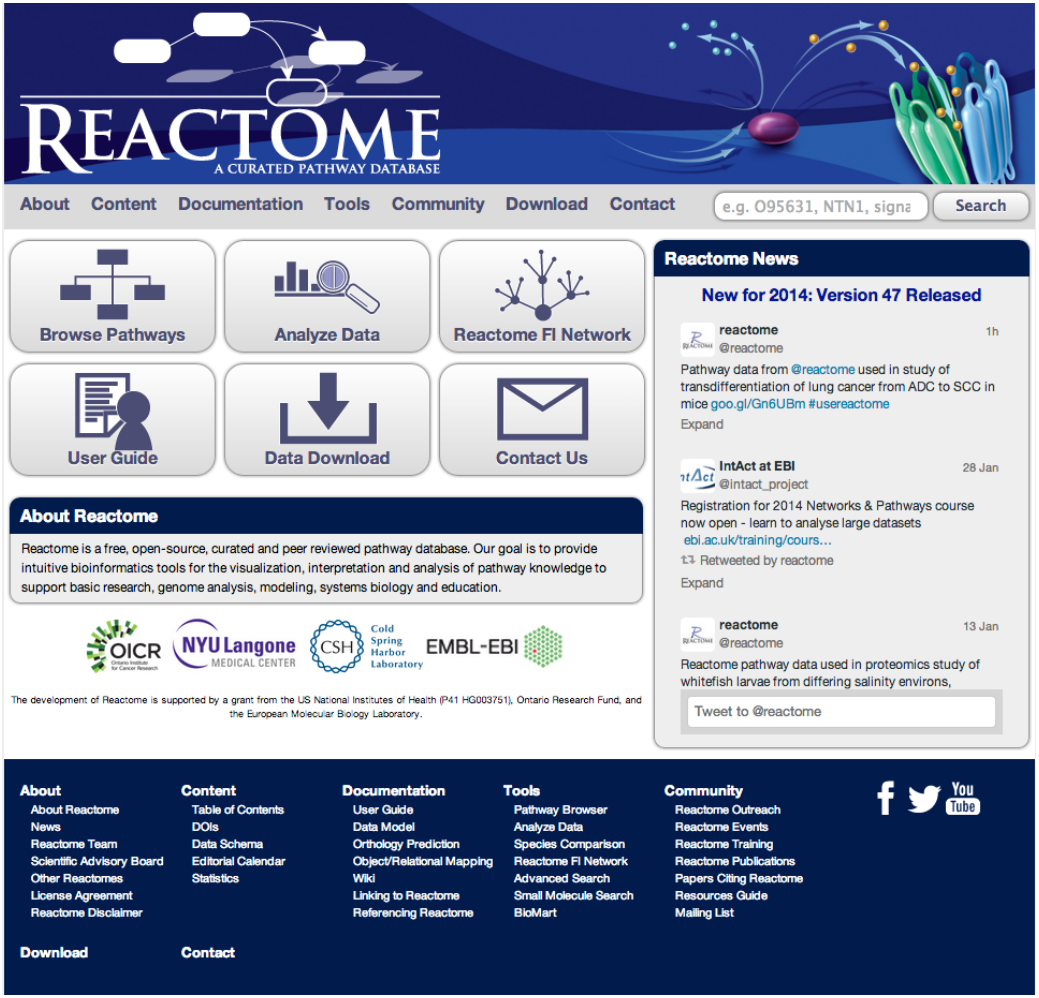
www.reactome.org

The Reaction

- Reactome is a Reaction Network Database
  - explicitly describe biological processes as a series of biochemical reactions and events.
  - represents many events and states found in biology.



Reactome Homepage



www.reactome.org

Full-text Search Tool

- Supports accurate and efficient querying of the Reactome knowledgebase, including protein, set, complex, chemical compound, reaction and pathway annotations.

Search results for *PTEN*

Showing **20** of **66**

Species

- [x] Homo sapiens (66)
- [ ] Drosophila melanogaster (70)
- [ ] Danio rerio (62)
- [ ] Rattus norvegicus (30)
- [ ] Bos taurus (14)
- [ ] Caenorhabditis elegans (14)

More...

Types

- [ ] Protein (29)
- [ ] Reaction (23)
- [ ] Pathway (9)
- [ ] Set (3)
- [ ] Complex (1)
- [ ] RNA Sequence (1)

Compartments

- [ ] cytosol (52)
- [ ] plasma membrane (21)
- [ ] extracellular region (4)
- [ ] endoplasmic reticulum lumen (1)

Reaction types

- [ ] activates (1)
- [ ] binds (1)
- [ ] dephosphorylates (1)

Protein (5 results from a total of 29)

PTEN (Homo sapiens)

Primary external reference: UniProt PTEN: P60484

PTEN S170N (Homo sapiens)

Primary external reference: UniProt PTEN: P60484
PTEN missense mutation that results in the substitution of serine at position 170 with asparagine affects the

PTEN H123Y (Homo sapiens)

Primary external reference: UniProt PTEN: P60484
PTEN missense mutation that results in the substitution of histidine at position 123 with tyrosine affects the

PTEN G129E (Homo sapiens)

Primary external reference: UniProt PTEN: P60484
PTEN missense mutation that results in the substitution of glycine at position 129 with glutamic acid affects the

PTEN G129V (Homo sapiens)

Primary external reference: UniProt PTEN: P60484
PTEN missense mutation that results in the substitution of glycine at position 129 with valine affects the conserved

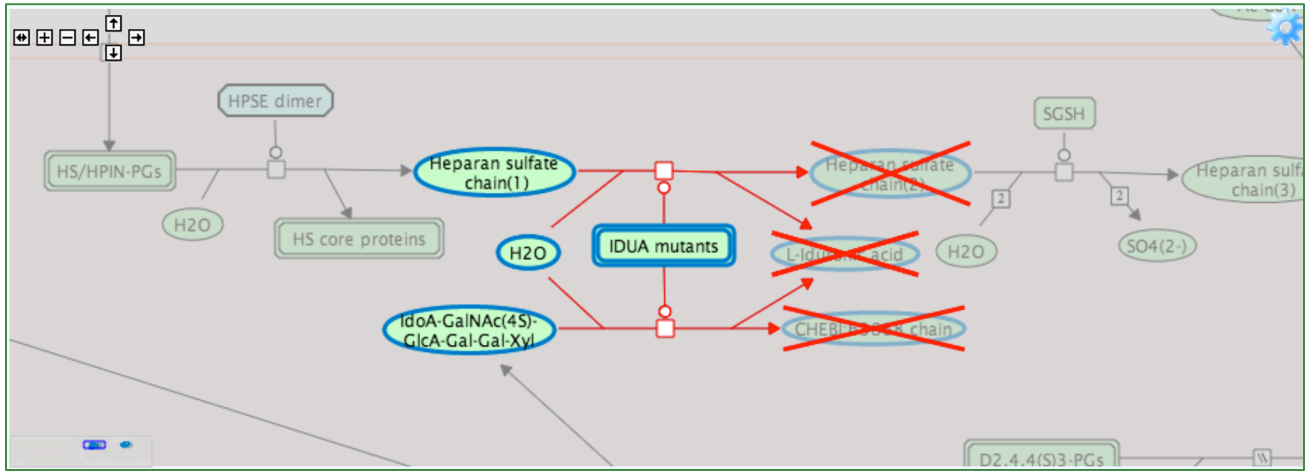
RNA Sequence (1 results from a total of 1)

PTEN mRNA (Homo sapiens)

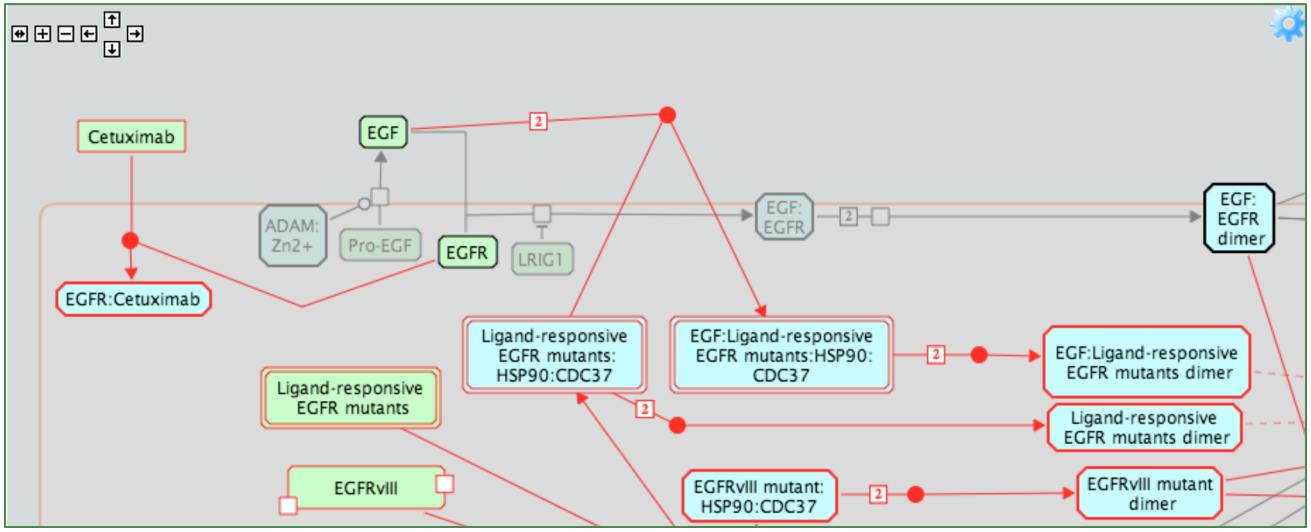
Primary external reference: ENSEMBL : ENST00000371953

Disease Pathway Curation

Metabolic disorders
e.g. mucopolysaccharidoses



Complex disorders
e.g. EGF pathway in cancer



SBGN Pathway Browser

- Google-map style pathway diagrams

REACTOME

Pathways for: Homo sapiens

Protein | Small molecule | Complex

Event Hierarchy:

- The citric acid (TCA) cycle and respiratory electron transp
  - Pyruvate metabolism and Citric Acid (TCA) cycle
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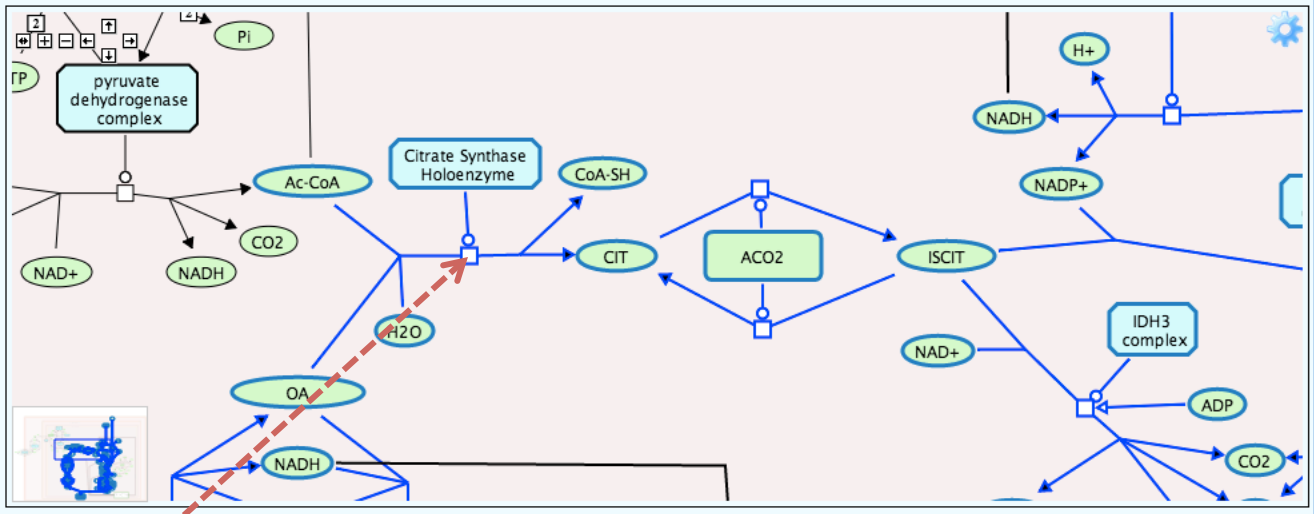
- Metabolism of nucleotides



Overview | Molecules | Structures (0) | Expression | Processes | Downloads

Citric acid cycle (TCA cycle) | Species: Homo sapiens

DOI

10.3180/REACT_1785.1

Stable Identifier

REACT_1785.3

Summation

In the citric acid or tricarboxylic acid (TCA) cycle, the acetyl group of acetyl CoA (derived primarily from oxidative decarboxylation of pyruvate, beta-oxidation of long-chain fatty acids, and catabolism of ketone bodies and several amino acids) can be completely oxidized to CO2 in reactions that also yield one high-energy phosphate bond (as GTP or ATP) and four reducing equivalents (three NADH + H+, and one FADH2). The NADH and FADH2 are then oxidized by the electron transport chain to yield nine more high-energy phosphate bonds (as ATP). All reactions of the citric acid cycle take place in the mitochondrion.

Eight canonical reactions mediate the synthesis of citrate from acetyl-CoA and oxaloacetate and the metabolism of citrate to re-form oxaloacetate. Six additional reactions are included here. Three reversible reactions, the interconversions of citrate and isocitrate, of fumarate and malate, and of malate and oxaloacetate are annotated in both their canonical (forward) and reverse directions. The synthesis of succinate from succinyl-CoA can be coupled to the

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REACTOME

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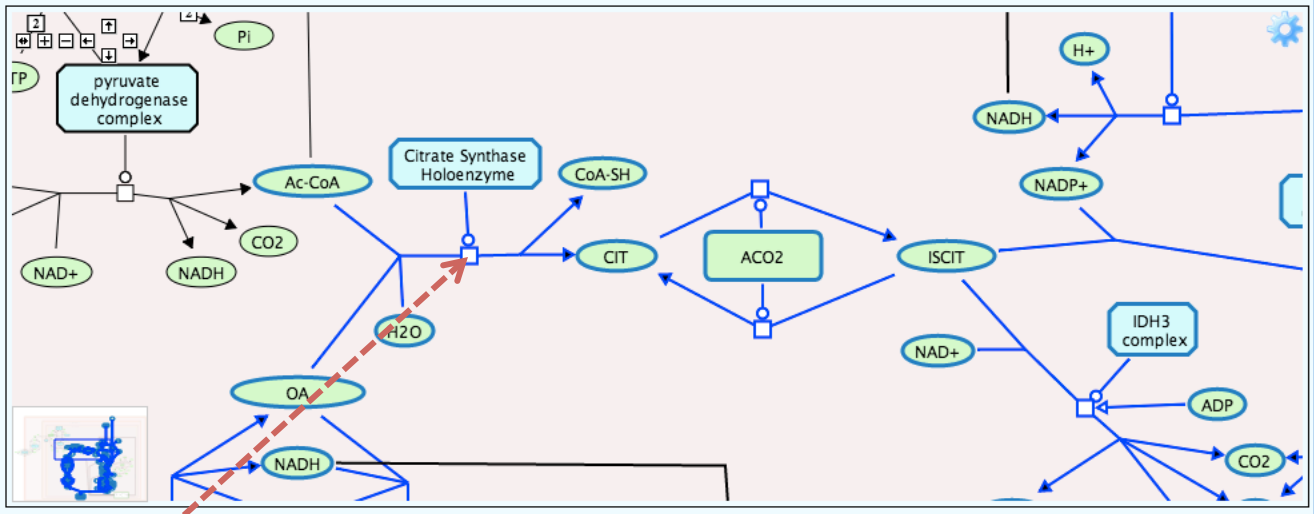

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Protein structures from PDBe

REACTOME

Pathways for: Homo sapiens

Protein | Small molecule | Complex

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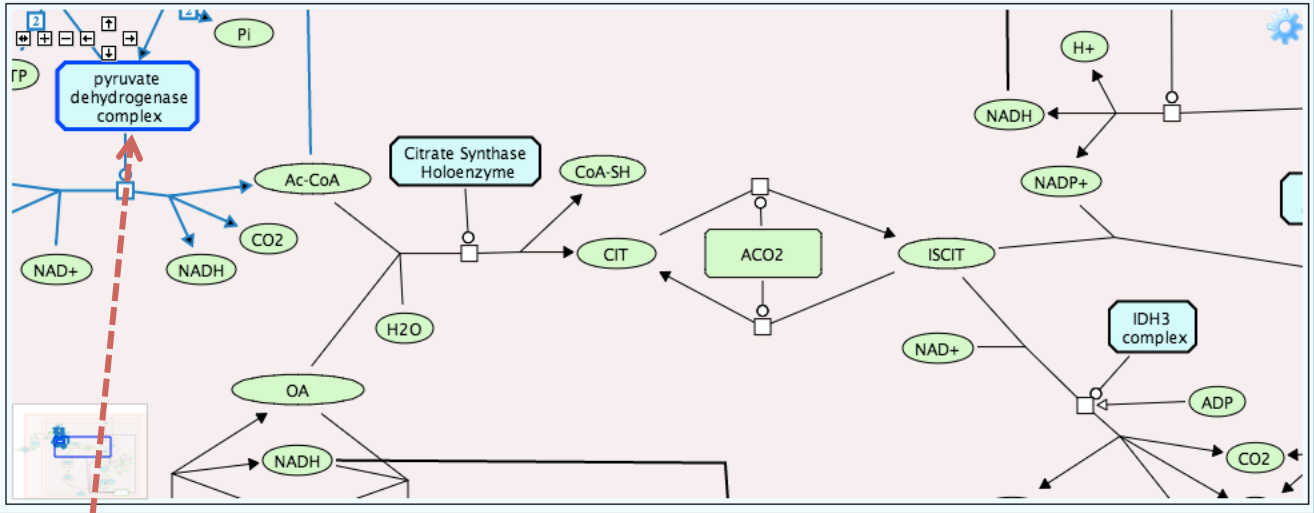
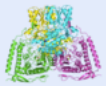


Overview | Molecules | Structures (5/5) | Expression | Processes | Downloads

UniProt: P10515 DLAT Chain: A Resolution: 8.80 Coverage: 0.37 PDB Range: [1, 239] UniProt Range: [409, 647]

3b8k EM PDBe

▶ All other structures for P10515



UniProt: P08559 PDHA1 Chain: C Resolution: 1.90 Coverage: 0.93 PDB Range: [5, 365]
UniProt Range: [30, 390]

2oz1 X-RAY PDBe

▶ All other structures for P08559

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REACTOME A CURATED PATHWAY DATABASE

Expression data from the Gene Expression Atlas

REACTOME

Pathways for: Homo sapiens

Protein | Small molecule | Complex

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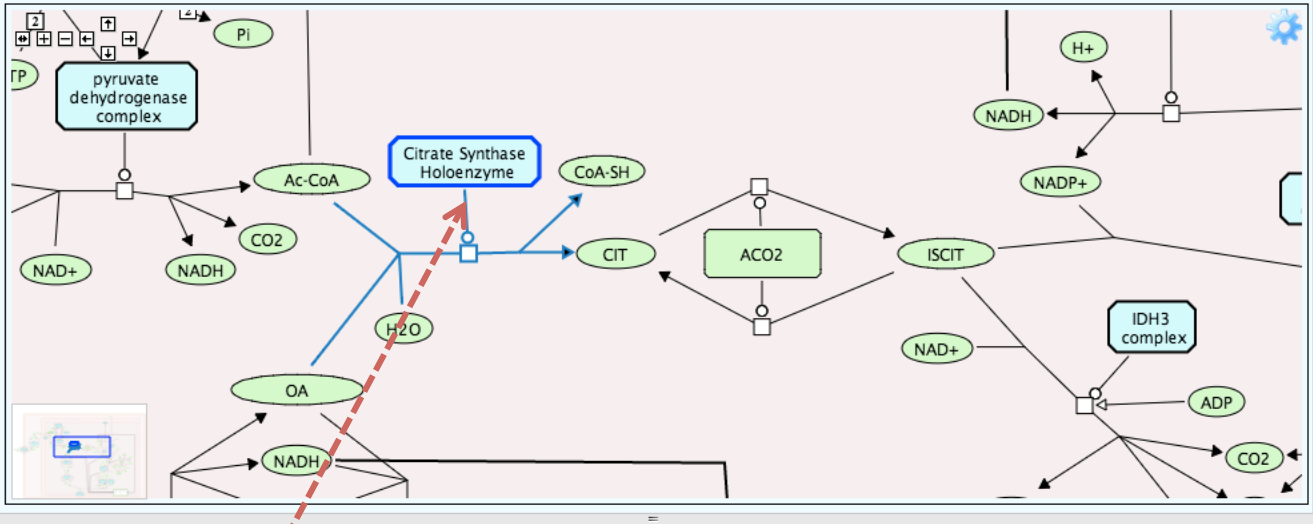


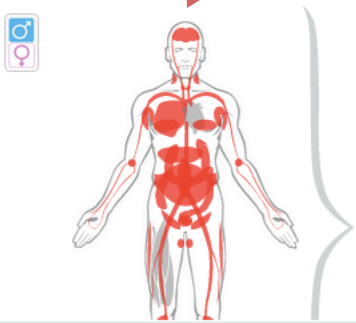
Overview | Molecules | Structures (0/1) | Expression | Processes | Downloads

E-MTAB-513

RNA-Seq of human individual tissues and mixture of 16 tissues (Illumina Body Map)

Organism(s): *Homo sapiens*

Reference(s): 22496456 22955988 23258890



Showing 1 of 1 genes found:

Display levels

Gene	adipose	adrenal	brain	breast	colon	heart	kidney	leukocyte	liver	lung	lymph node	ovary	prostate	skeletal muscle	testis	thyroid
CS																

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REACTOME A CURATED PATHWAY DATABASE

Analyzing OMICS data with Reactome Tools

- Pathway Mapping and Overrepresentation Analysis
  - What pathways are represented in my dataset?
- Expression Overlay onto Pathways
  - Which pathways are expressed in my dataset?

REACTOME

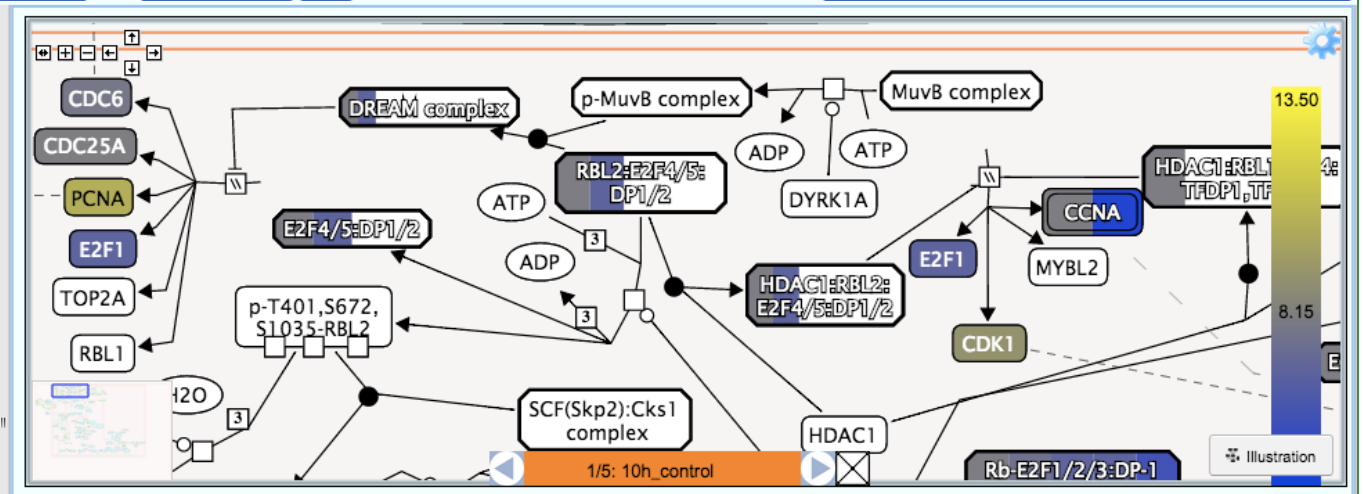
Pathways for: Homo sapiens

Tour this pathway browser? Hide

Protein | Small molecule | Complex

Event Hierarchy:

- Apoptosis (74/161) FDR: 1.44E-15
- Binding and Uptake of Ligands by Scavenger Receptors (
- Cell Cycle (126/532) FDR: 1.44E-15
  - Cell Cycle Checkpoints (75/118) FDR: 1.44E-15
  - Cell Cycle, Mitotic (115/461) FDR: 1.44E-15
    - Mitotic G1-G1/S phases (89/135) FDR: 1.44E-15
      - G0 and Early G1 (12/25) FDR: 8.7E-5
      - G1 Phase (14/38) FDR: 2.52E-4
      - G1/S Transition (81/109) FDR: 1.44E-15
    - S Phase (86/123) FDR: 1.44E-15
    - Regulation of DNA replication (58/75) FDR: 1.44E-15
    - Mitotic G2-G2/M phases (18/124) FDR: 2.03E-1
    - M Phase (48/287) FDR: 3.21E-3
    - M/G1 Transition (66/82) FDR: 1.44E-15
    - Regulation of mitotic cell cycle (41/82) FDR: 6.66E-1
  - Chromosome Maintenance (22/79) FDR: 1.73E-4
  - Meiosis (14/85) FDR: 1.3E-1
- Cell-Cell communication (4/138) FDR: 10E-1
- Cellular responses to stress (33/236) FDR: 1.12E-1
  - Cellular response to hypoxia (3/25) FDR: 4.81E-1
  - Detoxification of Reactive Oxygen Species (4/29) FDR:
  - Cellular response to heat stress (6/37) FDR: 3.17E-1



Overview | Molecules | Structures | Expression | Analysis (964) | Processes | Downloads

Results for: UNIPROT (964) | Type: Expression | [Data: Probeset] | Results | Identifiers not found: 20

Pathway name	Entities found	Entities Total	Entities ratio	Entities pValue	Entities FDR	Reactions found	Reactions total	R
Phenylalanine and tyrosine catabolism	7	9	0.001	5.41E-5	2.16E-4	8	10	
Cyclin D associated events in G1	14	38	0.005	6.31E-5	2.52E-4	7	11	
G1 Phase	14	38	0.005	6.31E-5	2.52E-4	7	11	
Intrinsic Pathway	9	17	0.002	9.29E-5	3.72E-4	16	16	

Result | Mapping | 241-260 of 964

Reactome supports Open Data Standards

SBGN

Standard graphical languages for representing biological processes and interactions

SBML

SBML level 2.4

Open access interchange format for computer models of biochemical pathways, reactions and networks.

REACTOME
A CURATED PATHWAY DATABASE

BioPAX

BioPAX level 2 & 3

Standard language that aims to enable integration, exchange, visualization and analysis of biological pathway data.

Proteomics Standards Initiative

PSICQUIC level 2.5

PSICQUIC is an effort to standardize the access to molecular interaction databases.

PSI-MITAB is the data exchange format.

the combine
computational modeling in biology network

Reactome Web Services


```
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<sbml xmlns="http://www.sbml.org/sbml/level2/version4" level="2" version="4">
    <model id="pathway_977225" name="Amyloids" metaid="metaid_0">
        <notes><p xmlns="http://www.w3.org/1999/xhtml">Amyloid is a term used to describe typically ext
            proteins, sometimes known as plaques. Abnormal accumulation of amyloid is amyloidosis, a te
            and tissues, particularly neurodegenerative diseases such as Alzheimer's, Parkinson's and H
            predominantly of amyloid fibrils, rigid, nonbranching structures that form ordered assembli
            betasheet structure where the sheets run parallel to the direction of the fibril (Sawaya et
            lefthanded twist (Nelson    Eisenberg 2006). At least 27 human proteins form amyloid fibril
            proteins have nonpathological functions; the trigger that leads to abnormal aggregations di
            well understood but in many cases the peptides are abnormal fragments or mutant forms arisi
            that the initial event may be aggregation of misfolded or unfolded peptides. Early studies
            widely accepted model that assembly was a nucleationdependent polymerization reaction (Tepl
            be more complex, with multiple 'offpathway' events leading to a variety of oligomeric struc
            (Roychaudhuri et al. 2008). An increasing body of evidence suggests that these oligomeric f
            the neurotoxic effects of Amyloidbeta (Roychaudhuri et al. 2008), alphasynuclein (Winner et
            2009, MerazRios et al. 2010). Amyloid oligomers are believed to have a common structural mo
            protein involved and not present in fibrils (Kayed et al. 2003). Conformation dependent, ag
            that there are 3 general classes of amyloid oligomer structures (Glabe 2009) including annu
            responsible for the widely reported membrane permeabilization effect of amyloid oligomers.
            preceeds the appearance of plaques in mouse models (Ferretti et al. 2011). </p><p xmlns="ht
            are often associated with other molecules, notably heparan sulfate proteoglycans and Serum
            universally associated and seem to stabilize fibrils, possibly by protecting them from degr
        <annotation>
            <p xmlns="http://www.w3.org/1999/xhtml">SBML engine: Jsbml</p
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                x="273.0" y="267.0"/><glyph class="unit of information" i
                w="56.0" x="289.0" y="255.0"/></glyph></glyph><glyph clas
                bbox h="36.0" w="90.0" x="282.0" y="675.0"/></glyph><glyp
                bbox h="45.0" w="168.0" x="930.0" y="468.0"/><glyph class
                "APCS(20-223), Ca2+"/><callout target="entityVertex_71936
                x="1114.0" y="537.0"/></glyph></glyph><glyph class="unspe
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                class="simple chemical" id="entityVertex_7193684"><label
                glyph><glyph class="complex" id="entityVertex_7193685"><l
                y="933.0"/><glyph class="annotation" id="entityVertex_719
                Serum amyloid P-component homopentamer, HSPG2(22-4391), G
                y="969.0"/></callout><bbox h="24.0" w="760.0" x="2450.5"
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                homopentamer"/><callout target="entityVertex_7193687"><po
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                "Double_stranded"/><bbox h="36.0" w="183.0" x="915.0" y="
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                ></glyph></glyph><glyph class="process" id="reactionVerte
```


Amyloid SBML file: http://reactomews.oicr.on.ca:8080/ReactomeRESTfulAPI/RESTfulWS/sbmlExporter/977225

Reactome Web services

Our new RESTful API provides outside users with direct access to pathway data in Reactome. The Reactome pathway analysis tools are also available for integration into third party websites.

- RESTful API is available to access the Reactome data (Note: The RESTful API has been moved to reactomews.oicr.on.ca for better performance.). For details about this API, please see this document: Reactome RESTful API.
- SOAP based Web Services API is available to access the Reactome data. For details about this API, please follow the following links:
  - Simple Description for the Reactome Web Services API.
  - Training Materials for the Reactome Web Services API
    - Reactome SOAP WS User's Guide in PDF (1M).
    - Reactome SOAP WS Tutorial in Power Point Slides (2M).
    - Reactome SOAP WS Tutorial in Flash Movie (640 x 480) (11M).
    - Reactome SOAP WS Tutorial in Flash Movie (800 x 600) (12M).

Pathway Analysis Service

Provides an API for pathway over-representation and expression analysis as well as species comparison tool

Contact the developer
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download : download — Show/Hide | List Operations | Expand Operations | Raw

GET	/download/{token}/entities/found/{resource}/{filename}.csv	Downloads those identifiers found for a given analysis and a certain resource
GET	/download/{token}/entities/notfound/{filename}.csv	Downloads a list of the not found identifiers
GET	/download/{token}/pathways/{resource}/{filename}.csv	Downloads all hit pathways for a given analysis

identifier : identifier — Show/Hide | List Operations | Expand Operations | Raw

GET	/identifier/{id}	Analise the identifier over the different species in the database
GET	/identifier/{id}/projection	Analise the identifier over the different species in the database and projects the result to Homo Sapiens

identifiers : identifiers — Show/Hide | List Operations | Expand Operations | Raw

species : species — Show/Hide | List Operations | Expand Operations | Raw

token : token — Show/Hide | List Operations | Expand Operations | Raw

[BASE URL: http://www.reactome.org/AnalysisService/api-docs , API VERSION: 1.0]

Analysis Service: http://www.reactome.org/AnalysisService/

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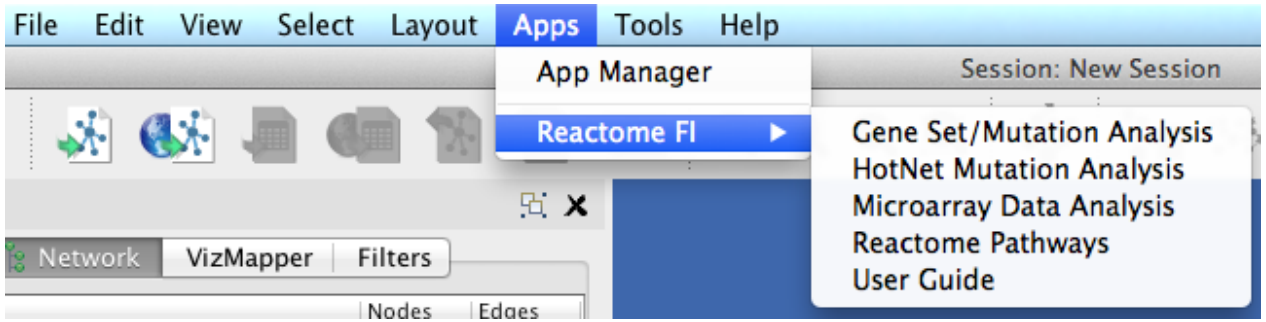
REACTOME A CURATED PATHWAY DATABASE

ReactomeFIViz Cytoscape app

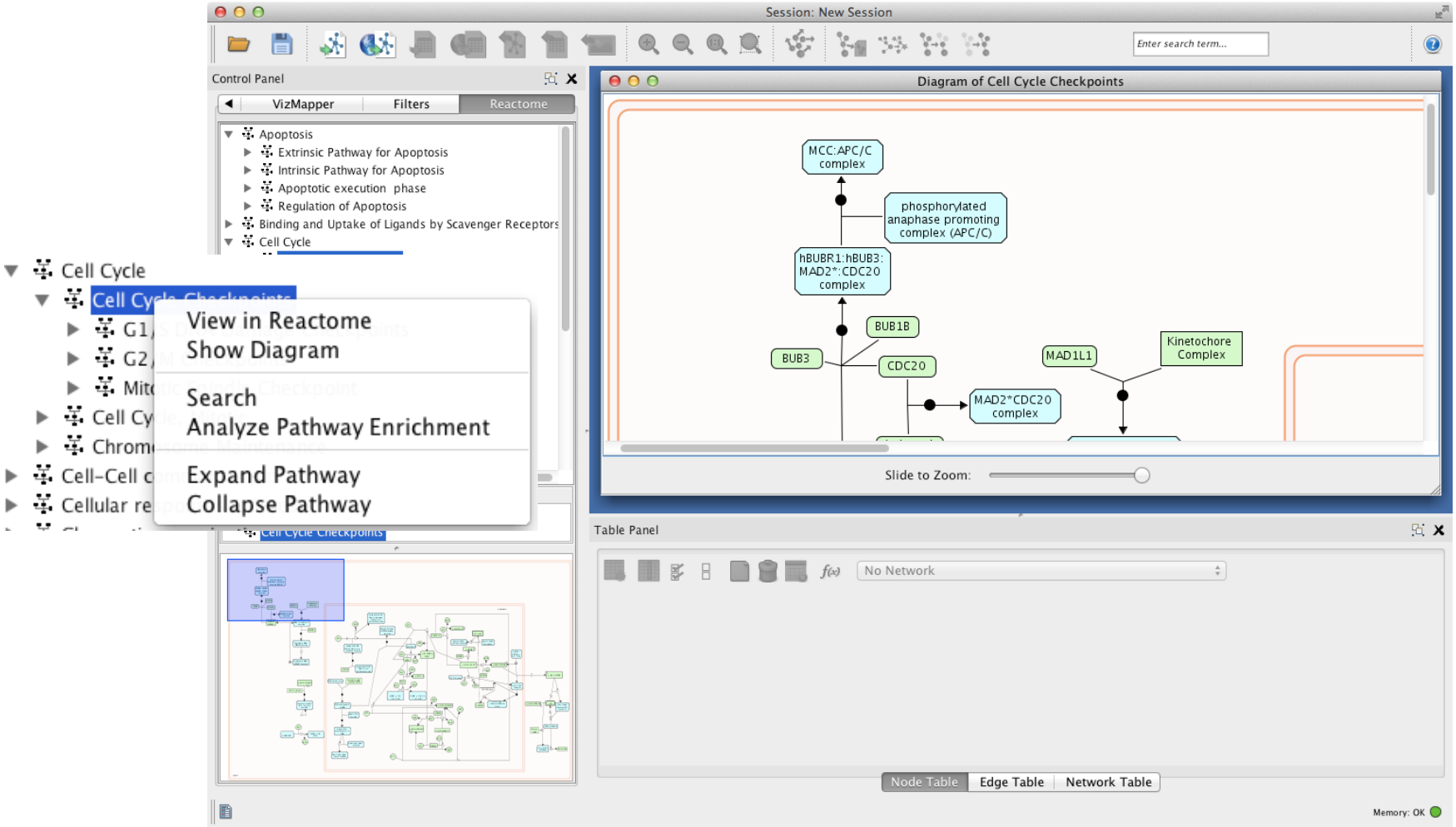
- View Reactome Pathway Diagrams in Cytoscape
  - Perform pathway-based data analysis
- Create Gene Networks based upon the Reactome FI Network
  - Perform network-based data analysis



- Install ReactomeFIViz from Cytoscape App Store
- Choose Plugins, Reactome FI.

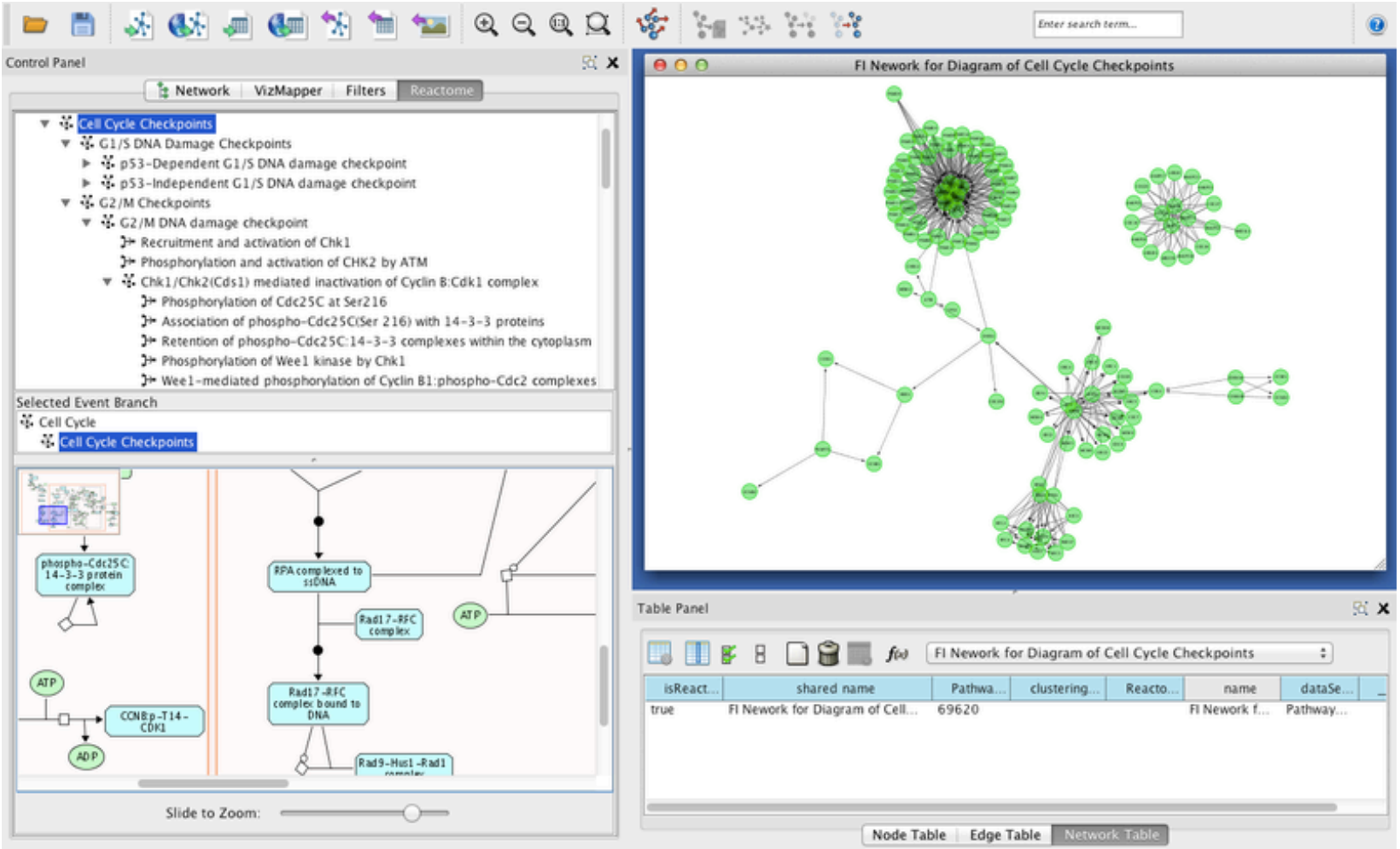
Reactome Pathways in Cytoscape

- Display Reactome pathways in Cytoscape



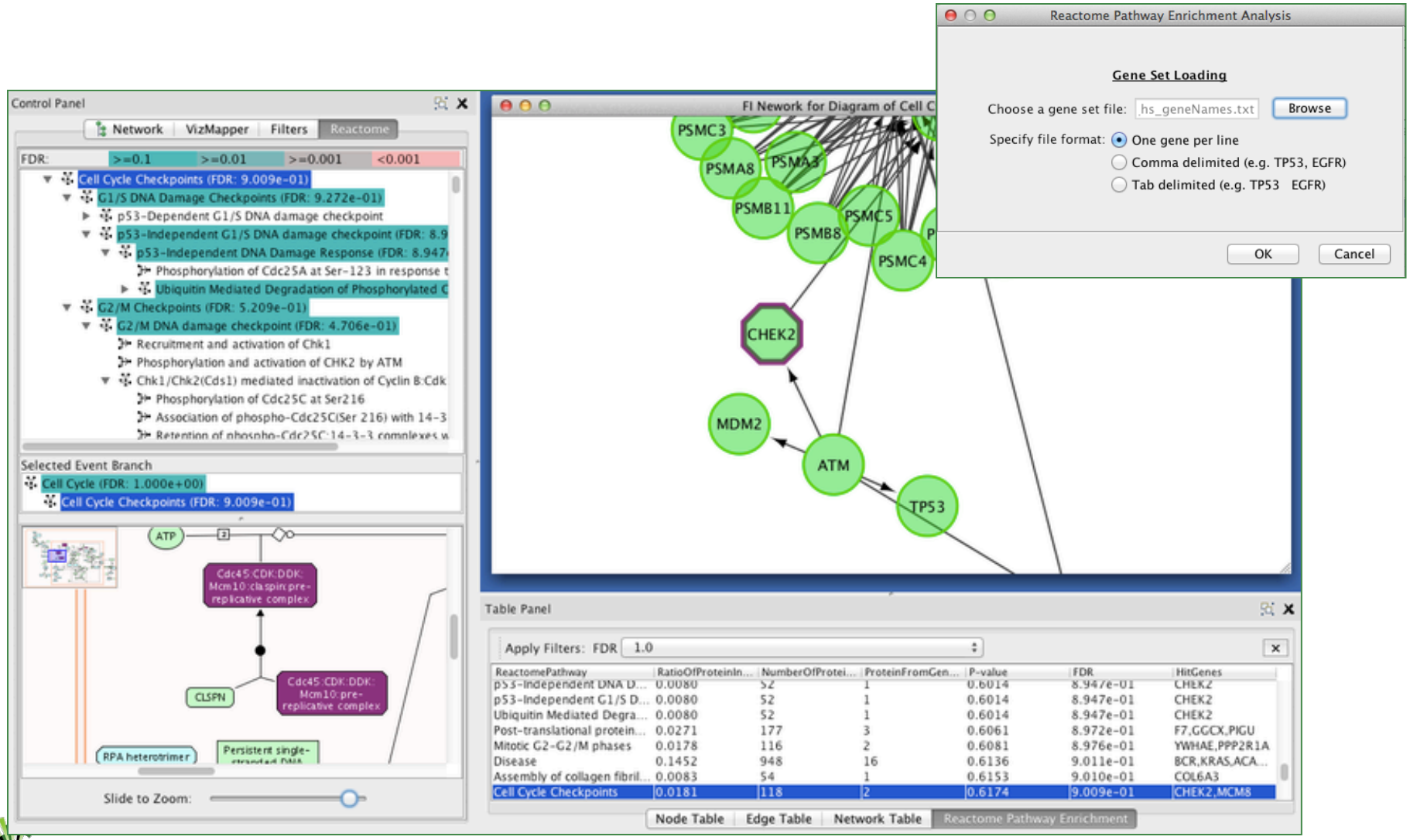
Display Reactome Pathways in the FI Network View

- Convert Reactome pathway into Reactome FI network



Pathway Enrichment Analysis

- Perform enrichment analysis and colourize pathway/network diagrams



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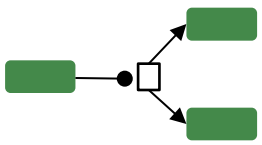
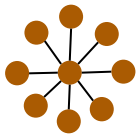
REACTOME A CURATED PATHWAY DATABASE

Network Module Based Analysis of Disease OMICS Datasets



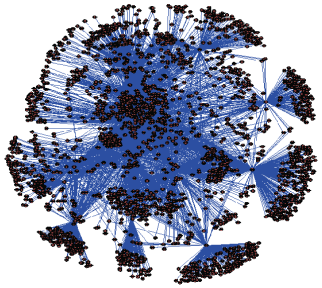
Curated Pathway DBs

+



Uncurated Interaction Evidence

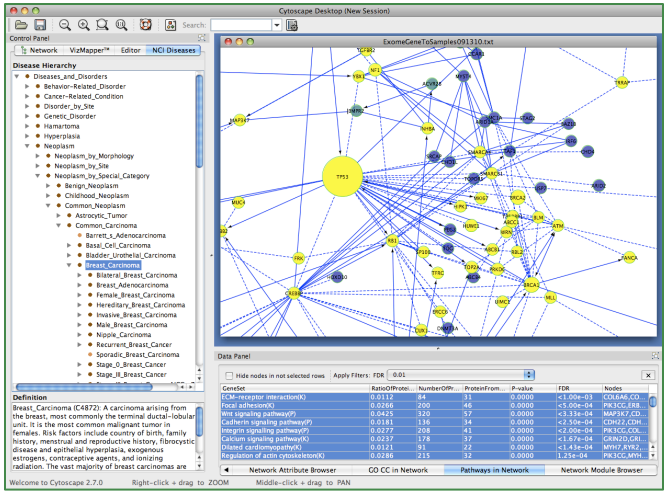
Machine Learning



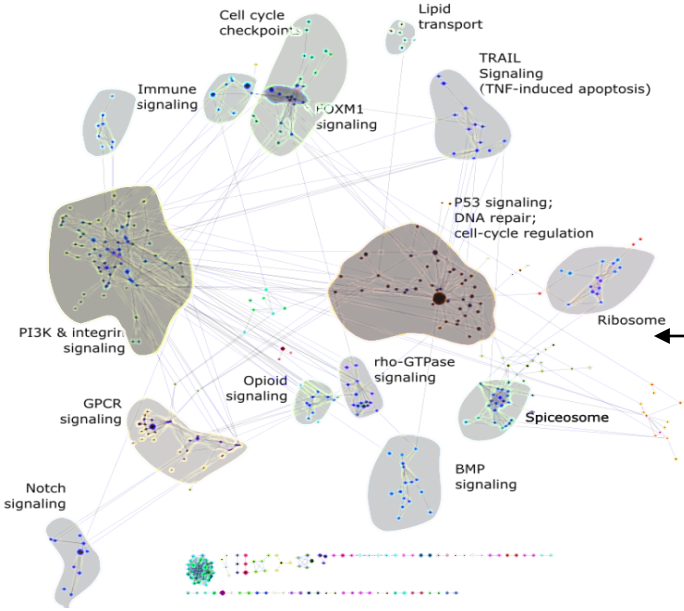
Reactome Functional Interaction Network
(~11K proteins; ~270K interactions)

+

Project your data into Reactome FI Network



Extract and Cluster, and Annotate Altered Genes



Disease "modules" (10-30)

Cytoscape v2.x/v3.x

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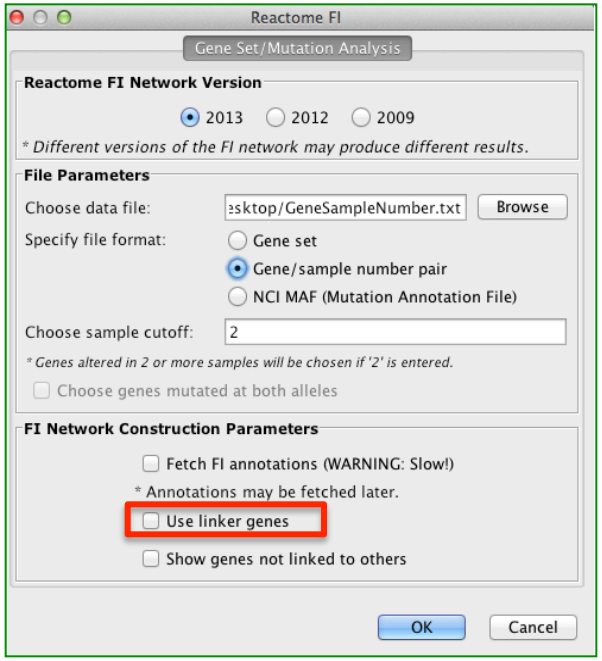
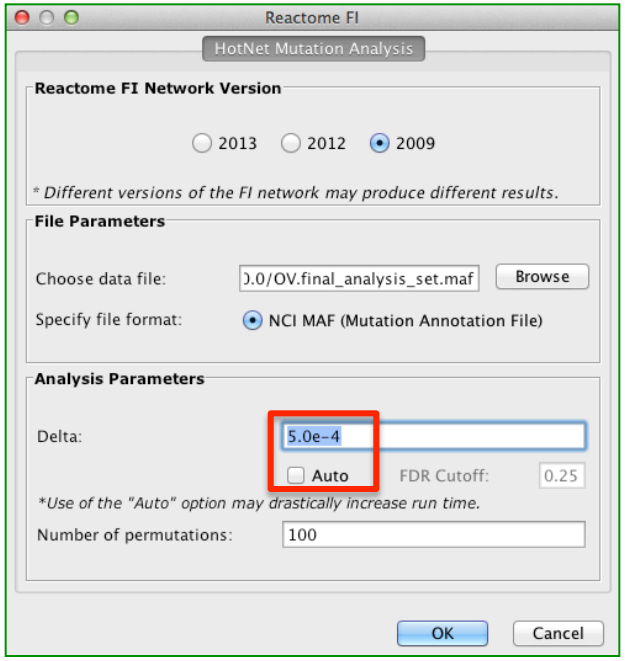
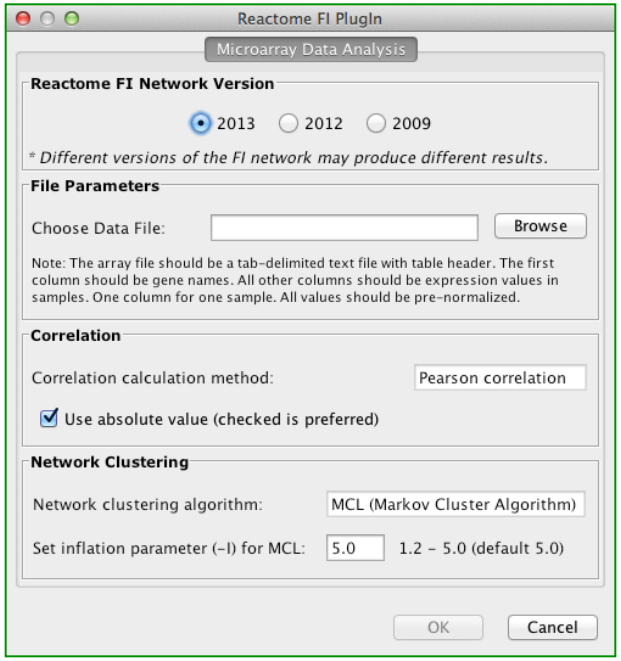
REACTOME A CURATED PATHWAY DATABASE

Using the FI Network - Upload your data







Gene Set/Mutation Analysis

Use linkers if you have small gene lists.

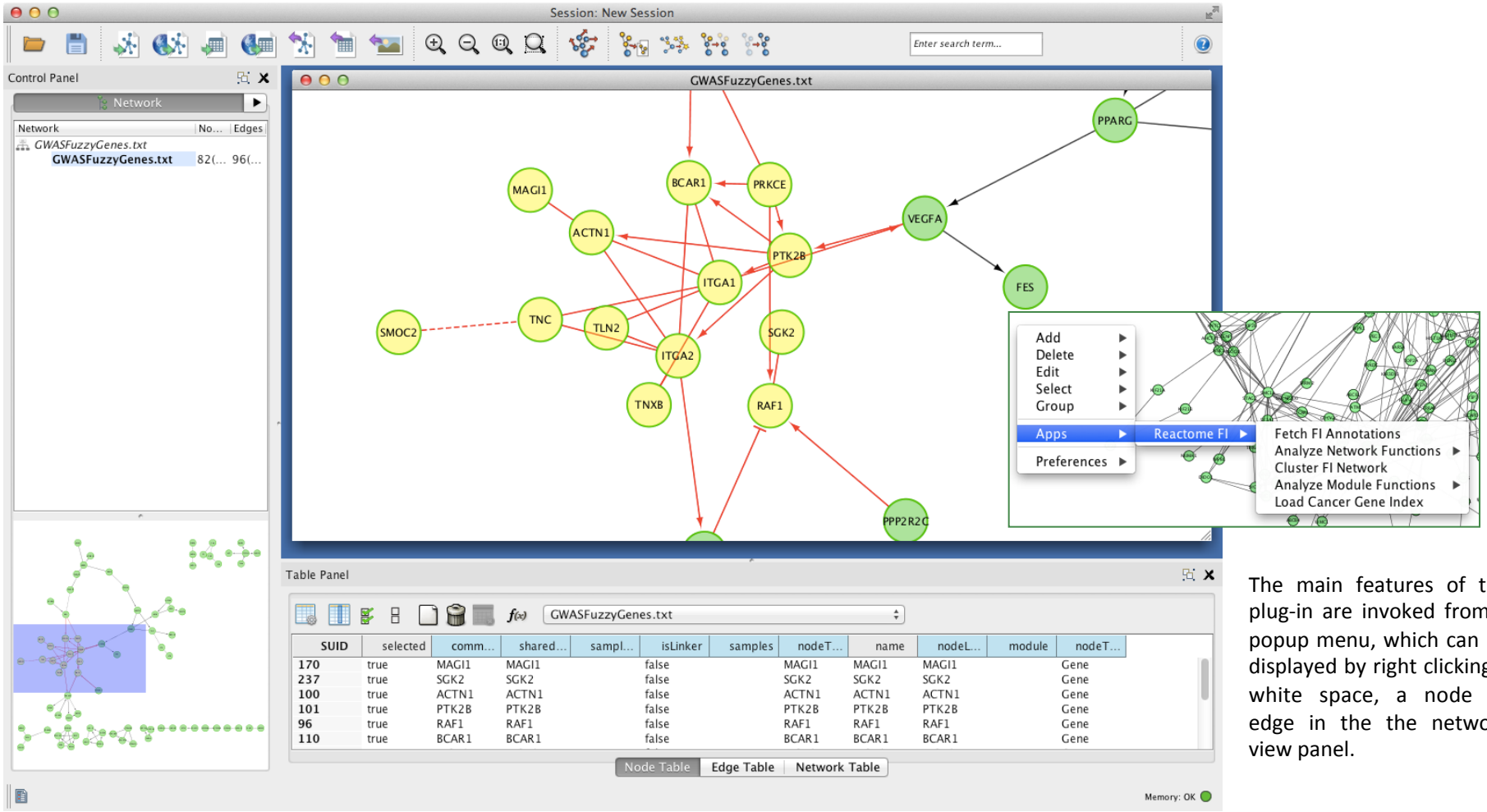
HotNet Mutational Analysis

Select “Auto” if unsure what delta value to use.

Microarray Data Analysis

FI Results Display

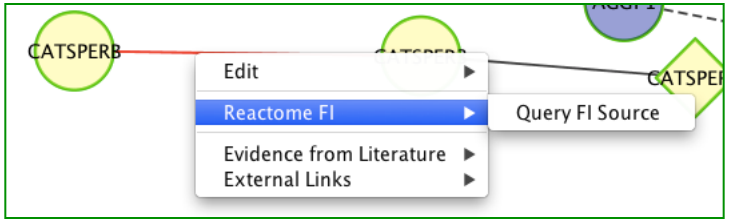
- Sub-network is displayed in the Network View panel using an FI specific visual style

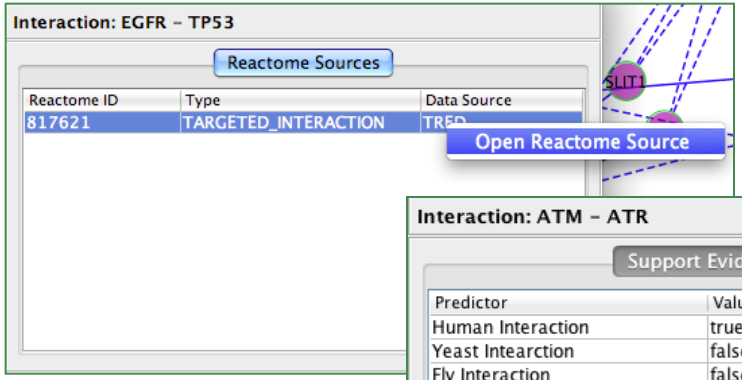


The main features of the plug-in are invoked from a popup menu, which can be displayed by right clicking a white space, a node or edge in the the network view panel.

Node and Edge Features

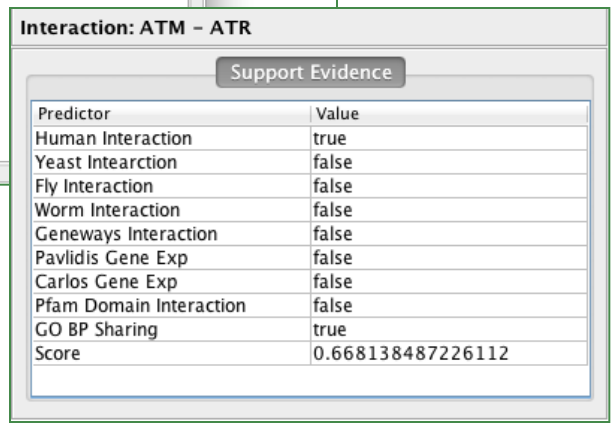
- Query FI Source





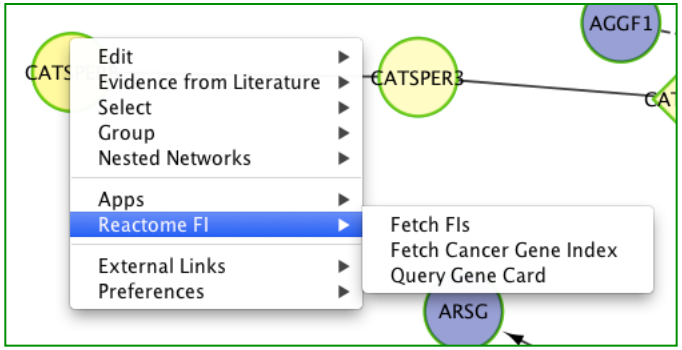
Annotated FIs

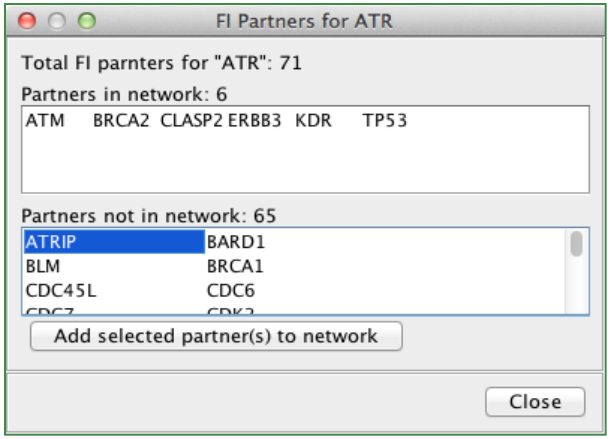
Predicted FIs



Predictor	Value
Human Interaction	true
Yeast Intearction	false
Fly Interaction	false
Worm Interaction	false
Geneways Interaction	false
Pavlidis Gene Exp	false
Carlos Gene Exp	false
Pfam Domain Interaction	false
GO BP Sharing	true
Score	0.668138487226112

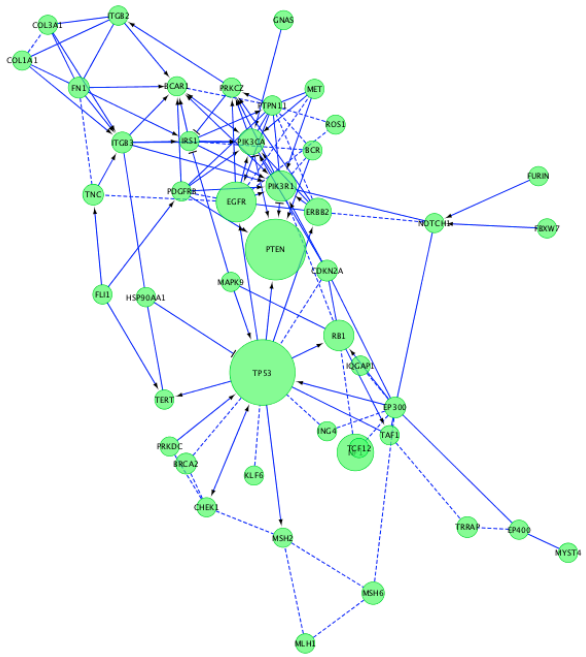
- Fetch FIs for node



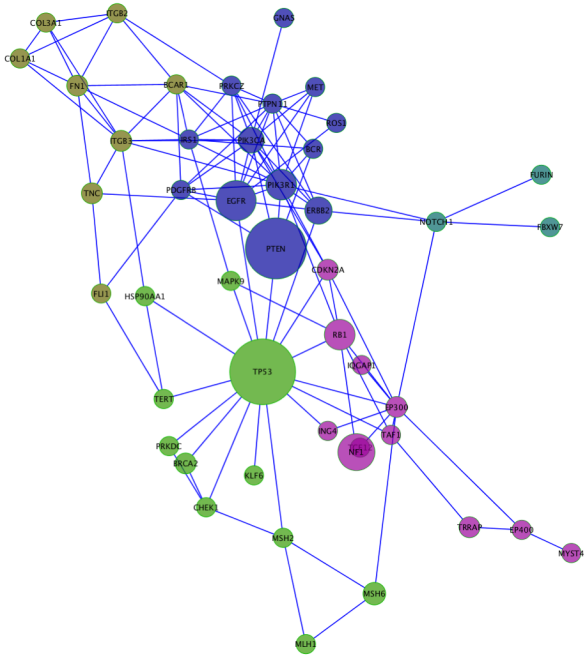


Cluster FI Network

- Runs spectral partition based network clustering (Newman, 2006) on the displayed FI network.
- Analyze cancer mutation data with HotNet algorithm (Vandin, 2012)
- Apply MCL graph clustering algorithm to networks derived from microarray data (micans.org/mcl/)
- Nodes in different network modules will be shown in different colours (max 15 colours).

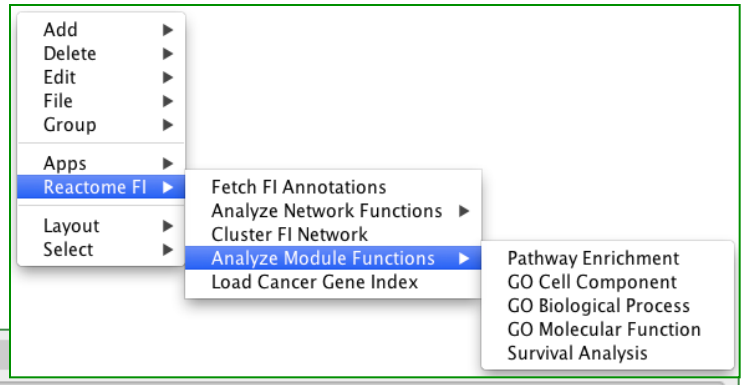


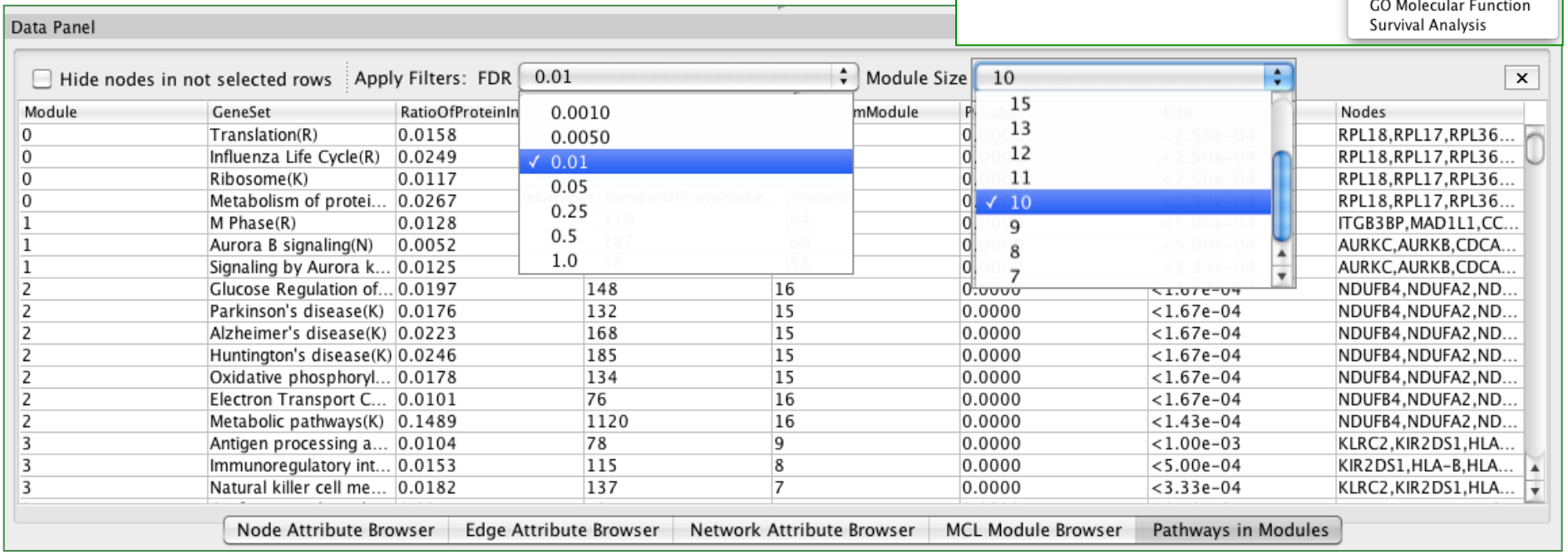
Fetch FI Annotations
Analyze Network Functions ▶
Cluster FI Network
Analyze Module Functions ▶
Load Cancer Gene Index



Analyze Module Functions

- Pathway or GO term enrichment analysis on individual network modules.
  - Use filter to remove small network modules
  - Filter by FDR





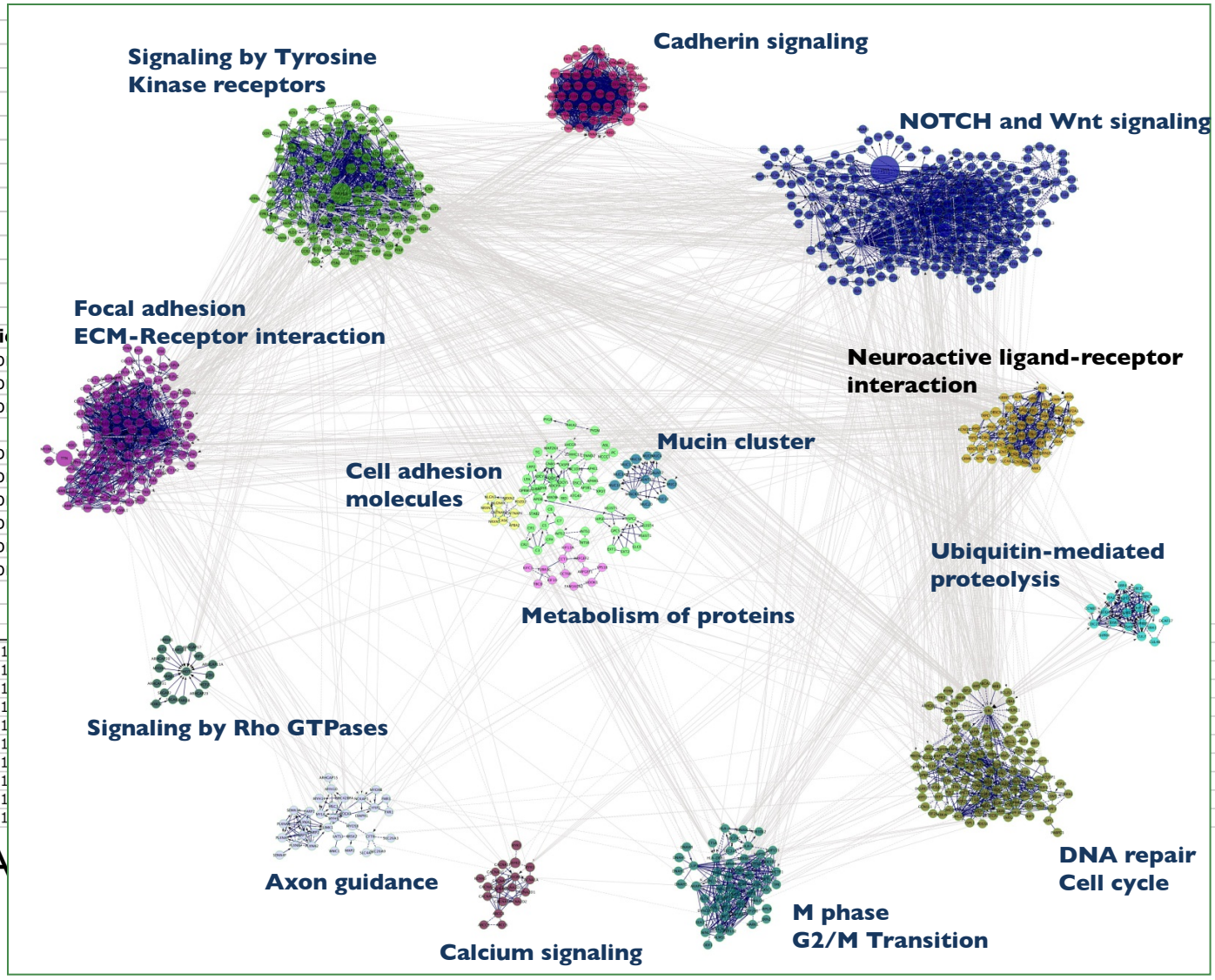
Clustering of TCGA Breast Cancer Mutations

Hugo_Symbol
BAI2
LRRC41
C1orf173
SSX2IP
NTNG1
PGLYRP3
FCRL5
FBXO28
OR2M2
MKX
.....

Variant_Classifi
Missense_Mutatio
Missense_Mutatio
Missense_Mutatio
Silent
Missense_Mutatio
Missense_Mutatio
Missense_Mutatio
Missense_Mutatio
Missense_Mutatio
Missense_Mutatio

Matched_No	Match_
TCGA-04-1331-10A-01	
TCGA-04-1331-10A-01	
TCGA-04-1331-10A-01	
TCGA-04-1331-10A-01	
TCGA-04-1331-10A-01	
TCGA-04-1331-10A-01	
TCGA-04-1331-10A-01	
TCGA-04-1331-10A-01	
TCGA-04-1331-10A-01	
TCGA-04-1331-10A-01	

NCI MA



	BAM_file	Sequencer
		x
		x
		x
		x
		x
		x
		x
		x
		x
		x

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REACTOME A CURATED PATHWAY DATABASE

Conclusions

- Reactome is a highly reliable, curated database of biological pathways.
- Web site provides tools and datasets for visualizing pathway data and interpreting your experimental data.
- ReactomeFIViz Cytoscape app provides a powerful way to visualize and analyze cancer and disease data sets.
- All data and software are open to public; no licensing required.

Acknowledgements

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