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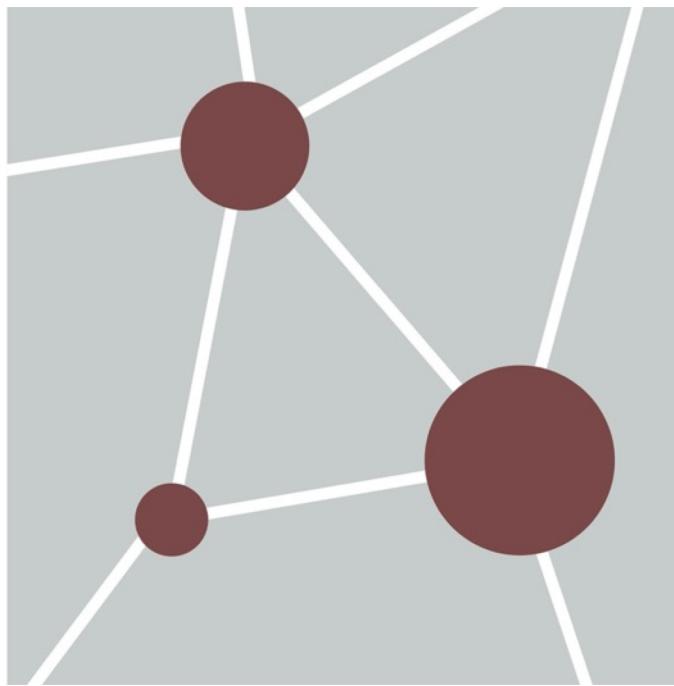
More Depth on Pathway & Network Analysis Lab



Robin Haw

Pathway and Network Analysis of -Omics Data

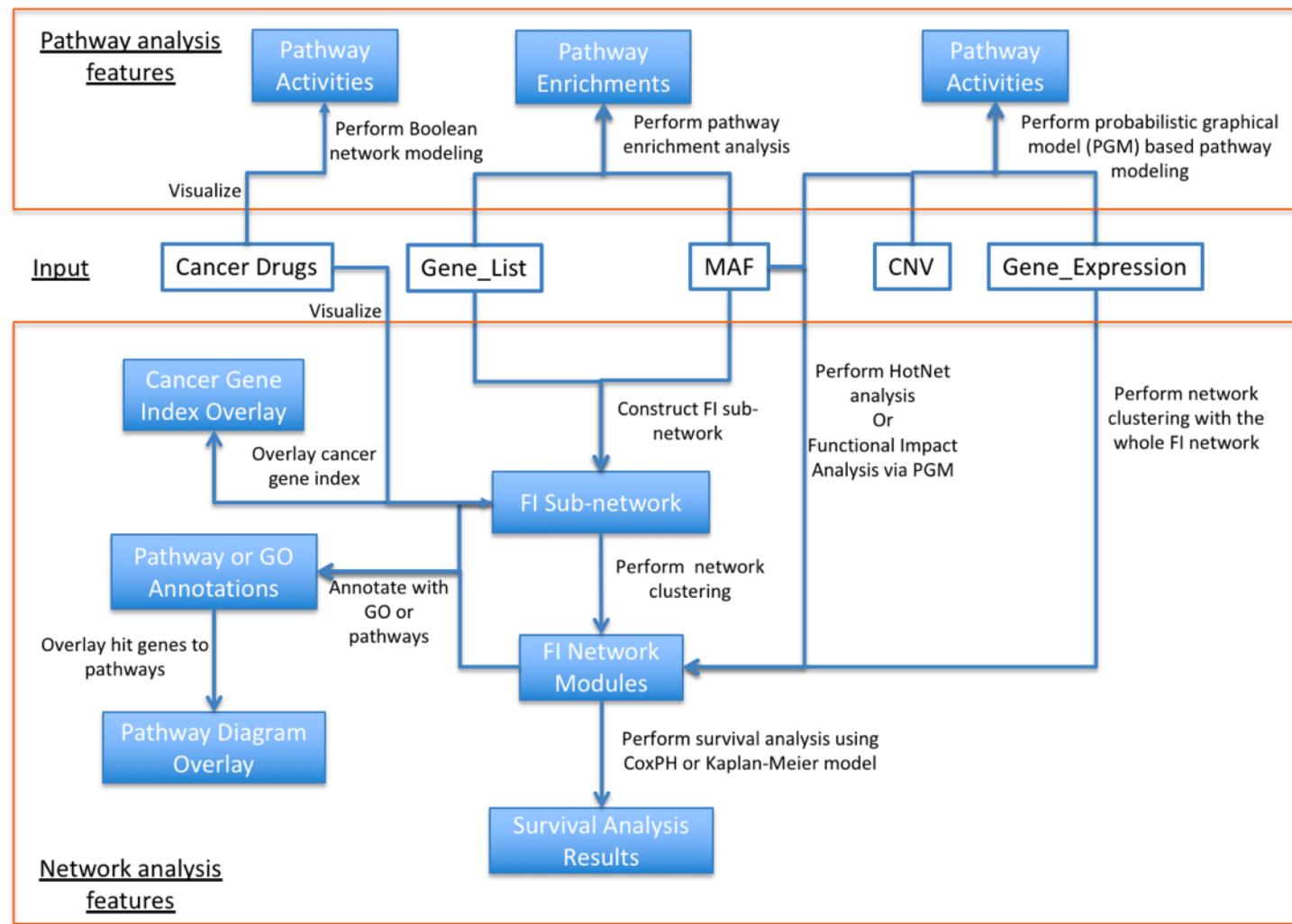
July 27-29, 2020



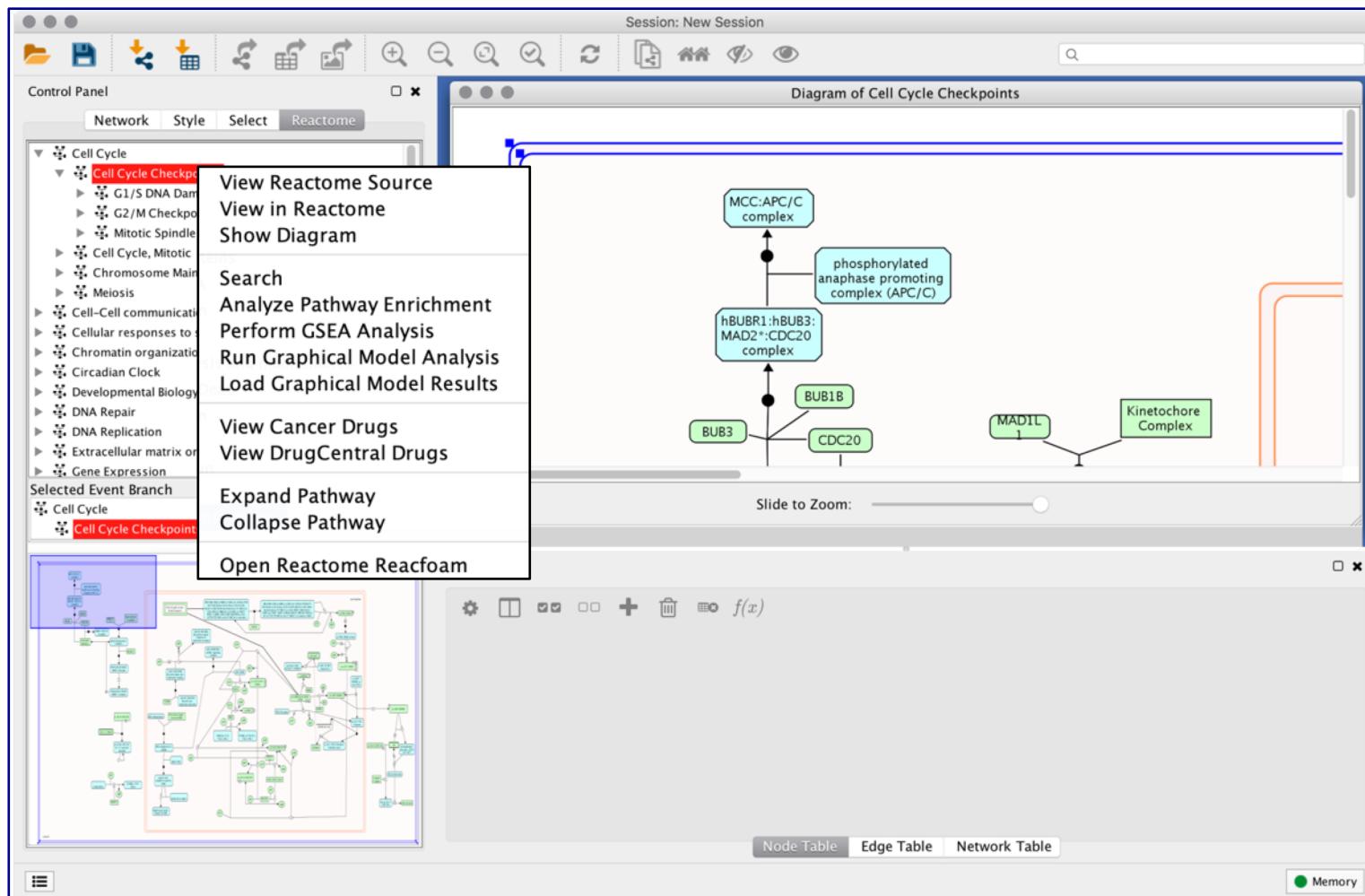
Learning Objectives of Module

- Be able to perform pathway and network-based data analysis using ReactomeFIViz app

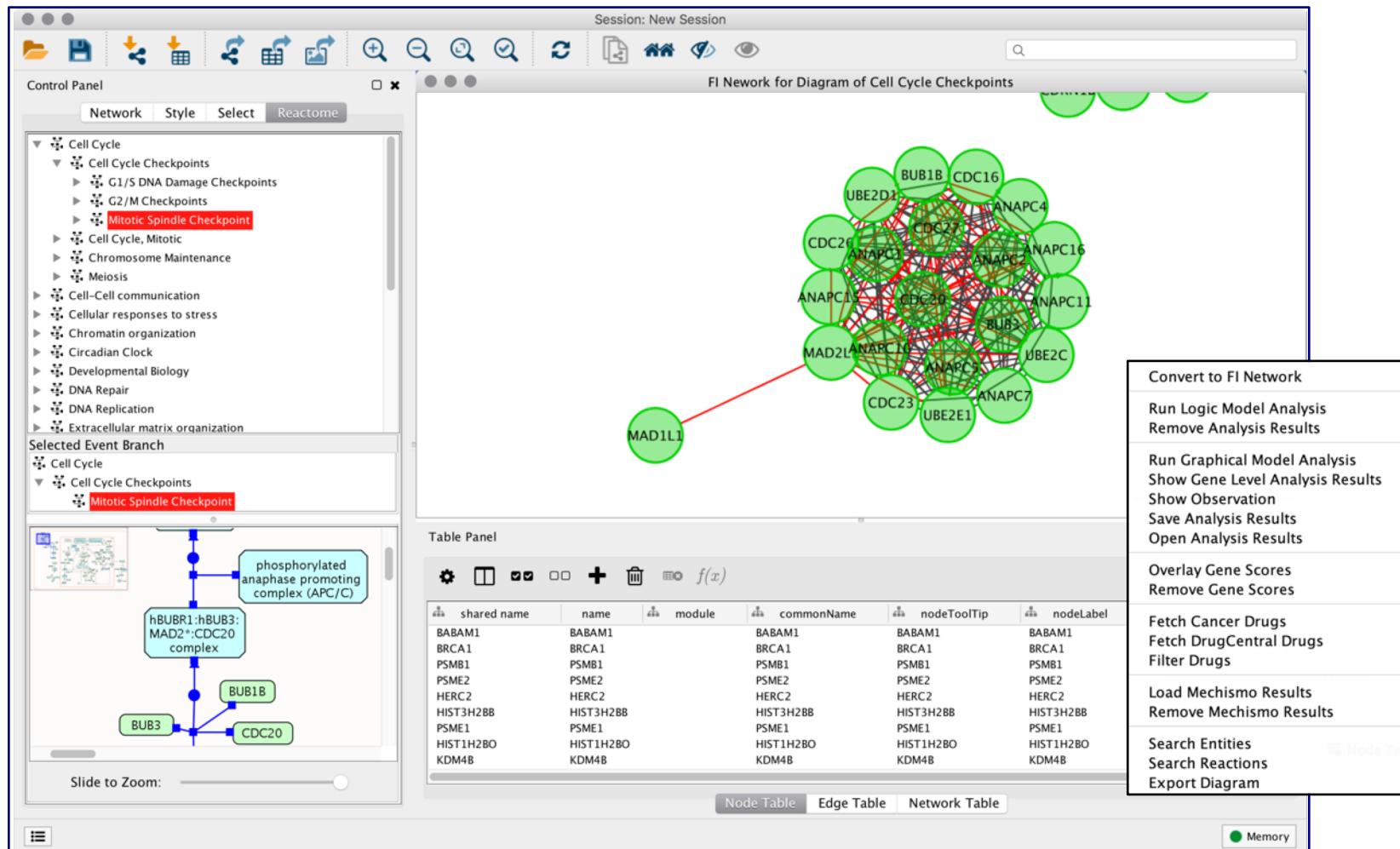
Major Features in ReactomeFIViz



A1) Reactome Pathway Enrichment Analysis



Displaying Reactome Pathways in the FI Network View



Pathway Enrichment Analysis

Session: New Session

Control Panel

Network Style Select Reactome

FDR: >=0.1 >=0.01 >=0.001 <0.001

Interleukin-7 signaling (FDR: 0.091)

- IL7 binds HGF(495-728)
- IL7R binds JAK1
- IL2RG binds JAK3
- IL7 binds IL7R:JAK1
- IL7:IL7R:JAK1 binds IL7
- IL7R is phosphorylated
- IL7:p-Y449-IL7R:JAK1
- IL7:p-Y449-IL7R:JAK1
- IL7:p-Y449-IL7R:JAK1
- Interleukin-11 receptor a
- Interleukin-11 receptor a
- IL27 is a dimer of IL27A and IL27B
- IL27 binds IL27RA:gp130

View Reactome Source
View in Reactome
Show Diagram
Search
Analyze Pathway Enrichment
Perform GSEA Analysis
Run Graphical Model Analysis
Load Graphical Model Results
View Cancer Drugs
View DrugCentral Drugs
Expand Pathway
Collapse Pathway
Open Reactome Reacfoam

Selected Event Branch

Immune System (FDR: 0.291)

Cytokine Signaling in Immune system (FDR: 0.089)

Signaling by Interleukins (FDR: 0.045)

Interleukin-7 signaling (FDR: 0.091)

Diagram of Interleukin-7 signaling and JAK3 deficiency causes SCID (IL7R)

The diagram illustrates the signaling pathway where HGF(495-728) binds to IL7R, which then activates JAK1. This leads to the phosphorylation of IL7:IL7R:JAK1, which in turn activates IL7R:JAK1. IL2RG binds to JAK3, which is also activated by the phosphorylated IL7:IL7R:JAK1 complex. The activated JAK3 then phosphorylates STAT3, leading to its dimerization and nuclear translocation. The STAT3 dimer then activates the transcription of target genes.

Reactome Pathway Enrichment Analysis

Gene Set Loading

Choose a gene set file: hs_geneNames.txt

Specify file format: One gene per line
 Comma delimited (e.g. TP53, EGFR)
 Tab delimited (e.g. TP53 EGFR)

OK Cancel

Table Panel

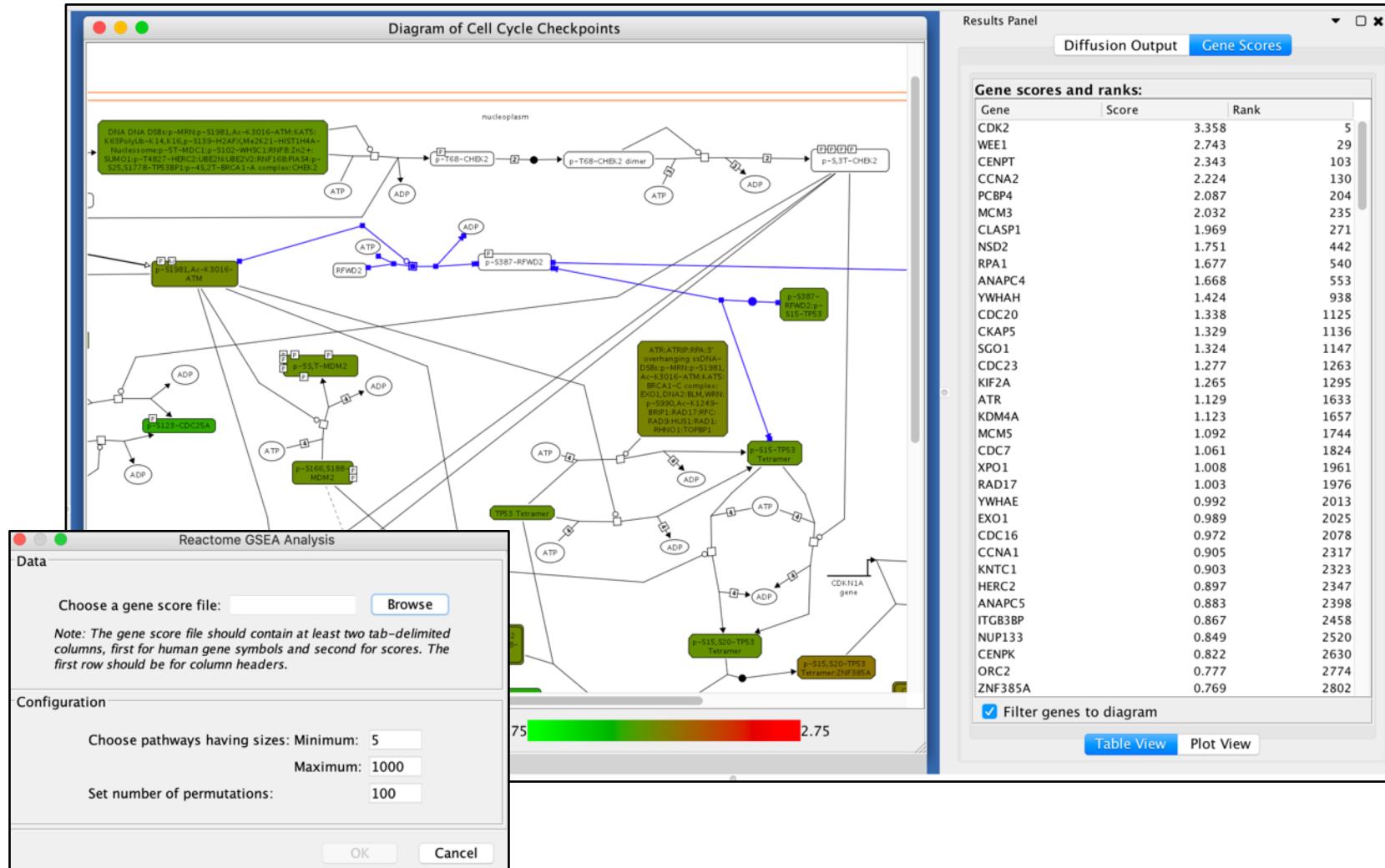
Apply Filters: FDR 1.0

ReactomePathway	RatioOfProteinInPat...	NumberOfProteinIn...	ProteinFromGeneSet	P-value	FDR	HitGenes
Laminin interactions	0.0032	23	5	0.0111	0.0890	ITGA6,LAMC1,LAMB...
Activation of Rac	0.0011	8	3	0.0114	0.0911	ROBO1,SOS1,SLT2
Interleukin-7 signal...	0.0011	8	3	0.0114	0.0911	IL7R,HGF,JAK1
CREB phosphorylati...	0.0021	15	4	0.0115	0.0917	GRIN2B,GRIN2A,AKA...
Mismatch Repair	0.0021	15	4	0.0115	0.0917	RPA1,POLD3,MLH1,...
M Phase	0.0315	225	22	0.0117	0.0937	KNTC1,NDE1,UBC,A...
GABA receptor activ...	0.0074	53	8	0.0124	0.0993	GABBR2,GNAT3,GAB...
Mitotic Prometaphase	0.0139	99	12	0.0131	0.1016	KNTC1,NDE1,PDSSB...
Digestion of dietary ...	0.0004	3	2	0.0132	0.1016	MGAM,LCT
Mitotic Anaphase	0.0227	162	17	0.0136	0.1016	KNTC1,NDE1,UBC,A...
TGF-beta receptor s...	0.0022	16	4	0.0142	0.1016	UBC,PARD3,TGFBR2...

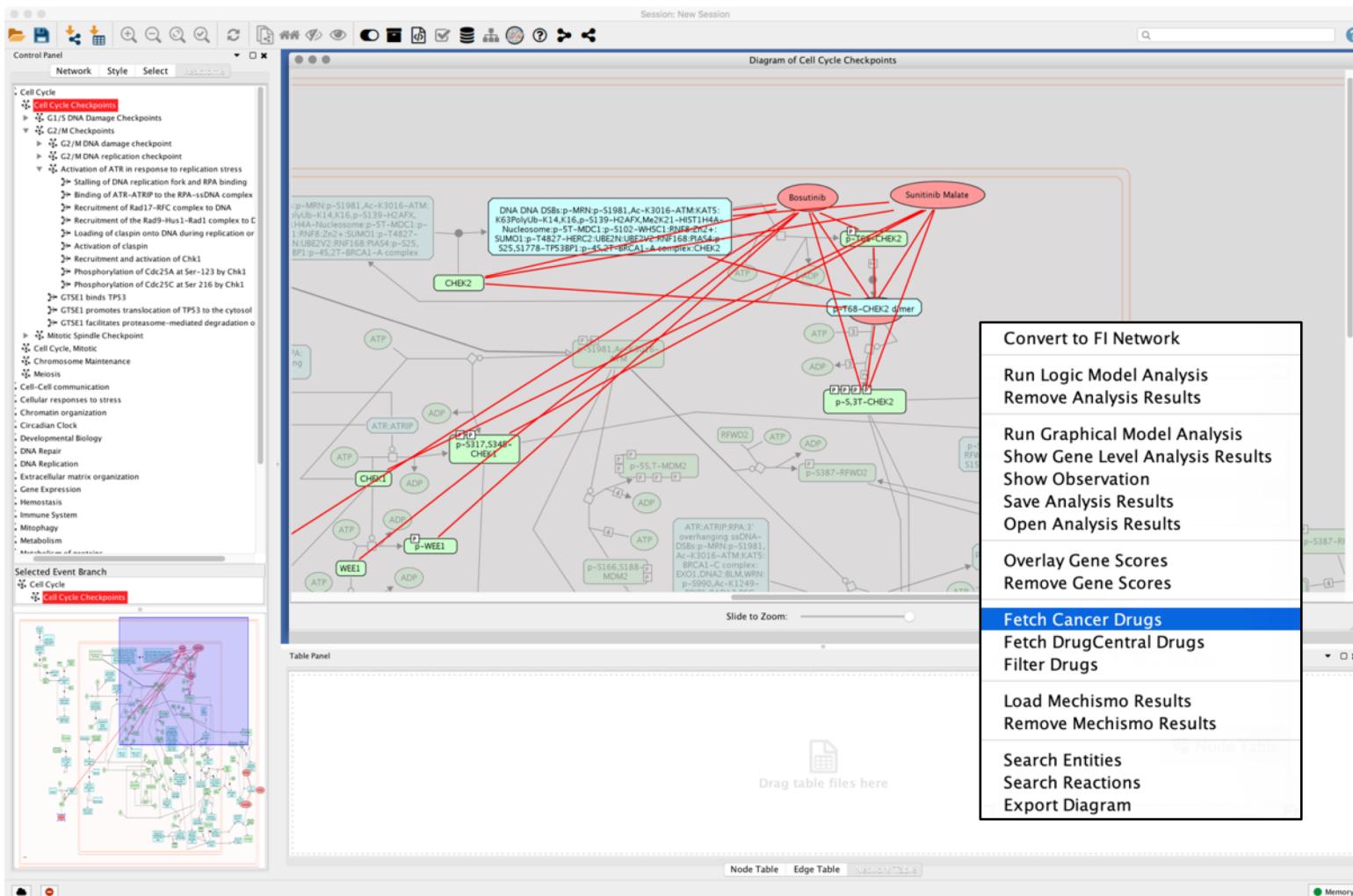
Node Table Edge Table Network Table Reactome Pathway Enrichment

Memory

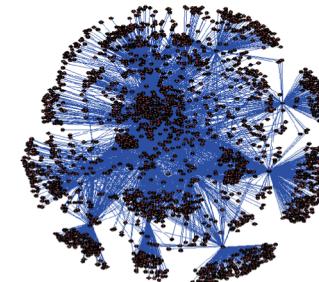
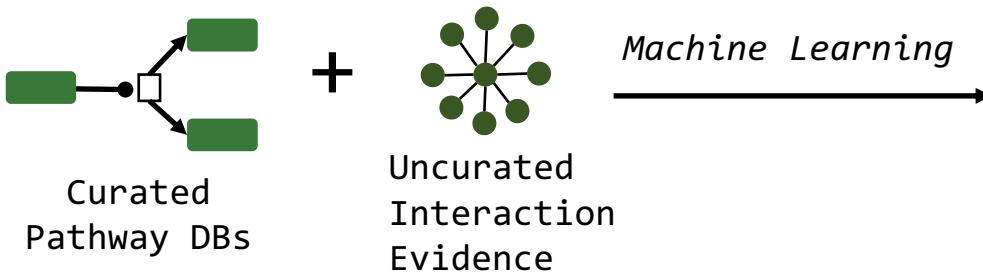
Gene Set Enrichment Analysis (GSEA)



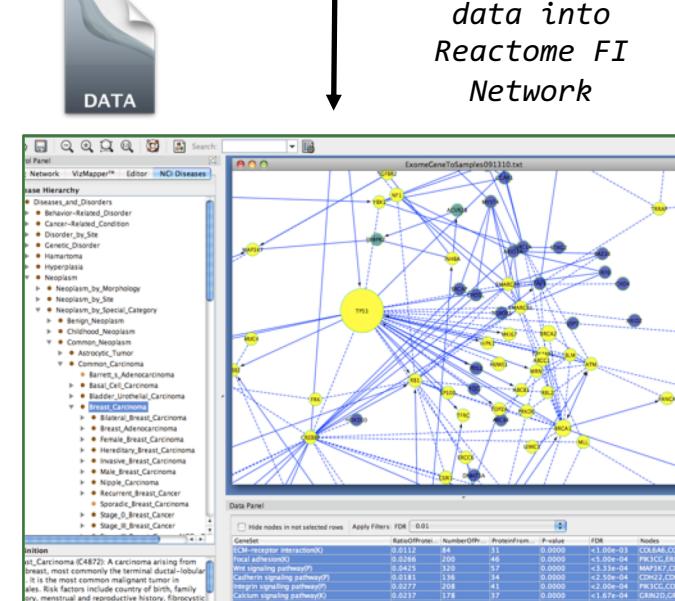
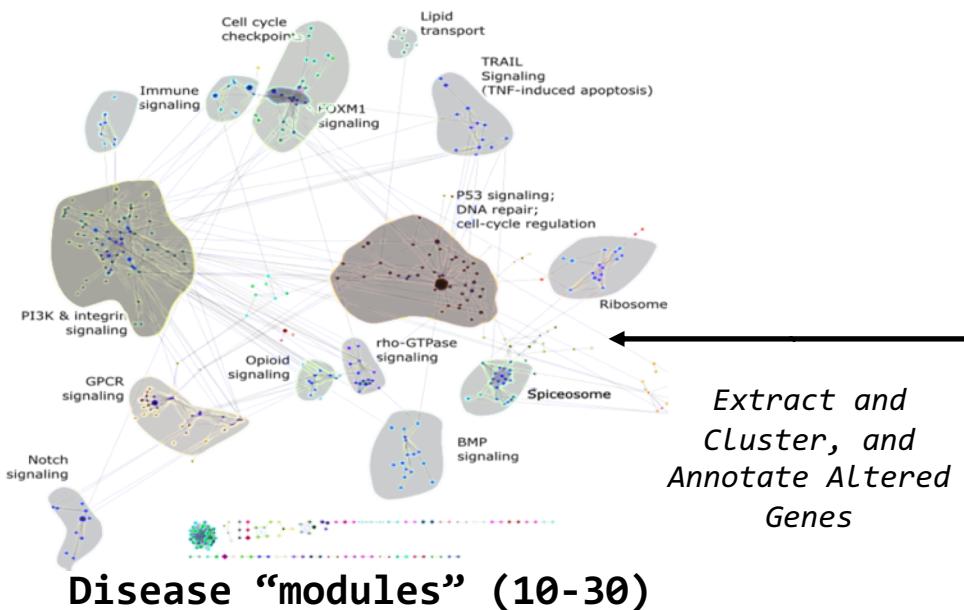
Visualize Cancer Targetome in Reactome Pathways



A2) De Novo Subnetwork Construction & Clustering

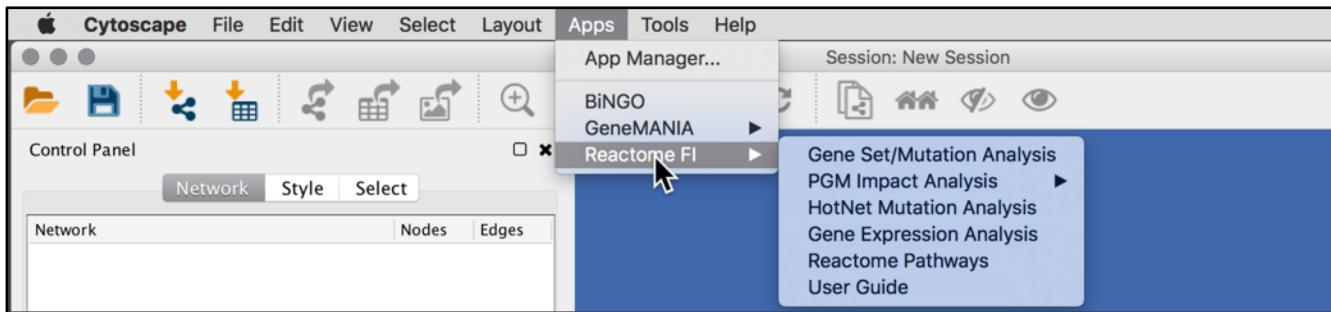


Reactome Functional Interaction Network
(~13K proteins; ~436K interactions)



Cytoscape using ReactomeFIViz app

Upload your data



- FI plug-in supports four file formats:
 - Simple gene set: one line per gene
 - Gene/sample number pair. Contains two required columns, gene and number of samples having gene mutated, and an optional third column listing sample names (delimited by semi-colon ;)
 - NCI MAF (mutation annotation file)
 - Sample Gene Expression data file

File Formats

- Choose Plugins, Reactome FIs.

Simple Gene List

MSI2
PTPRT
PELO
SLC18A1
TACC2
FAM148B
PRC1
MSTN
ATP6V1G2
APOE
IMPA2
AGER
XPO5
MEST
RRBEB1
BAT1
WIPI1

Gene/Sample Number Pairs

Gene	Sample_Number	Samples
IFT88		TCGA-10-0937
TACC2		5 TCGA-24-2288;TCGA-09-1662;TCGA-13-0755;TCGA-13-0920;TCGA-24-2035
ADAD2		1 TCGA-24-1419
PODXL2		1 TCGA-24-2290
RTN3		1 TCGA-13-0726
TADA2B		1 TCGA-25-1313
CD274		1 TCGA-25-1627
SULF1		2 TCGA-24-2262;TCGA-09-2056
SYCP2		3 TCGA-24-1563;TCGA-61-2008;TCGA-24-1427
CD200R1L		1 TCGA-13-1488
RCBTB2		1 TCGA-61-2113
TOP2B		1 TCGA-13-0923
C1orf50		1 TCGA-25-2392
ATP9A		5 TCGA-25-1329;TCGA-04-1530;TCGA-24-2262;TCGA-10-0933;TCGA-13-0795
NUDTP5		1 TCGA-61-2003
ZNF189		1 TCGA-24-2254
KCNB1		1 TCGA-23-1028
FERMT3		1 TCGA-24-1464
ZCHC2		1 TCGA-61-1998
DDX18		1 TCGA-13-1509
TGM1		2 TCGA-24-0975;TCGA-25-1321
SAMD7		1 TCGA-09-2051
OR2F2		3 TCGA-13-0723;TCGA-24-2267;TCGA-25-2392
ZSWIM3		2 TCGA-24-1466;TCGA-23-1118
EIF2AK2		2 TCGA-59-2355;TCGA-24-1463
KIAA2018		4 TCGA-23-1024;TCGA-04-1367;TCGA-24-2288;TCGA-24-2289
.....		

NCI MAF (mutation annotation file)

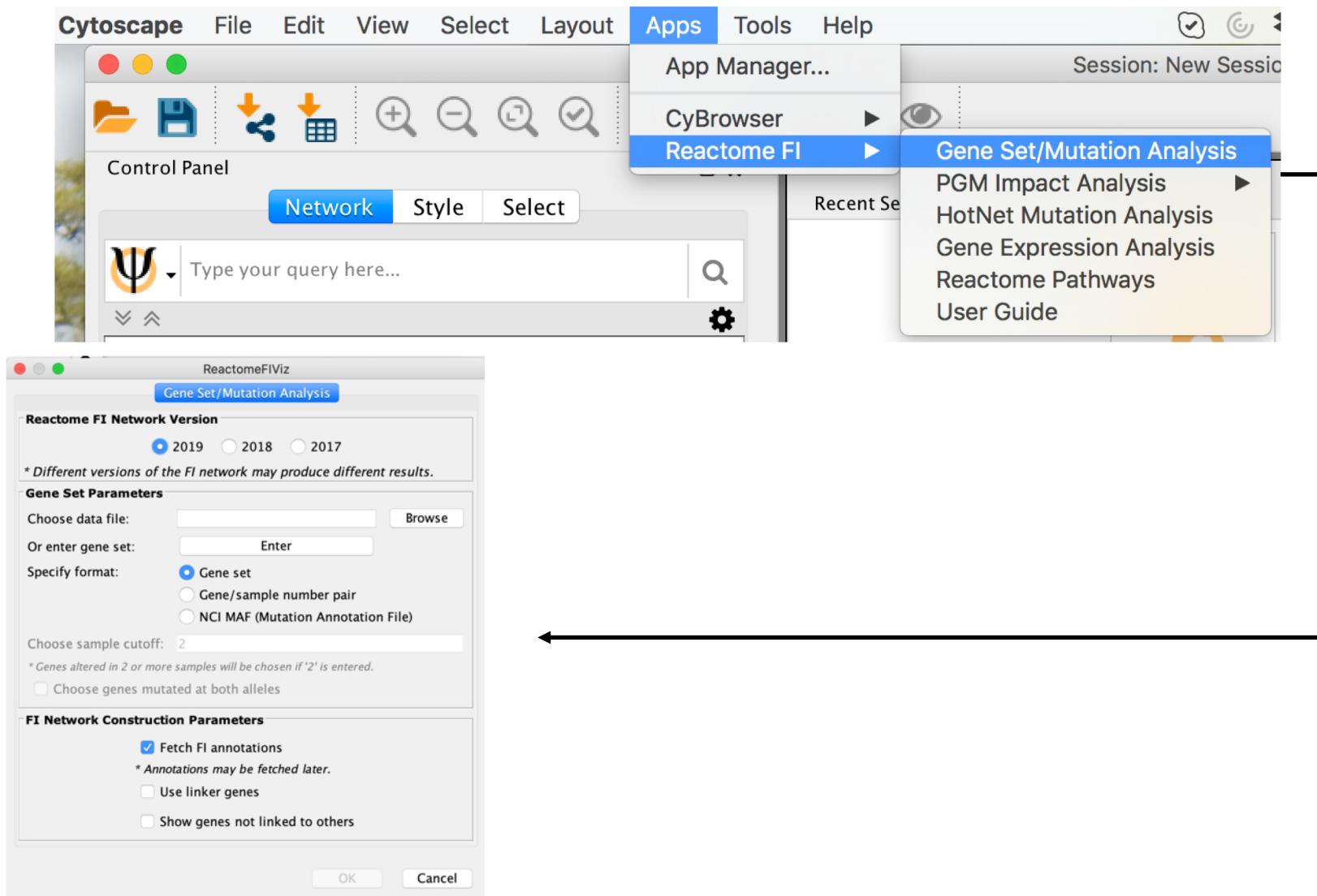
Hugo_Symbol	Entrez_Gene_Center	NCBI_Build	Chromosome	Start_position	End_position	Strand
BA12	576	broad.mit.edu	36	1	31974808	31974808
RCCR41	10489	broad.mit.edu	36	1	46524584	46524584
C1orf173	127254	broad.mit.edu	36	1	74828082	74828082
SDF3	117100	broad.mit.edu	36	1	84000000	-
TINCLG1	22845	broad.mit.edu	36	1	107668441	107668441
PLVYR3P	114771	broad.mit.edu	36	1	151514551	151514551
FCRL5	83416	broad.mit.edu	36	1	155783467	155783467
FBXO28	23219	broad.mit.edu	36	1	22388418	22388418
OR2M2	391194	broad.mit.edu	36	1	246410342	246410342
MKK	283078	broad.mit.edu	36	10	28063690	28063690

Variant_Classification	Variant_Type	Reference_Allele	Tumor_Seq_Allele1	Tumor_Seq_dbSNP_RS	dbSNP_Val_Status
Misense_Mutation	SNP	C	C	TGCA-04-13	novel
Misense_Mutation	SNP	C	C	TGCA-04-13	novel
Misense_Mutation	SNP	T	T	TGCA-04-13	novel
Silent	SNP	A	A	TGCA-04-13	novel
Misense_Mutation	SNP	G	G	TGCA-04-13	novel
Misense_Mutation	SNP	G	G	TGCA-04-13	novel
Misense_Mutation	SNP	G	T	TGCA-04-13	novel
Misense_Mutation	SNP	A	A	TGCA-04-13	novel
Misense_Mutation	SNP	A	A	TGCA-04-12	novel
Misense_Mutation	SNP	G	G	TGCA-04-13	novel
Misense_Mutation	SNP	C	C	TGCA-04-13	novel

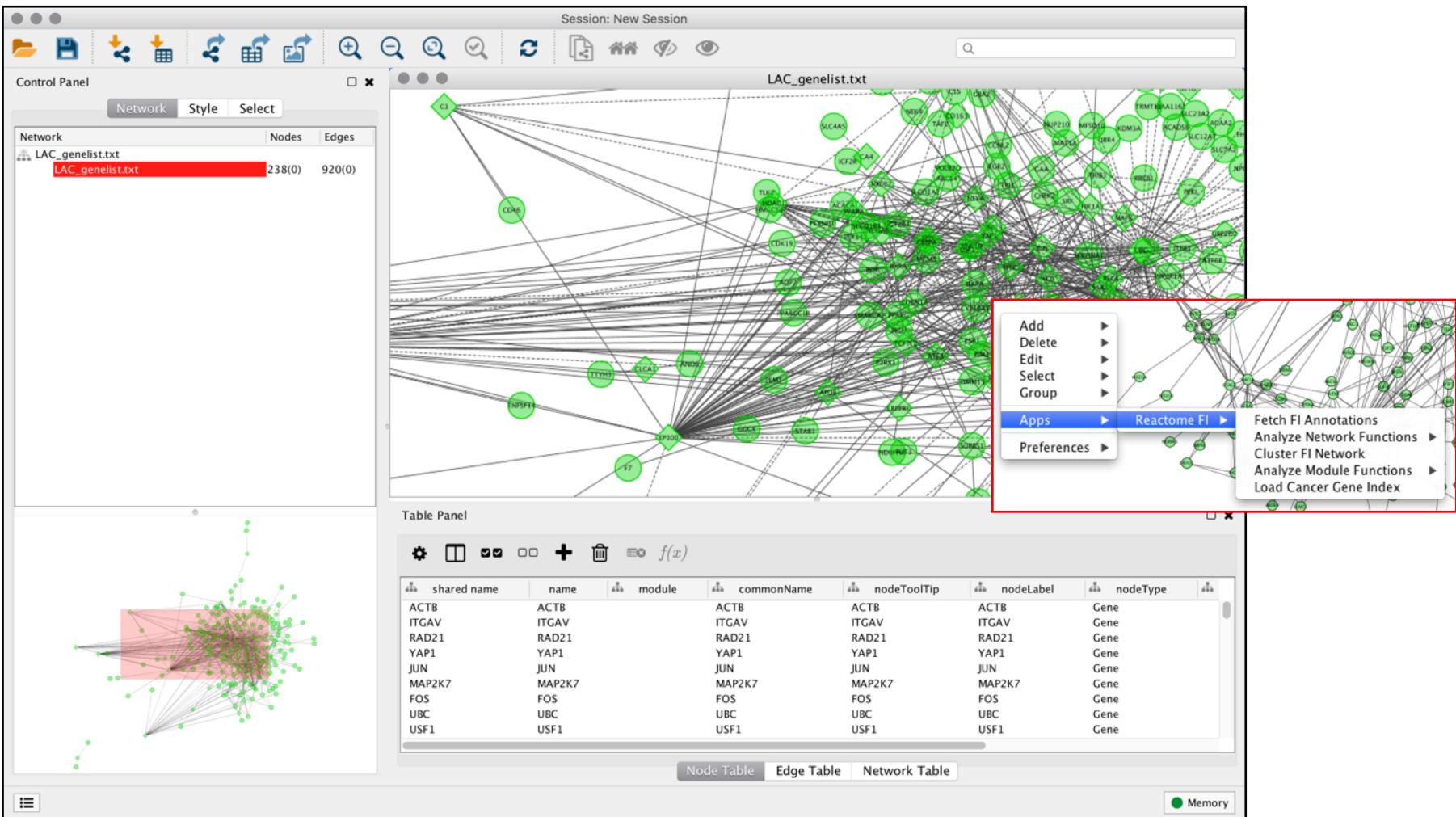
Microarray (array) data file

gene	Sample 122	Sample 123	Sample 124	Sample 125	Sample 126	Sample 127	Sample 128	Sample 129	Sample 130
IFIT8	1.43357937	0.749571365	0.204170171	1.37637523	0.049504161	0.91237692	0.464660294	0.106468375	0.40767808
KIF9B	0.34962239	0.03947168	-0.568902093	0.177455762	-0.30739793	-0.574121582	-0.772445942	0.850743793	0.19883291
CP5F3	-0.62884687	-0.519774477	0.200101088	-0.38888826	-0.049393584	0.549138111	-0.44005917	-0.247094525	0.421706786
TACR2	0.98529915	-0.73525555	0.103645941	-0.058786422	0.370122474	-0.554418157	0.281012472	0.463706367	0.965951722
C14orf174	1.249528811	0.108467045	0.542096007	-0.436446162	-1.528525911	-0.467450388	-0.278116395	-0.525776594	-0.106893198
RTN3	0.10643433	-0.26862028	-0.329056423	0.548598273	0.105469991	-0.62778828	-0.462525025	0.39883285	-0.589604374
PDXDL2	-0.031430138	-0.390412805	-0.073587375	-0.412394215	0.085789704	-0.07365917	-0.054048071	-0.104692114	0.13830989
CORO1A	-0.247037235	0.664838693	-0.423713196	-0.00197059	0.488162732	-0.435111645	0.564947799	-0.463607768	0.050201666
RBM17	-0.360070659	-0.142615078	-0.239314802	0.18396914	-0.130696373	-0.394766028	0.818193293	-0.626633675	0.993237363
WT1	0.768481855	-0.694912898	0.763665041	-0.674522401	-0.168167157	-0.393931693	0.906241952	-0.35285021	-0.593251635
SULF1	0.863562291	0.158894776	0.272263522	-0.419487000	0.401966747	-0.081472544	-1.17805453	0.327289133	-0.21903675
SYCP2	0.365259800	1.246319117	-0.107060762	0.618562863	0.914563566	0.091453376	-0.376967692	0.727095627	0.00262058
PHYH	-0.252934465	-0.340129465	0.084219531	0.613340462	-1.85732425	0.479503258	-0.229544553	-1.103697457	0.370551225
RBCTB2	1.21604479	0.113736773	-0.741641602	0.63679988	-0.695953562	-0.46841374	-0.34889208	-0.130544852	-0.574231973
TOPBP2	1.329376011	0.277684069	0.636481097	0.611284991	0.464606891	0.98295854	0.479308713	0.397117399	0.050669942
SEC22B	-0.71205025	0.615516262	-0.33943161	0.917245507	0.427725935	0.413113408	0.58388633	0.632302107	0.487617603
ATP9A	1.547427859	0.44411132	1.145509578	-0.14324565	0.540051894	0.510070468	0.233468933	-0.149520936	0.047584083
TGFBR1	-0.782212802	-0.264862477	-0.123003856	0.027019162	-0.239823997	-0.27719409	-0.773868442	0.110632736	0.270499777
NUDT5	-0.161643202	-0.11759470	0.072831699	-0.025664715	0.37488737	0.43398528	-0.88999992	-0.030023072	0.112320265
VT11B	1.252187159	0.155526231	0.07352974	0.707902019	-0.386468833	0.168434408	0.191395423	0.967344934	0.163535918
RP5K6B	-0.387163384	0.639591359	-0.597648114	-0.392291795	0.932161509	0.563760969	0.782463975	0.460540384	0.674567453
RAPGEF4	0.202545543	0.24092029	0.106670963	0.1564856103	0.55713630	-0.027704365	0.65129739	-0.612292266	-1.17852869
PR10596	-0.010404297	0.228155329	0.228155329	0.455045984	0.148635394	0.077918194	0.376195587	0.138032748	0.03703761
CKN1B	0.93447088	-0.061402118	0.135678453	0.628377569	0.656315308	1.458927537	1.181563563	-0.469637634	0.346835207
ALDH9A1	0.702468807	-0.111692273	0.963729452	-0.18130816	-0.083824904	0.69904754	0.844724649	-0.387823255	0.154579805
ZCHC2	0.55864339	-0.12059056	0.84570548	-0.479704052	0.477522496	-1.144895382	0.389385183	0.55323533	0.097318121
LOC51273	-0.291416641	-0.262471345	0.134705668	-0.211743876	-0.073822271	0.699406086	0.971399049	-0.218858994	-0.146357258
DDX18	0.3496719	0.29488342	-0.0084030	0.10530753	0.140036175	0.07623395	0.167045532	0.51373466	0.106725088

Gene Set-based Analysis



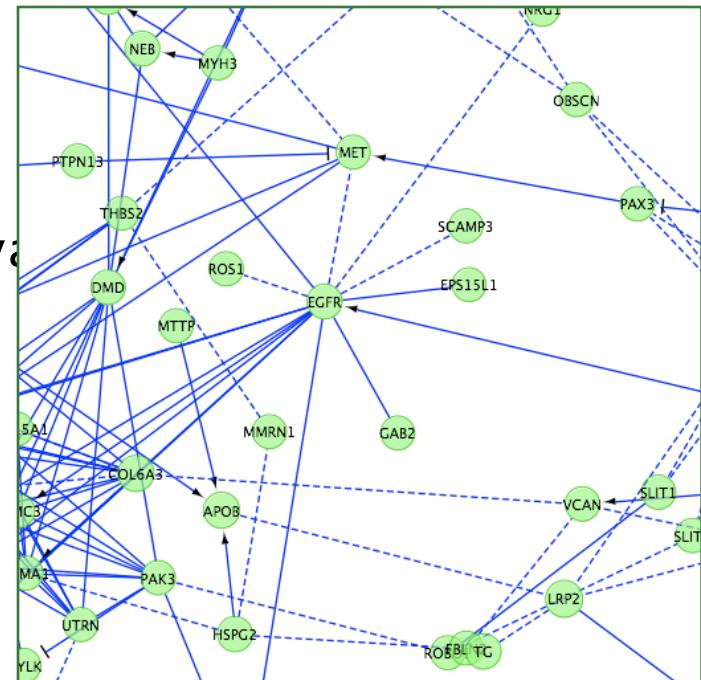
FI Results Display



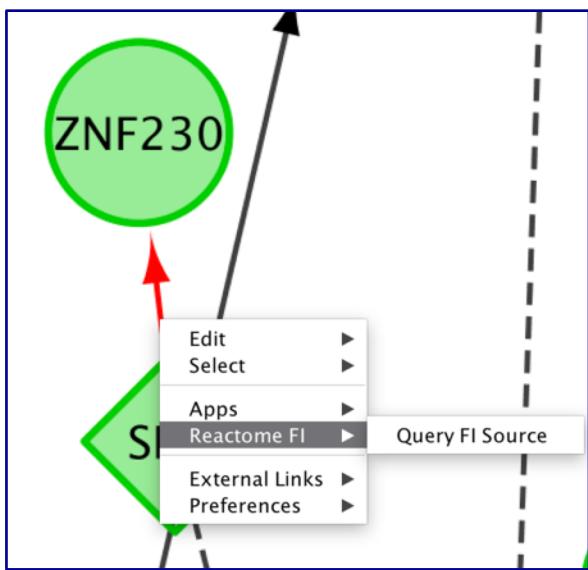
- Constructed network is displayed in the Network View panel using an FI specific visual style

FI Annotations

- Provides detailed information on selected FIs.
- Three edge attributes are created:
 - FI Annotation.
 - FI Direction.
 - FI Score (for predicted FI).
- Edges display direction attribute values:
 - --> for activating/catalyzing.
 - --| for inhibition.
 - solid line for complexes or inputs.
 - --- for predicted FIs.



Query FI Source



Annotated FIs

A screenshot of the "Interaction Info" window for the interaction between SIX5 and ZNF230. The window has two main sections: "Reactome Sources" and "Reactome Instance View".

Reactome Sources:

Reactome ID	Type	Data Source
6951674	TARGETED_INTERACTION	ENCODE

Reactome Instance View:

classType	TargetedInteraction
dbId	6951674
displayName	SIX5 ZNF230
dataSource	ENCODE
definition	ENCODE proximal_filtered TF/target interaction; supported by GO BP sharing
factor	SIX5
species	Homo sapiens
target	ZNF230

Buttons: "View Reactome Source" and "Close".

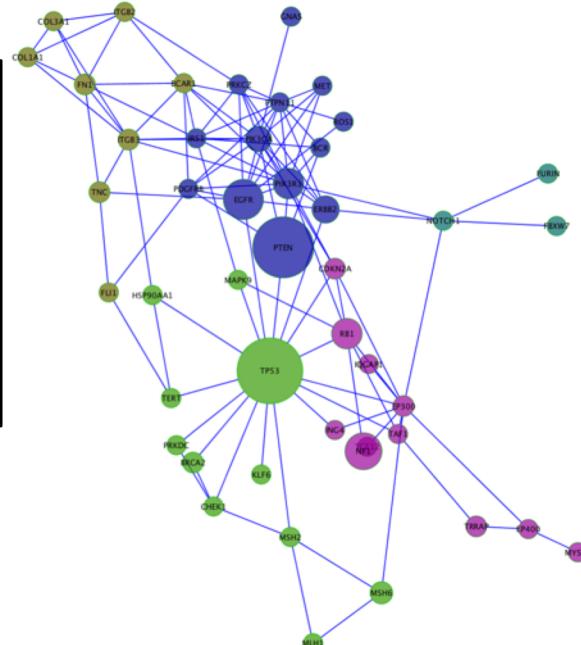
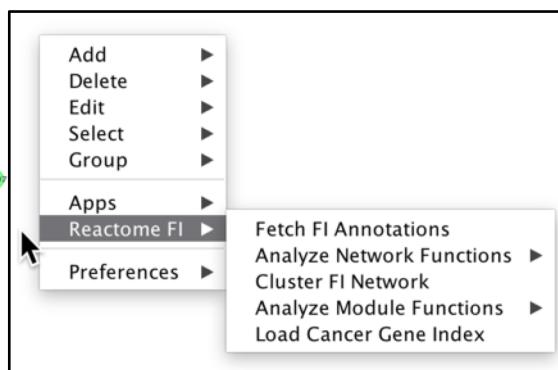
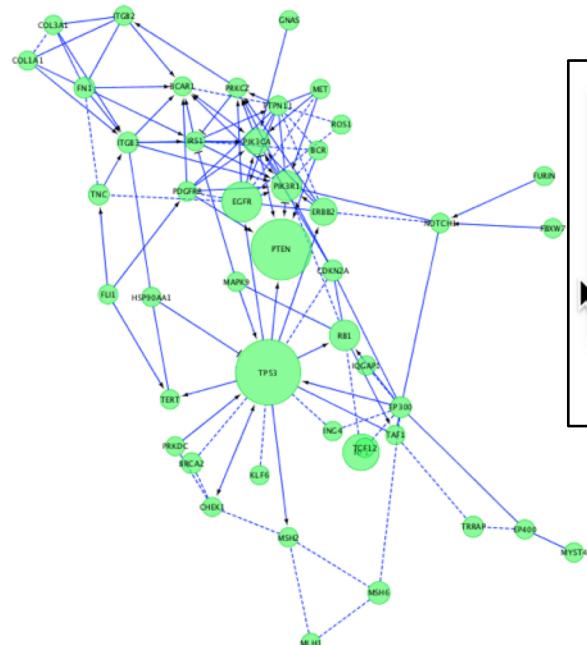
Predicted FIs

A screenshot of the "Interaction Info" window for the interaction between SNX4 and SNX6. The window has a single section titled "Support Evidence".

Predictor	Value
Human Interaction	true
Yeast Interaction	false
Fly Interaction	false
Worm Interaction	false
Mouse Interaction	false
Pavlidis Gene Exp	false
Carlos Gene Exp	false
PfamDomain Interaction	true
GO BP Sharing	true
Score	0.9642255584531738

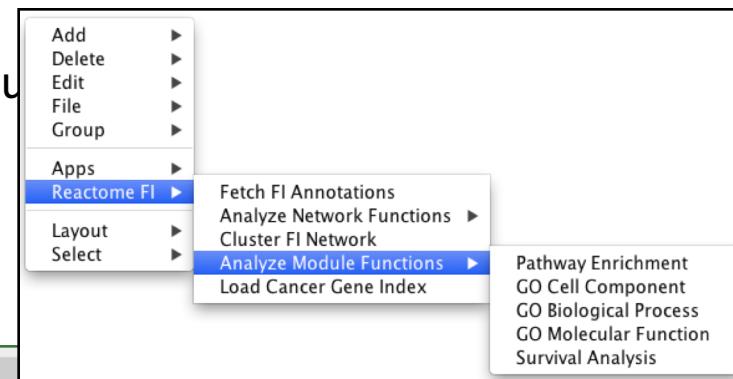
Cluster FI Network

- Runs spectral partition based network clustering ([Newman, 2006](#)) on the displayed FI network.
- Nodes in different network modules will be shown in different colours (max 15 colours).
- Analyze cancer mutation data with HotNet algorithm ([Vandin, 2012](#))



Analyze Module Functions

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



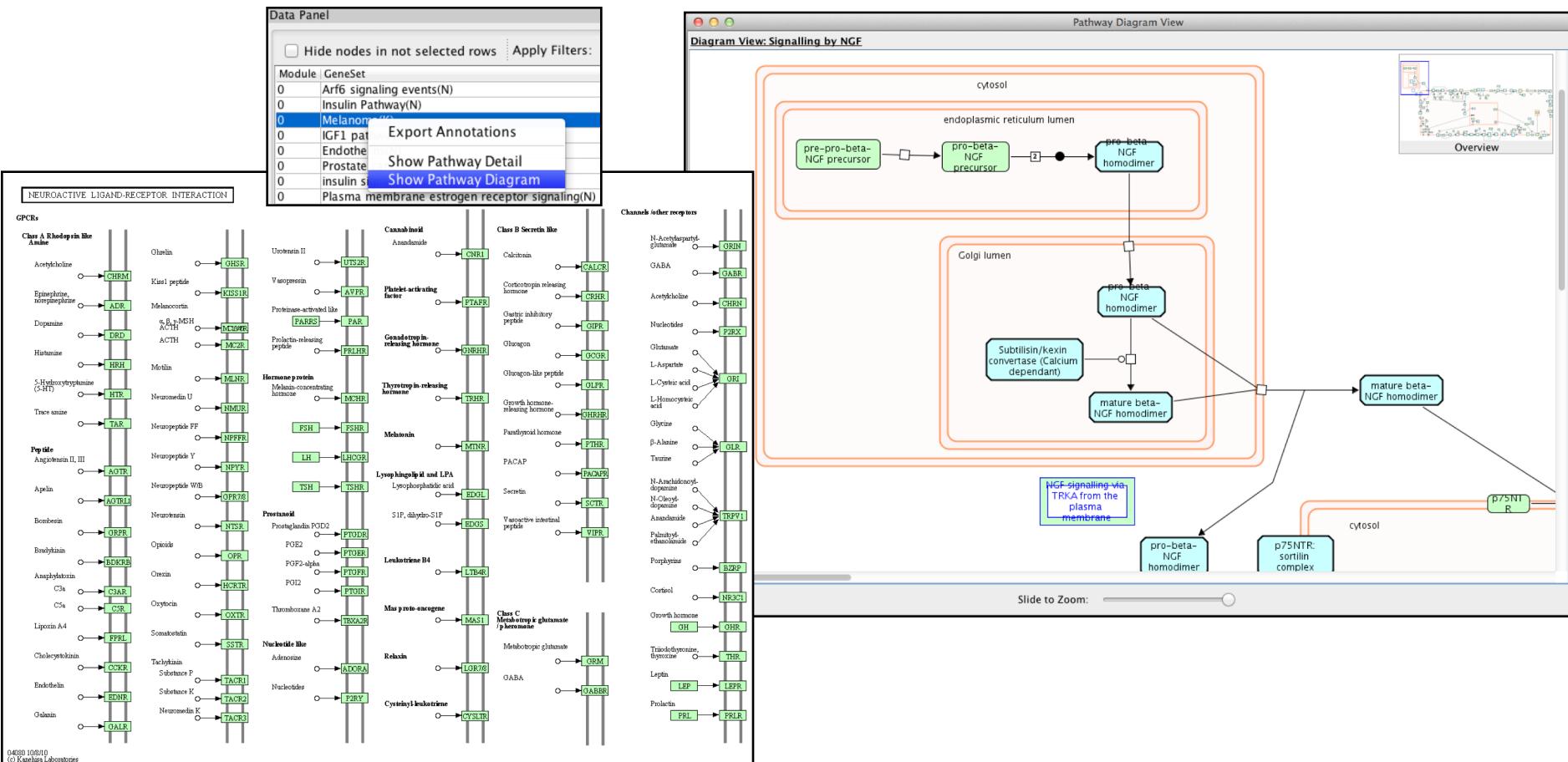
Data Panel

Module	GeneSet	RatioOfProteinInModule	Module Size	FDR	Nodes
0	Translation(R)	0.0158	15	<1.30e-04	RPL18,RPL17,RPL36...
0	Influenza Life Cycle(R)	0.0249	13	<2.30e-04	RPL18,RPL17,RPL36...
0	Ribosome(K)	0.0117	12	<2.30e-04	RPL18,RPL17,RPL36...
0	Metabolism of protein...	0.0267	11	<2.30e-04	RPL18,RPL17,RPL36...
1	M Phase(R)	0.0128	64	<1.30e-04	ITGB3BP,MAD1L1,CC...
1	Aurora B signaling(N)	0.0052	60	<5.00e-04	AURKC,AURKB,CDCA...
1	Signaling by Aurora k...	0.0125	58	<3.30e-04	AURKC,AURKB,CDCA...
2	Glucose Regulation of...	0.0197	148	<1.07e-04	NDUFB4,NDUFA2,ND...
2	Parkinson's disease(K)	0.0176	132	<1.67e-04	NDUFB4,NDUFA2,ND...
2	Alzheimer's disease(K)	0.0223	168	<1.67e-04	NDUFB4,NDUFA2,ND...
2	Huntington's disease(K)	0.0246	185	<1.67e-04	NDUFB4,NDUFA2,ND...
2	Oxidative phosphoryl...	0.0178	134	<1.67e-04	NDUFB4,NDUFA2,ND...
2	Electron Transport C...	0.0101	76	<1.67e-04	NDUFB4,NDUFA2,ND...
2	Metabolic pathways(K)	0.1489	1120	<1.43e-04	NDUFB4,NDUFA2,ND...
3	Antigen processing a...	0.0104	78	<1.00e-03	KLRC2,KIR2DS1,HLA...
3	Immunoregulatory int...	0.0153	115	<5.00e-04	KIR2DS1,HLA-B,HLA...
3	Natural killer cell me...	0.0182	137	<3.33e-04	KLRC2,KIR2DS1,HLA...

Node Attribute Browser Edge Attribute Browser Network Attribute Browser MCL Module Browser Pathways in Modules

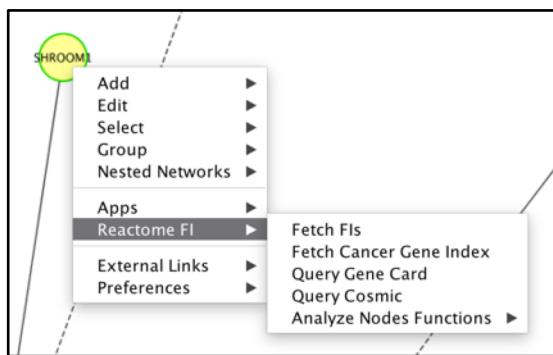
Show Pathway Diagrams

- Select a pathway in "Pathways in Network/Modules" tabs, right click, select "Show Pathway Diagram"



NCI Cancer Gene Index

- View detailed annotations for the selected gene or protein.
- Annotations are sortable by PubMed ID, Cancer type, status, and other criteria.



Cancer Gene Index Annotations for "MAF"

Order by: PubMedID ▾ Set Filters Current filters: None

Results: 1 to 8 of 8 First Prev Page 1 Next Last

Cancer type: tumors
Primary NCI role code: Gene_Has_Anormally
Other roles: not_assigned
Evidence code: EV-AS-TAS
Negation indicator: no
Cellline indicator: no
Status: finished
PubMedID: [16155016](#)
Comment: Anomalous_Detail: Chromosomal_Translocation
Nearly half of tumors are nonhyperdiploid, and mostly have one of five recurrent IgH translocations: 16% 11q13 (CCN D1), 3% 6p21 (CCN D3), 5% 16q23 (MAF), 2% 20q12 (MAFB), and 15% 4p16 (FGFR3 and MMSET).

Cancer type: tumors
Primary NCI role code: Gene_is_Biomarker_of
Other roles: not_assigned
Evidence code: EV-EXP-IEP, EV-EXP-IDB
Negation indicator: no
Cellline indicator: no
Status: finished
PubMedID: [15755896](#)

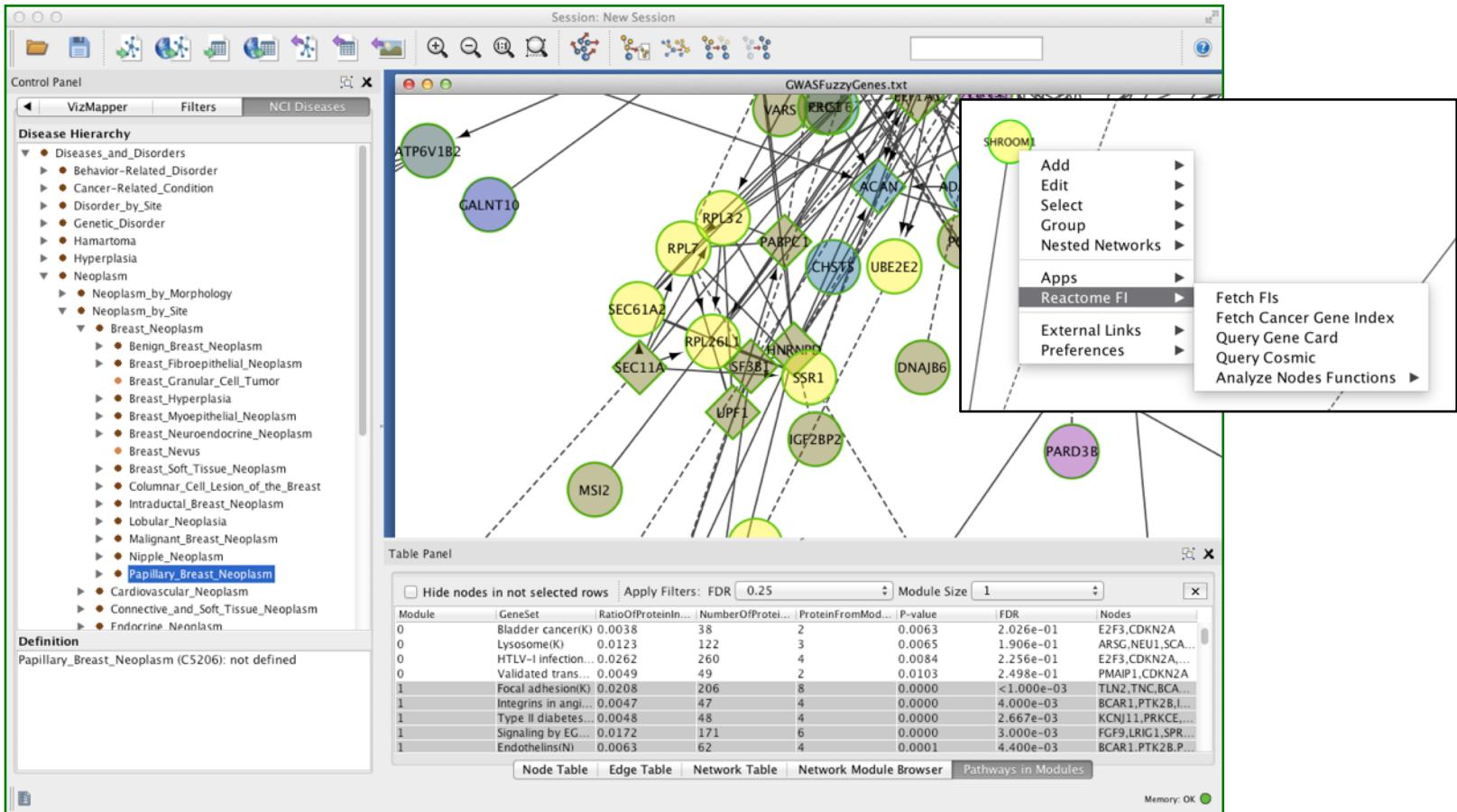
Using gene expression profiling to identify 5 recurrent translocations, specific trisomies, and expression of cyclin D genes. MM tumors can be divided into 8 TC (translocation/cyclin D) groups (11q13, 6p21, 4p16, maf, D1, D1+D2, D2, and none) that appear to be defined by early, and perhaps initiating, oncogenic events.

Cancer type: plasma-cell leukemias (pcl)
Negation indicator: no
Cellline indicator: no
Status: no_fact
PubMedID: [15543617](#)

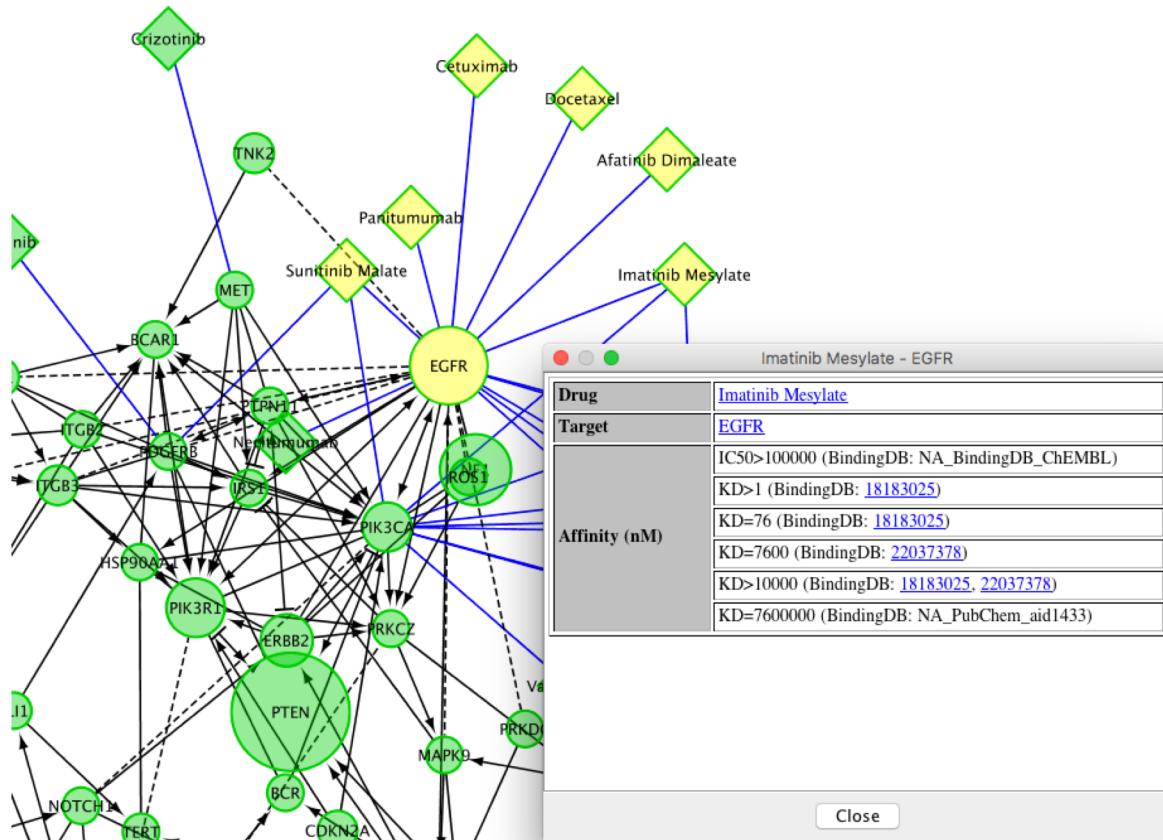
We investigated the expression profiles of the FGFR3/MMSET, CCND1, CCND3, MAF, and MAFB genes, which

Overlay Cancer Gene Index

- Load the NCI disease terms hierarchy in the left panel.
- Select a disease term in the tree to select all nodes that have this annotation or one of its sub-terms.



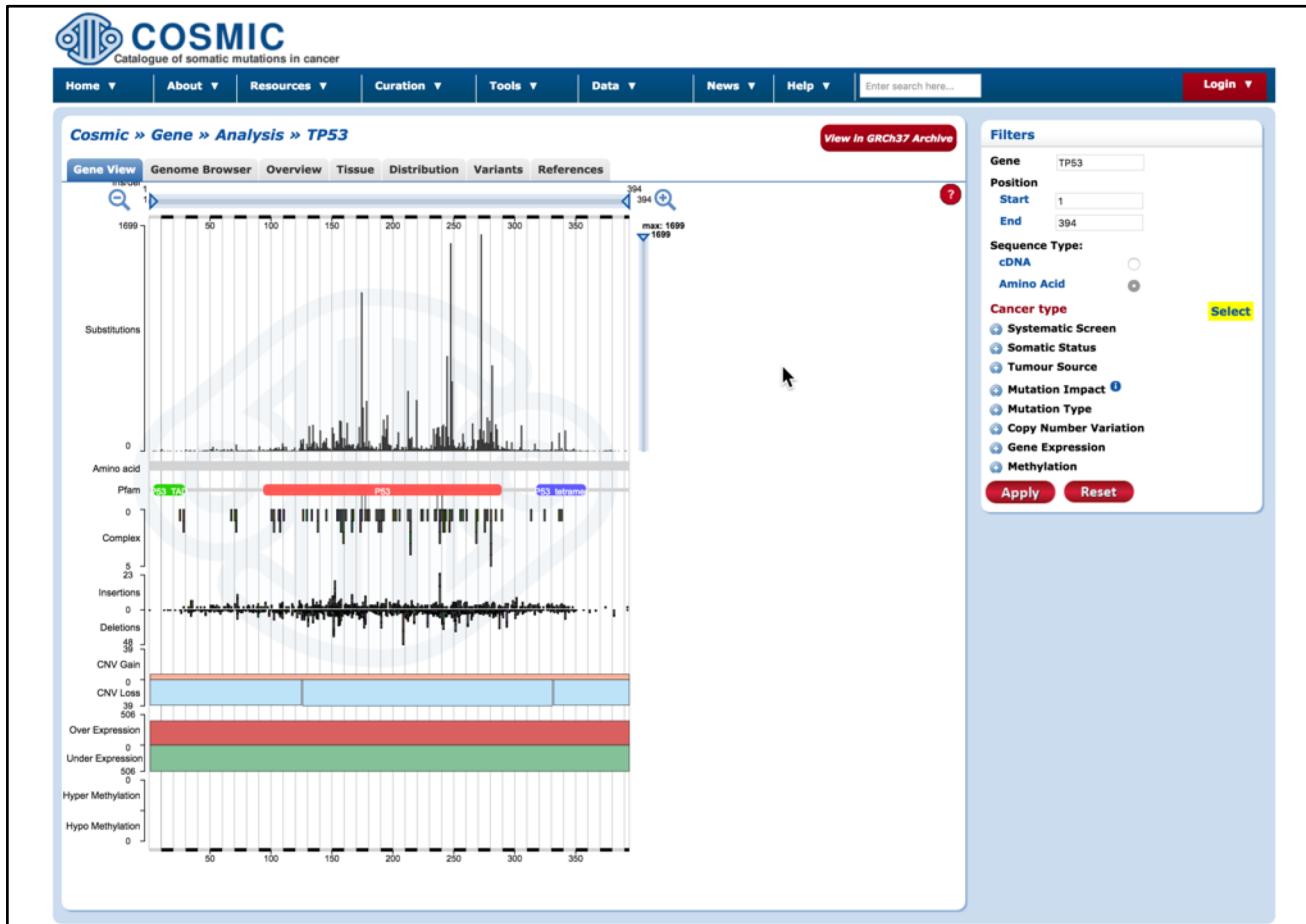
Visualize Cancer Targetome in the Reactome FI Network



TCGA GBM Mutation Profile

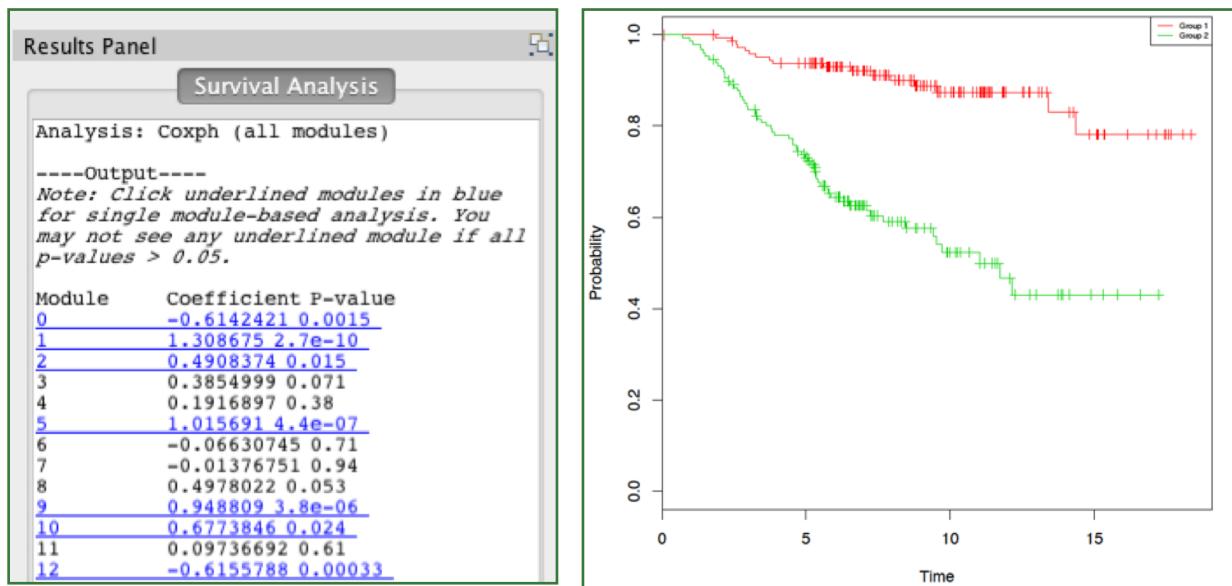
COSMIC

- View detailed variant annotations for the selected gene or protein from COSMIC database.



Module Based Survival Analysis

- Discover Prognostic Signatures in Disease Module Datasets.
- Based on a server-side R script that runs either CoxPH or Kaplan-Meyer survival analysis.
- Requires appropriate clinical data file.



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We are on a Coffee Break & Networking Session

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