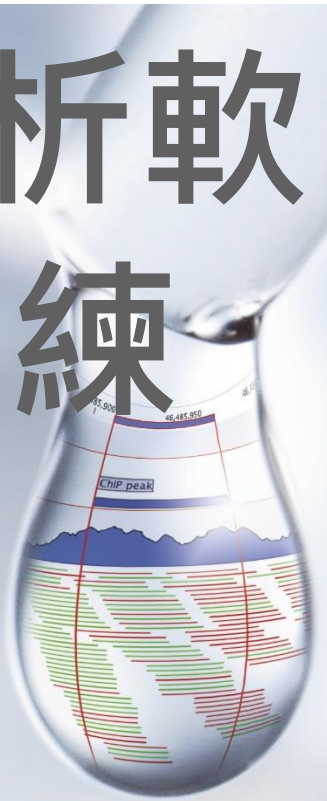
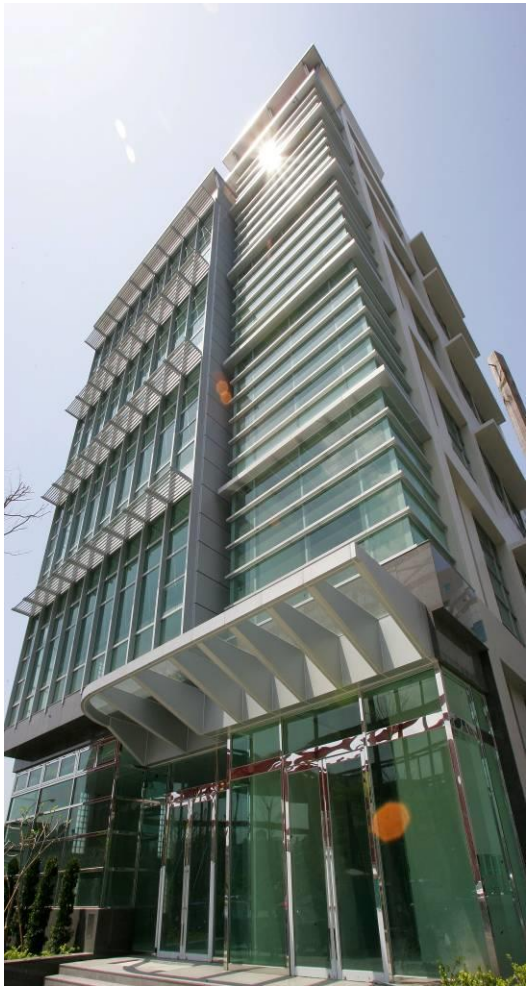
IPA 系統生物學分析軟體暨資料庫教育訓練



IPA以數據演算及人工閱讀的資料庫文獻，
提供您快速的在數千萬筆的研究分析資料中，
找到最關鍵的生物途徑與分子間調控關係。

Leo Hung 洪慈懋
創源生技 產品專員
Office: 02-2795-1777#3014 E-mail: LeoHung@gga.asia

Ingenuity Pathway Analysis



GGA is part of the BIONET Group (訊聯生物科技)

CEO: Christopher Tsai, Ph.D. 蔡政憲 博士

Established: Nov. 2008

Main Product & Service Areas:

- Genetic Testing & Molecular Diagnosis
- **Scientific Informatics & Bio IT**

IPO Date: September 17, 2012

Stock Ticker: 4160 (Taiwan OTC)

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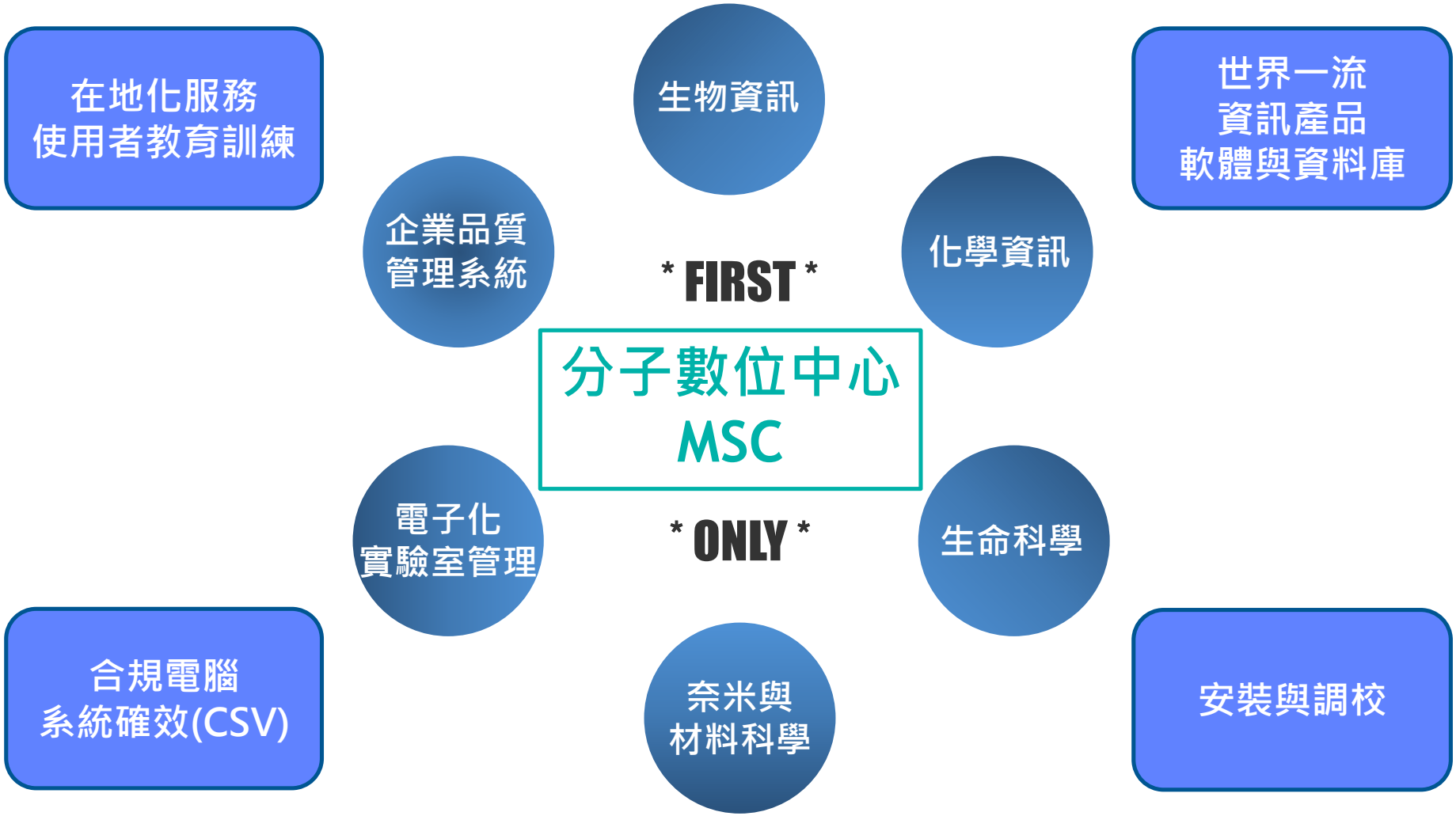
Molecular Science Center in GGA



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IPA Training Account

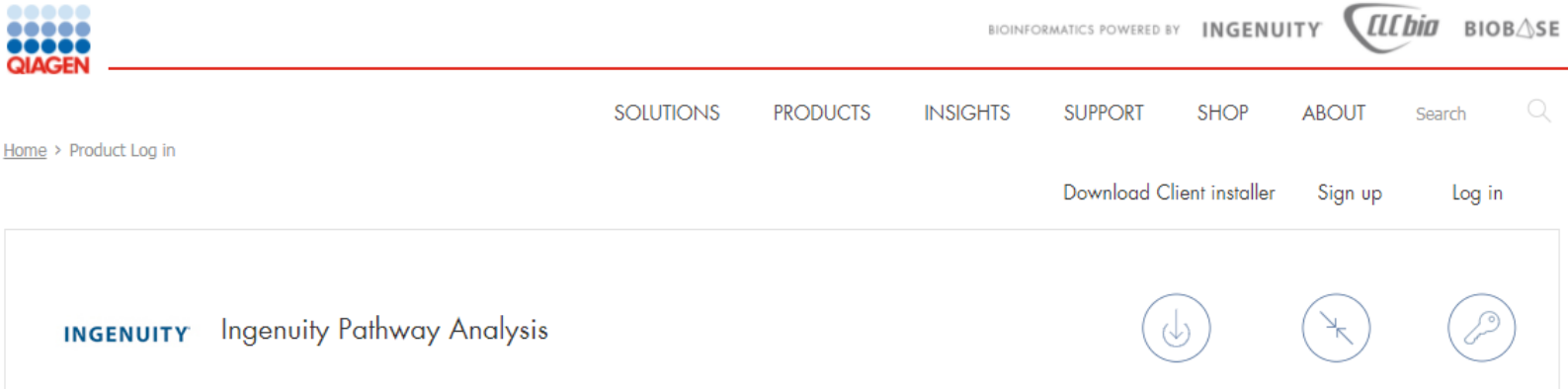
Account: clcXX@ingenuity.com

Password: leo123456

Dataset: https://goo.gl/mx2nuj

Client: (IPA Login)

https://analysis.ingenuity.com/pa/installer/select



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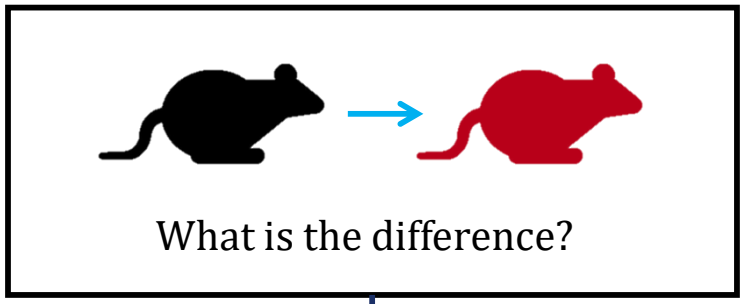
Why are we using IPA?



Your dataset

pathway

Disease

function

Relationship With other Observation

What are the relationship between each molecules?

What do they relate to each other?

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IPA Supported

IPA orthologous :

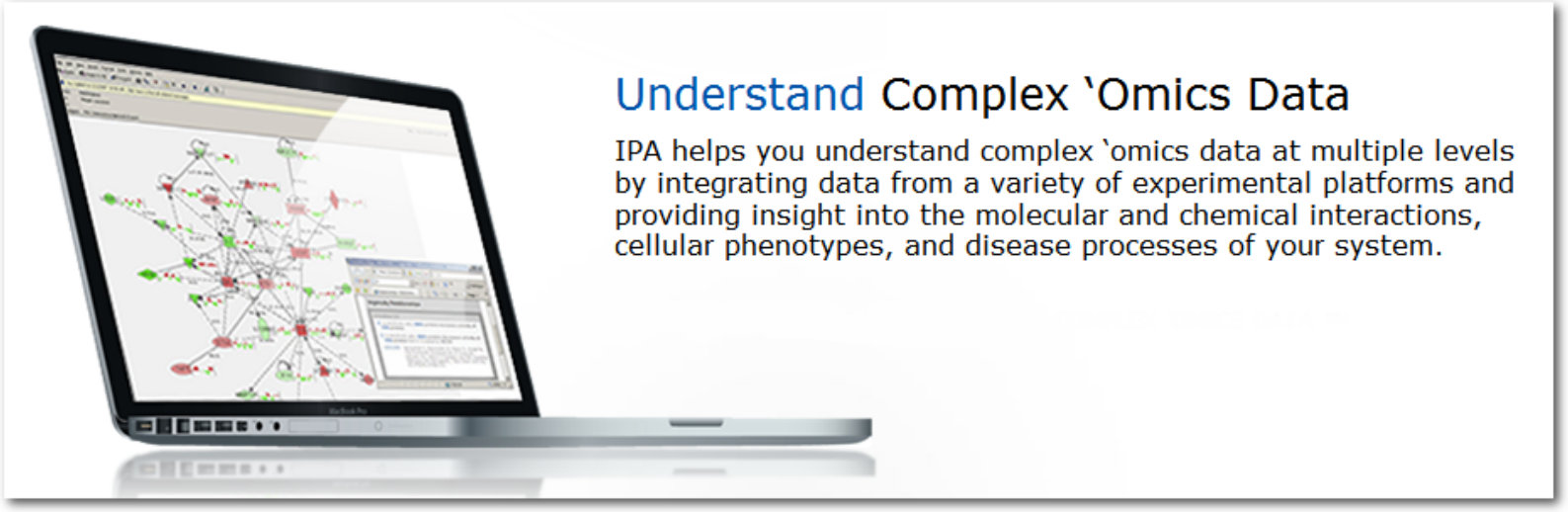
Arabidopsis thaliana
Bos taurus (bovine)
Caenorhabditis elegans
Gallus gallus (chicken)
Pan troglodytes (chimpanzee)
Danio rerio (zebrafish)
Canis lupus familiaris (canine)
Drosophila melanogaster
Macaca mulatta (Rhesus Monkey)
Saccharomyces cerevisiae
Schizosaccharomyces pombe

IPA supported platform :

- **Gene expression:**
  - qPCR analysis
  - Microarray
  - RNA-Seq (NGS)
  - microRNA
  - mRNA
- **Proteomics**
  - PhosphoProteomics[New]
- metabolomics

IPA application:

- Biomarker finding
- Toxicity Functions
- Diseases regulation



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Supported Identifiers for Data Upload

Get more complete mapping during dataset upload!

Vendor IDs	Gene	Protein	Transcript	microRNA	SNP	Chemical
Affymetrix (na36)	Entrez Gene (2020/10)	GenPept	Ensembl (101)	miRBase (mature)	Affy SNP IDs	CAS Registry Number
Agilent	GenBank (239)	International Protein Index (IPI)	RefSeq (human、mouse)	miRBase (stemloop)	dbSNP	HMDB
Life Tech (ABI)	Symbol-human (HUGO/ HGNC, EG)	UniProt/ Swiss-Prot Accession (2020_03)	UCSC (hg18)			KEGG
Codelink	Symbol- mouse (EG)		UCSC (hg19)			PubChem CID
Illumina	Symbol- rat (EG)		UCSC (hg38)			
Ingenuity	GI Number					
	UniGene					

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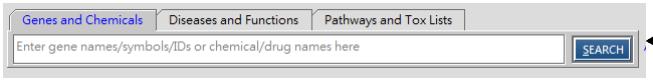
Entry Points in IPA

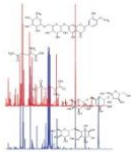
Biological Questions

Search



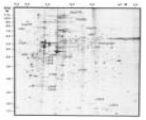
Experiment Data

Expression arrays



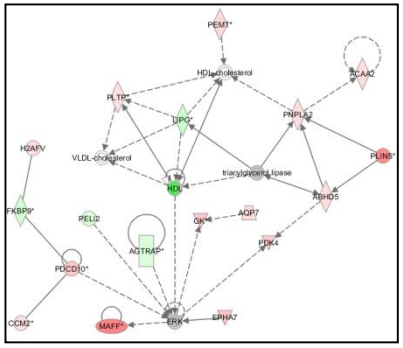
Mass spec

Protein arrays



2D Gel electrophoresis

Custom Pathway



Networks

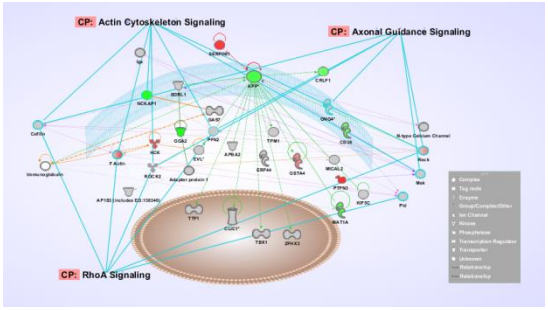
Core

IPA-Biomarker

IPA-Tox

IPA-Metabolomics

Bio/Tox Functions
Diseases/Disorders
Canonical Pathways
Upstream regulators
Mechanistic/Casual Network
Interaction Network



Communicate & Collaborate

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Agenda

1. IPA Knowledge Database in 2021 Spring Release
2. Upload dataset to IPA and Create core analysis
3. Realize the meaning of the IPA analysis result
4. Case Study : Investigating the tumor microenvironment
   - Explore key target molecules and disease indications
   - Evaluate the TME with ‘omics datasets
5. Conclusions

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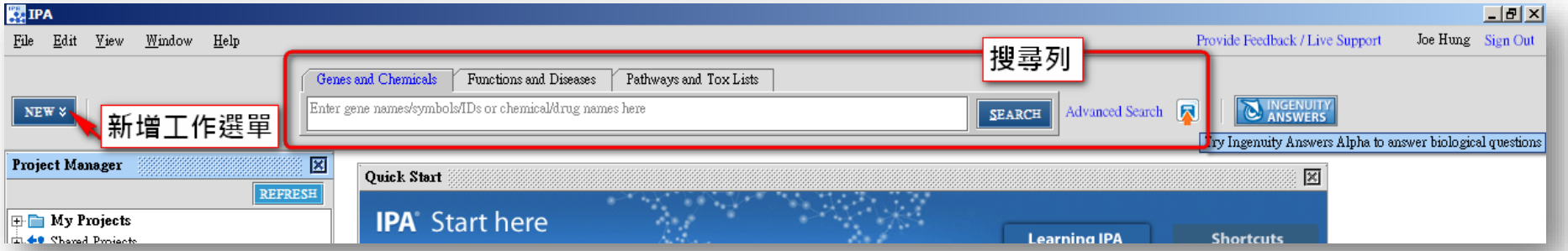
- **Genes and chemicals**
- **Diseases and Functions**
- **Pathways and tox lists**
- Advanced search: Limiting results to a molecule type, family or subcellular location



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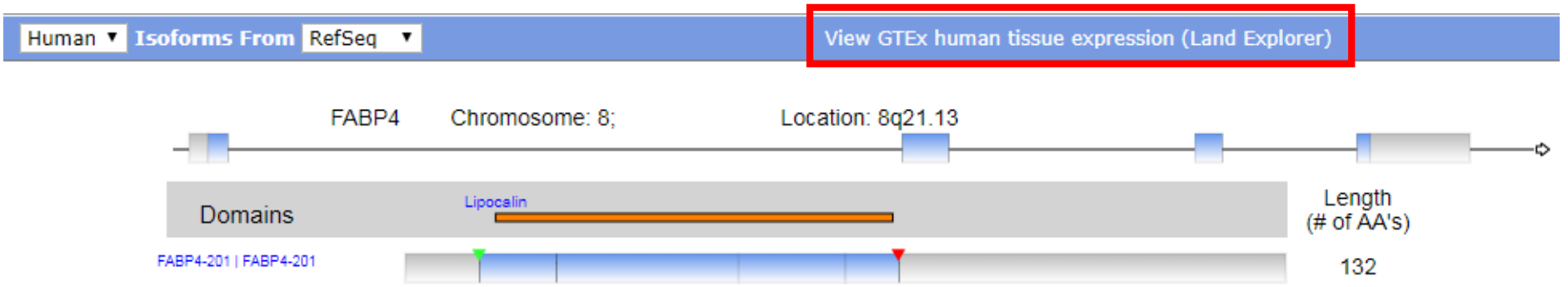
- **Explore sample-level human tissue expression through OmicSoft Land Explorer**



Now you can examine detailed expression patterns across human tissues directly from IPA's Isoform Views. IPA now offers access to a lite version of OmicSoft Land Explorer. With this new feature, you can provide interactive plots of gene expression in 51 different human tissues from the GTEx project, for both gene level and individual splice variants. You can filter the view for a particular tissue, or filter on metadata, such as tissue donor age or gender. You can also download the detailed sample-level expression data for the gene.

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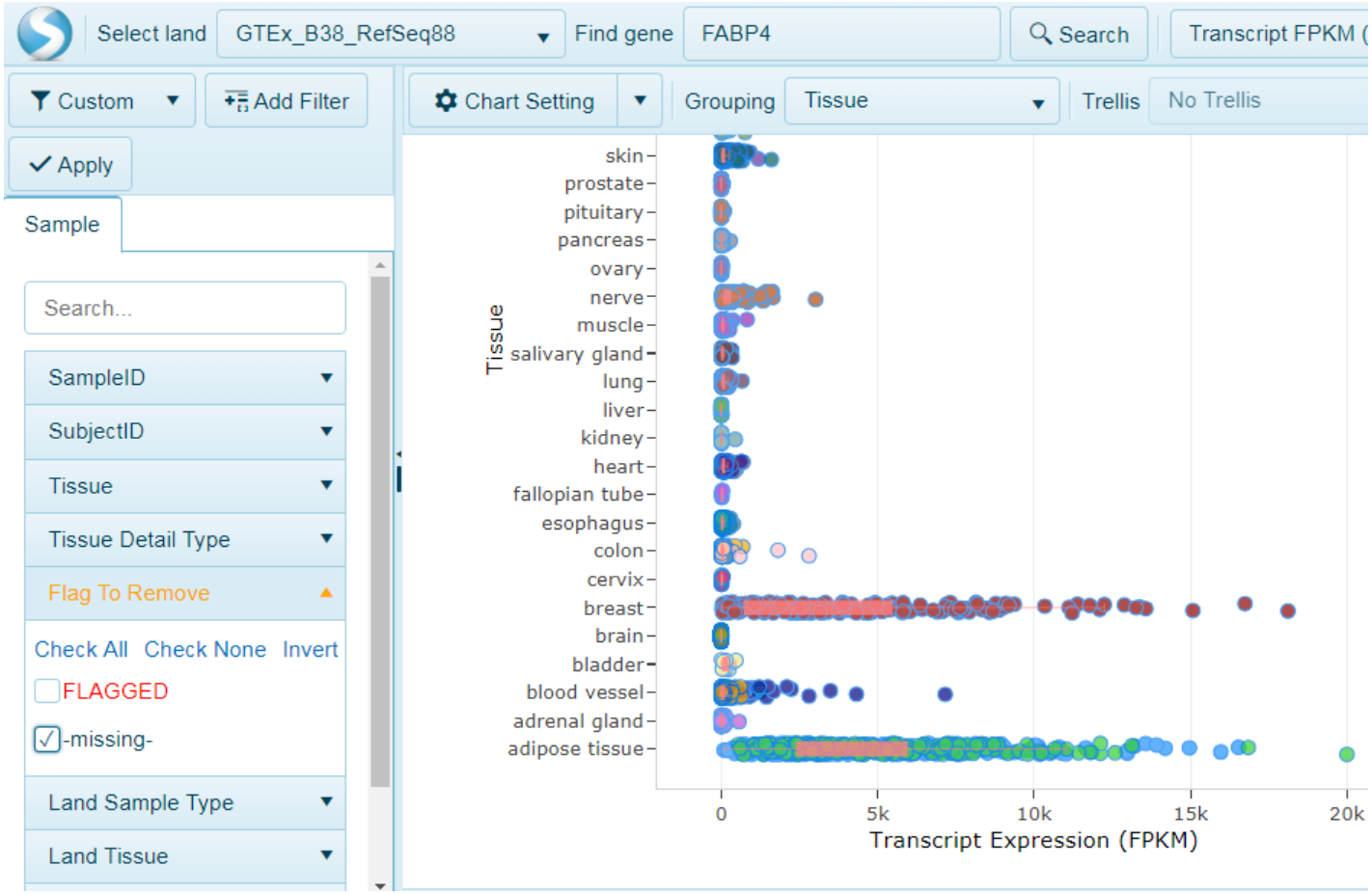
- **View of human isoform-level expression in human tissue samples for FABP4**



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- **Finding:7.8 million**
  - A single piece of evidence from a literature source or database in the **Ingenuity Knowledge Base**
  - Includes context of the fact such as experiment type, species, tissue/cell location, etc.

- **Canonical Pathway (Signaling and Metabolic)**
  - Are generated prior to data input, based on the literature
  - Do NOT change upon data input
  - Do have directionality
  - Total: 712

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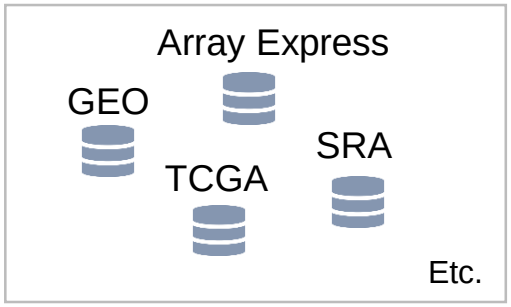
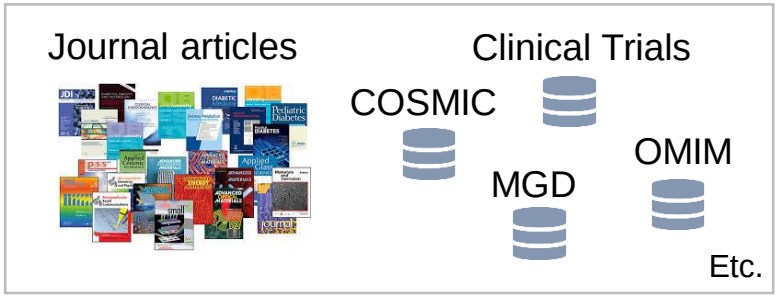
Unprecedented discovery, together





Curation, Processing, & QA

Curation & QA

Datasets integrated into OmicSoft Lands

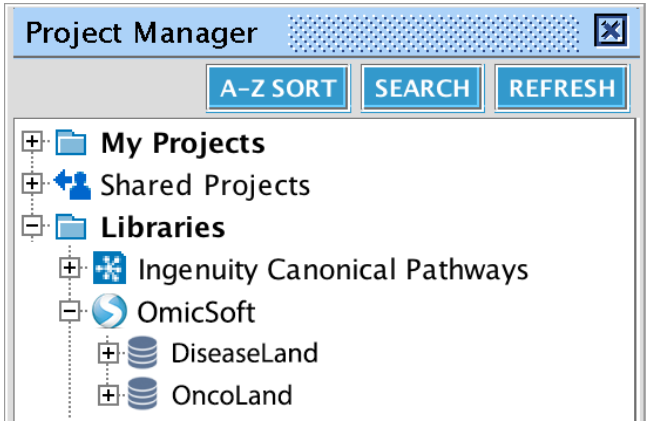
Curated Findings

OmicSoft Array Suite

OncoLand
DiseaseLand
SingleCellLand

90,000+ Expression comparison datasets

INGENUITY PATHWAY ANALYSIS



- Biological analyses of each dataset
- Compare your analysis to all OmicSoft analyses

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Analysis Match Database

>90,000 OmicSoft Analyses available in Analysis Match and Activity Plot

Land	Repository	Datasets Q4 2020	Datasets Q1 2021	Increase
DiseaseLand	HumanDisease	16,290	19,444	3,154
	MouseDisease	14,563	15,563	1,000
	RatDisease	5,480	5,480	
	LINCS	28,234	28,234	
OncoLand	OncoGEO	7,379	8,646	1,267
	OncoMouse	933	1,054	121
	TCGA	4,789	4,789	
	MetastaticCancer	81	81	
	Hematology	2,511	3,205	694
	Pediatrics	444	444	
SingleCellLand	HumanSingleCellCluster		207	207
	HumanSingleCellClusterUMI		548	548
	MouseSingleCellCluster		465	465
	MouseSingleCellClusterUMI		751	751
	HumanSingleCellHCL		1,476	1,476

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Basic Module and Advanced module on IPA

Basic Module

- Gene and Chem View
- Isoform View
- Disease View
- Canonical Pathway
- BioProfiler
- Upload Dataset
- Molecule Activity Predictor (MAP)
- Tox Lists and Tox Functions
- Interactive Disease and Functions Nodes
- Biomarker filter
- Path Designer

https://www.qiagenbioinformatics.com/products/features/

Advanced Analytics (AA)

- Causal Network Analysis
- Upstream regulator Analysis
- Downstream Effects Analysis
- Regulator Effects
- Network Analysis
- Mechanistic Network
- Activity Plot
- Graphic Summary
- Analysis Match

- MicroRNA Target Filter
- Relationship Export
- IsoProfiler
- Comparison Analysis
- PhosphoProteomics Analysis

https://www.qiagenbioinformatics.com/files/flyers/IPA_Advanced_Analytics_WEB.pdf

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Live Demo

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準備IPA分析用的Dataset

必須有一欄放入ID

Replicates

Average

Other observations (Comparison)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
1	CBCR-T In	Clone ID	Unigene C	Accession	Gene Sym	NAME	BPH-205	BPH-202	BPH-203	BPH-201	BPH-204	BPH Ave F	PCA-402	PCA-403	PCA-404	PCA-410	PCA-408	PCA-401	PCA-409
2	1-10-10-18	770890	Hs.109851	AA434409		ESTs	0.938	0.993	0.944	1.201	0.995	1.019	0.912	0.861	0.869	0.706	0.781	0.716	0.821
3	1-10-10-2	753420	Hs.240112	AA406422	KIAA0276	KIAA0276	0.942	1.083	1.312	1.115	1.285	1.113	0.724	0.868	1.021	0.742	0.591	0.491	0.531
4	1-10-10-3	366154	Hs.222909	AA062813	DKFZP434	DKFZP434	0.941	0.913	0.968	0.941	0.908	-1.06298	1.458	0.991	1.052	0.903	1.087	1.07	0.907
5	1-10-10-5	51746	Hs.79348	H23046	RGS7	regulator	1.054	0.9	0.853	0.826	0.8	-1.10102		1.113	1.082	0.803	1.031	1.003	0.942
6	1-10-10-6	781704	Hs.77558	AA431611	TRIP7	thyroid ho	0.996	1.38	1.605	1.172	1.115	1.28825	0.692	0.944	1.022	0.91	0.91	0.769	0.747
7	1-10-10-8	282051	Hs.71741	N53616		ESTs, High	1.016	1.051	1.062	0.992	1.027	1.03025	1.03	1.043	1.054	1.043	1.237	1.117	1.105
8	1-10-1-11	366966	Hs.27865	AA026562		ESTs	0.965	2.153	2.193	1.665	1.789	1.744	0.47	0.833	0.291	0.644	0.669	0.683	0.775
9	1-10-11-1	280752	Hs.79362	N50554	RBL2	retinoblas	0.993	1.229	1.39	1.146	1.107	1.1895	0.776	0.89	1.125	0.938	0.964	0.736	0.752
10	1-10-11-10	123646	Hs.117331	R02728		ESTs	1.007	0.904	0.895	0.818	0.892	-1.10375	1.033	0.889	1.07	0.919	1.081	1.143	1.016
11	1-10-11-13	200307	Hs.68647	R96804		ESTs, Wea	1.031	1.085	1.396	1.268	1.091	1.195	0.773	1.025	0.998	0.958	0.987	0.982	1.086
12	1-10-11-17	325138	Hs.82035	W49785		ESTs	0.868	0.995	1.124	1.211	1.219	1.0495	0.626	0.823		0.724	0.798	0.611	0.661
13	1-10-11-19	502287	Hs.83992	AA156781		ESTs	0.918	1.246	1.253	1.419	1.51	1.209	1.402	0.931	1.26	1.896	1.277	1.004	0.834
14	1-10-1-17	809473	Hs.29759	AA443119		Homo sap	0.929	0.993	1.796	1.359	2.58	1.26925	0.571	0.743	1.471	0.626	0.464	0.514	0.628
15	1-10-1-20	137890	Hs.92202	R68581		ESTs	0.931	1.218	1.226	0.969	1.313	1.086		0.415	0.689	0.744	0.728	0.946	0.897
16	1-10-12-12	213118	Hs.37978	H69576		ESTs	0.893	0.796	0.973	0.796	0.951	-1.15674	1.089	0.995	1.19	1.111	1.153	1.164	0.978
17	1-10-12-20	198607	Hs.58617	R94947	ROCK2	Rho-assoc	0.963	1.137	1.236	1.038	1.483	1.0935	0.65	0.866	1.154	0.68	0.76	0.778	0.758
18	1-10-14-2	755752	Hs.6151	AA496327		Human ml	0.944	1.141	1.221	1.11	1.077	1.104	0.963	0.987	1.053	1.053	0.973	0.942	0.873
19	1-10-14-20	427980	Hs.150390	AA001835	ZNF262	zinc finger	0.951	1.043	0.91	1.004	0.86	-1.02354	0.807	1.116	0.922	1.032	1.054	0.932	1.083
20	1-10-14-6	49260	Hs.12840	H16573		Homo sap	0.975	0.861	0.907	0.9	0.92	-1.098	1.124		1.067	0.938	1.171	1.122	1.113
21	1-10-15-14	810741	Hs.7719	AA457725	GABARAP	GABA(A) r	1.016	1.096	1.281	1.318	1.17	1.17775	1.14	1.291	1.178	1.156	0.986	0.908	1.128
22	1-10-15-17	265592	Hs.29826	N21407		ESTs	1.11	1.261	1.391	1.482	1.084	1.311	0.842	1.073	1.068	1.507	0.847	0.755	0.989
23	1-10-15-20	428737	Hs.103280	AA004648		ESTs	1.089	0.879	0.884	0.819	1.069	-1.08962	1.191	1.179	1.092	0.979	1.147	1.086	1.114
24	1-10-15-21	50182	Hs.89591	H17882	KAL1	Kallmann	0.958	1.564	1.308	1.224	0.79	1.2635	0.662	1.162	0.652	0.456	0.749	0.73	0.558
25	1-10-15-5	484535	Hs.198241	AA036974	AOC3	amine oxi	1.145	1.175	1.307	1.286	1.172	1.22825	0.731	0.929	1.248	0.873	1.041	0.673	0.999

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準備IPA分析用的Dataset

- 重複性實驗的數值平均、p-vlaue或fold-change等統計計算，要先在IPA分析之前完成。

- 將實驗資料用 Excel 表格檔案儲存，檔案裡面只能有一個Sheet存在。
  - Excel Sheet當中必須要有一欄是列出**分子的ID** (如Gene Symbol, Refseq number, Uniprot number, HMDB等常用命名皆支援)
  - 每個Excel Sheet 最多可以放入 **20個 observations** (即20個實驗變因的資料欄的意思)
  - 每個Observation可以有3個不同的表現值種類 (ex. p-Value，fold-change等)
  - **表格欄位最上方只能有一個Head row (首行)**
  - 資料上傳到IPA後，可以在cut-off 值欄位進行設定，讓使用者決定門檻來決定**表現顯著有差異**的生物分子。意味著原始實驗資料中有些分子的數值不夠顯著，可以用cut-off值作為門檻排除於分析運算中。那些通過cut-off值的分子們在IPA中稱之為Analysis-Ready Molecules。

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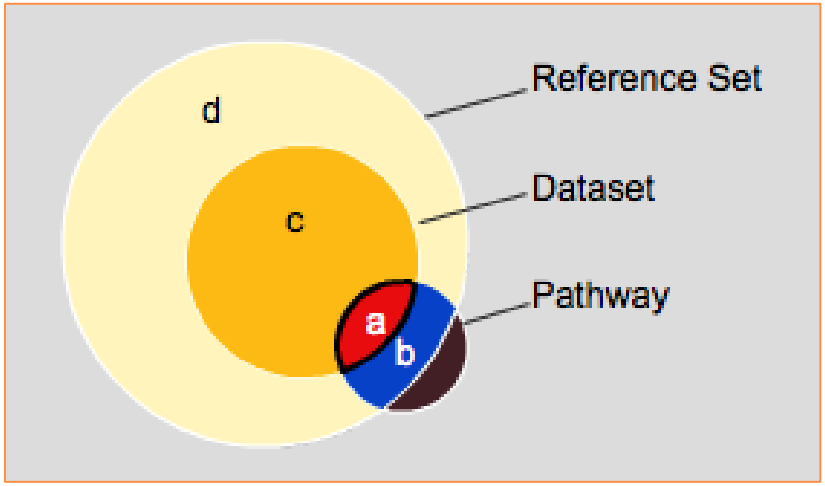
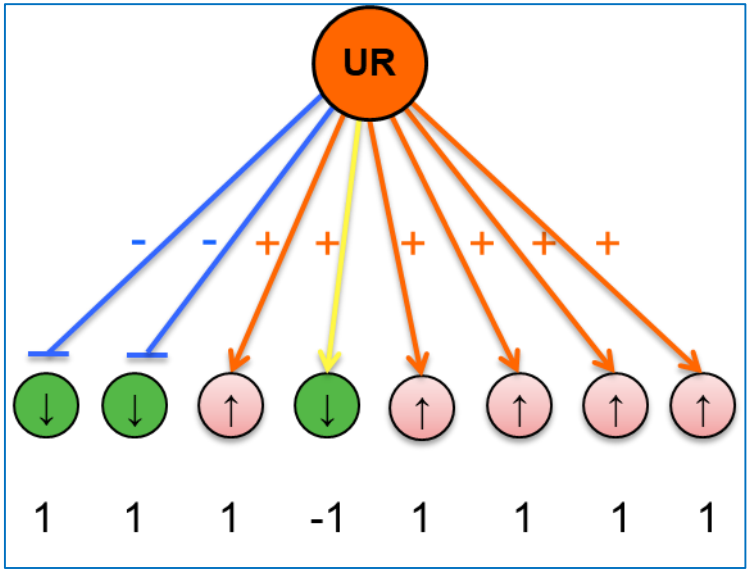
Statistical Analysis Used in IPA

P-value of overlap

- Null hypothesis: No overlap between molecule from dataset and disease/function/upstream regulator/pathway.
- Calculate using the right-tailed Fisher's Exact Test
- Significant p-value ≦ 0.05





Z-score

- Predicts Activation or Inhibition
- Correlation between what is known (IPA Knowledge Base) and your expression data

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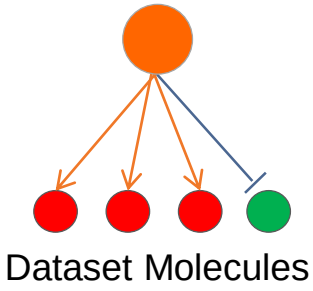
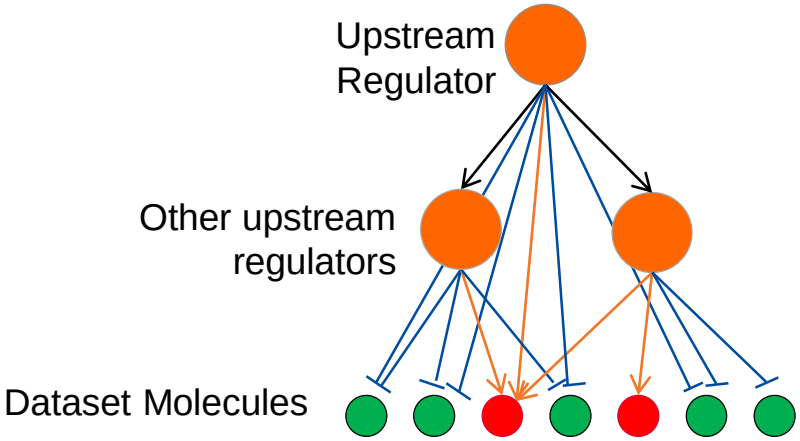
Network types in IPA

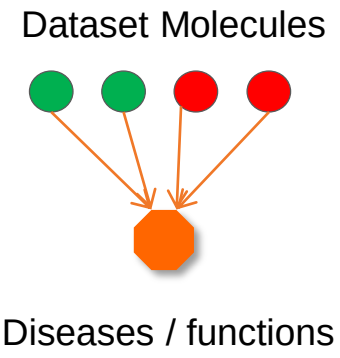
Upstream Analysis



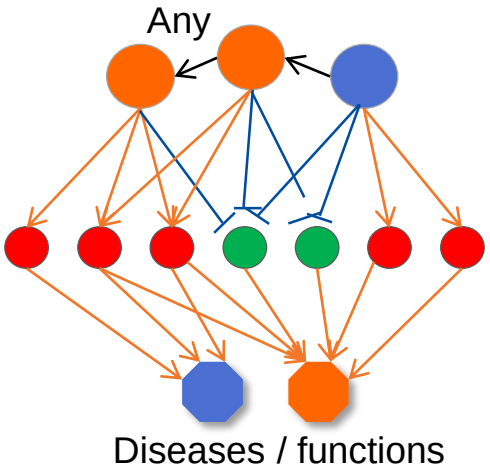
Mechanistic Network of Upstream Regulators



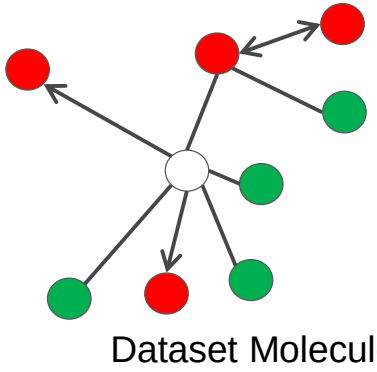
Function Analysis



Regulator Effect Network



Interaction Network



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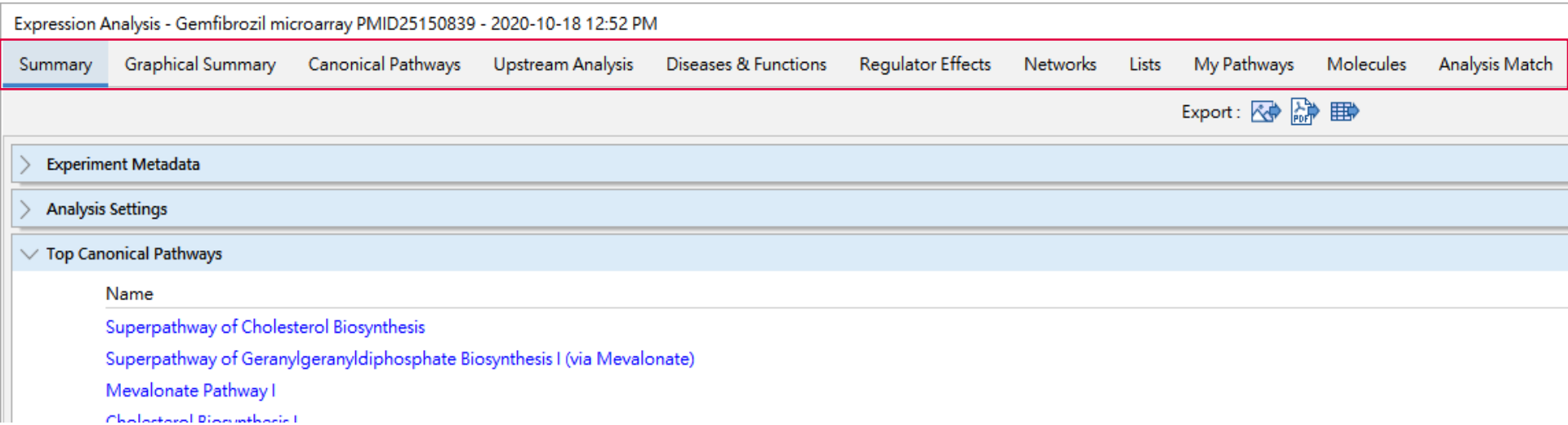

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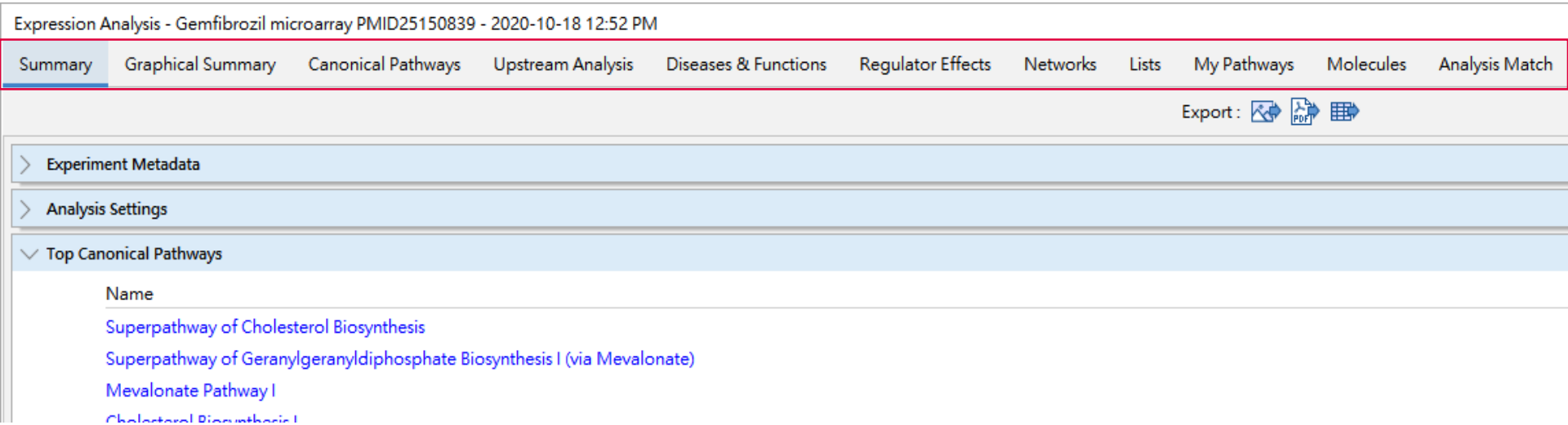

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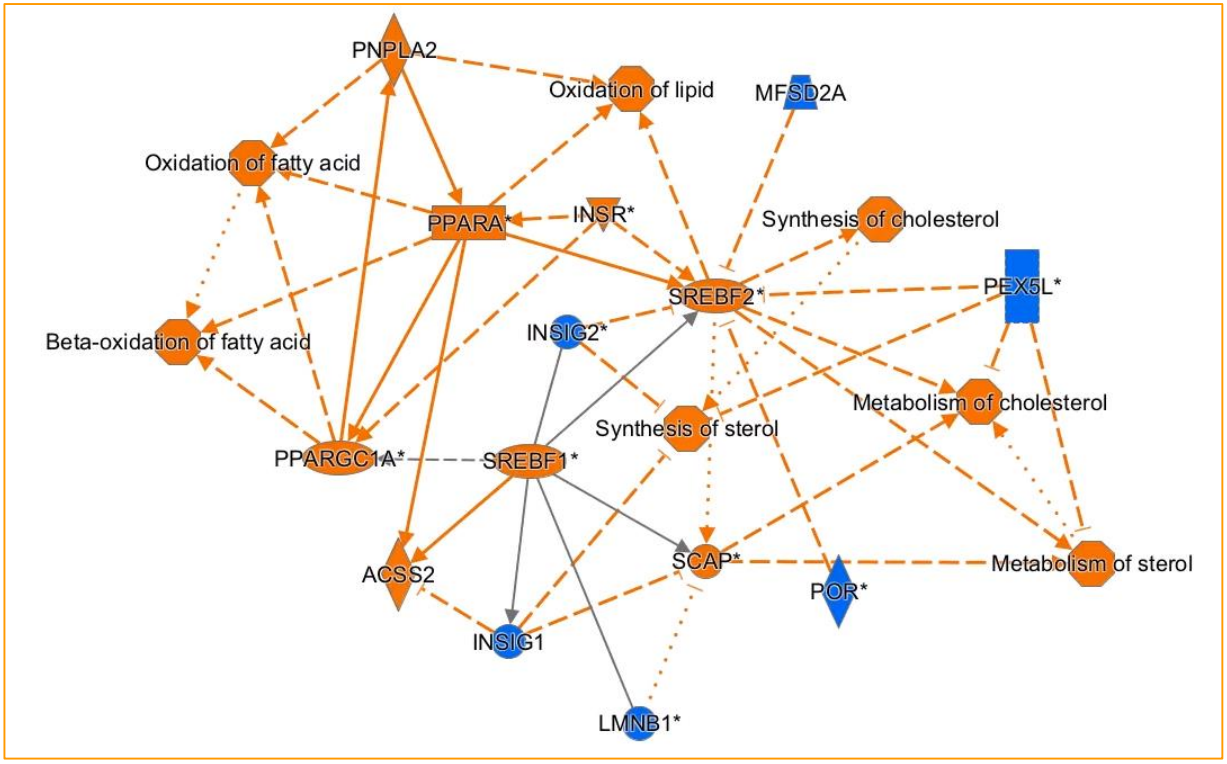
Graphical Summary

Graphical Summary結果:
將資料集最相關的生物主題以網路圖像呈現
(canonical pathways, upstream regulators, causal network master regulators, diseases, and biological functions)



Criteria for selection

- All entities:
  p-value < 0.05
- Diseases、Functions、Upstream regulators:
  z-score ≧ 2
- All molecules types (except chemicals)
- Activated nodes
  z-score ≧ 2
- Inhibited nodes
  z-score ≦ -2

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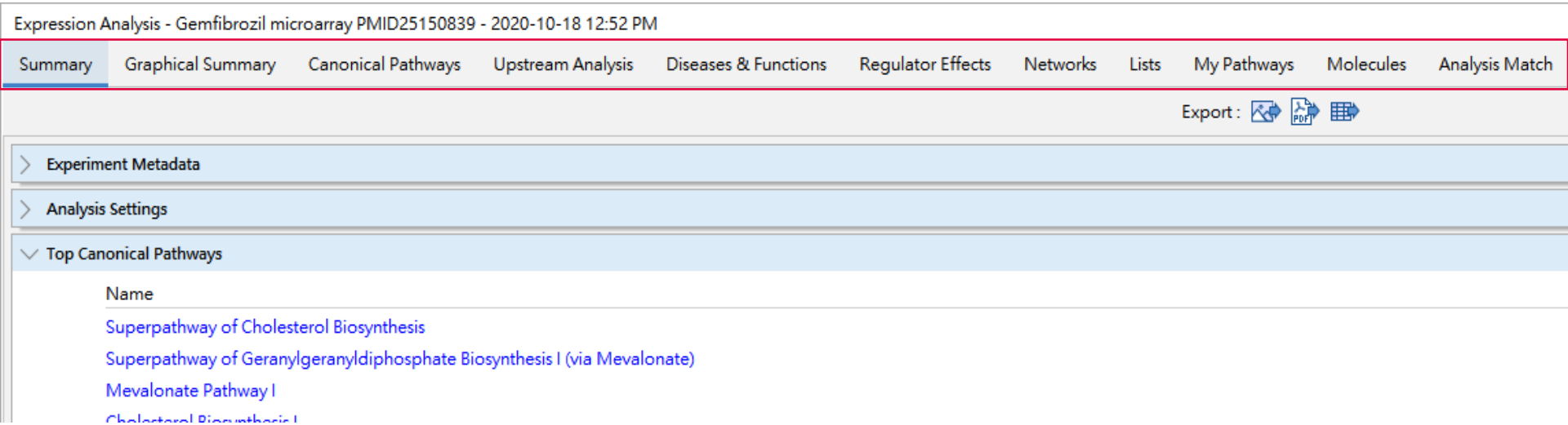

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Canonical Pathway Analysis

Canonical Pathways結果標籤:
受影響的Signaling Pathway與Metabolic Pathway 依照顯著性用條狀圖**排列**

點擊特定Canonical Pathway名稱上方的Bar條，下方視窗會出現dataset 中有參與組成該 pathway的分子 ID

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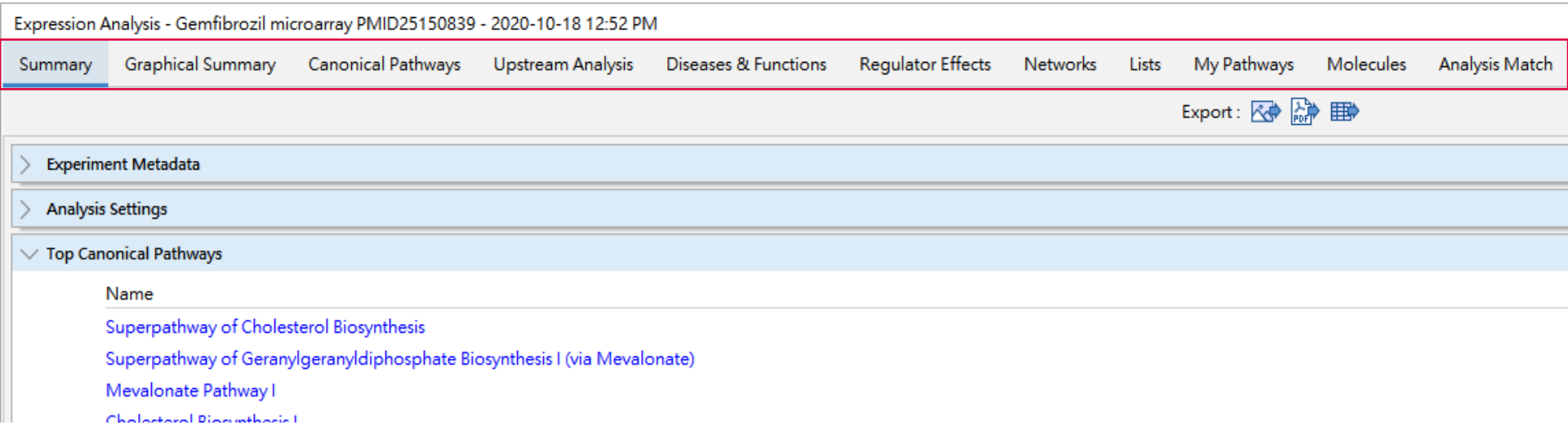

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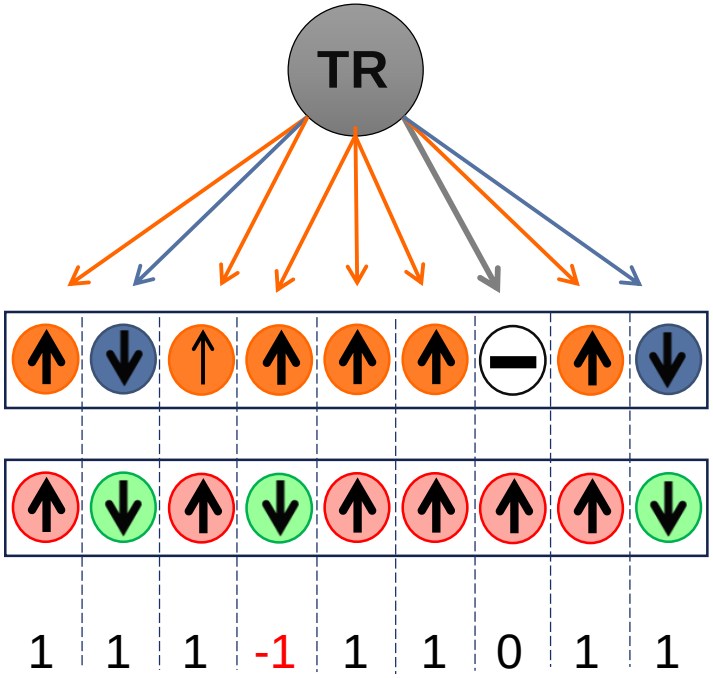
Upstream Analysis Activation z–score

Statistical measure of correlation between the transcription regulator (TR) and resulting gene expression



N = 8 genes

TR effect on downstream genes
(Literature)

Differential gene expression
(Uploaded Data)

z-score > 2 or < -2 is considered significant

Actual z-score *can* be weighted by relationship types, relationship bias, data bias

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Upstream Analysis Activation z–score

Statistical measure of correlation between the transcription regulator (TR) and resulting gene expression

Expression Analysis - Gemfibrozil microarray PMID25150839 - 2020-10-18 12:52 PM

Summary | Graphical Summary | Canonical Pathways | Upstream Analysis | Diseases & Functions | Regulator Effects | Networks | Lists | My Pathways | Molecules | Analysis Match

Upstream Regulators | Causal Networks

Add To My Pathway | Add To My List | Display as Network | Activity Plot | Customize Table | Mechanistic Networks

Upstream Regulator	Expr Log Ratio	Molecule Type	Predicted Activation State	Activation z-score
PPARA	↑0.994	ligand-dependent nuclear receptor	Activated	4.177
pirinixic acid		chemical toxicant	Activated	5.477
POR	↑1.358	enzyme	Inhibited	-3.507
ciprofibrate		chemical drug	Activated	4.535
SREBF2	↑0.968	transcription regulator	Activated	4.617
SLC27A2	↑0.407	transporter	Inhibited	-4.635
SCAP	↑1.442	other	Activated	5.112
ACOX1	↑1.093	enzyme	Inhibited	-4.146
fenofibrate		chemical drug	Activated	5.895
dexamethasone		chemical drug		-0.877
elaidic acid		chemical - endogenous mammalian	Activated	3.954
MAP2K5	↓-0.006	kinase	Activated	4.426
SREBF1	↑0.179	transcription regulator	Activated	5.084

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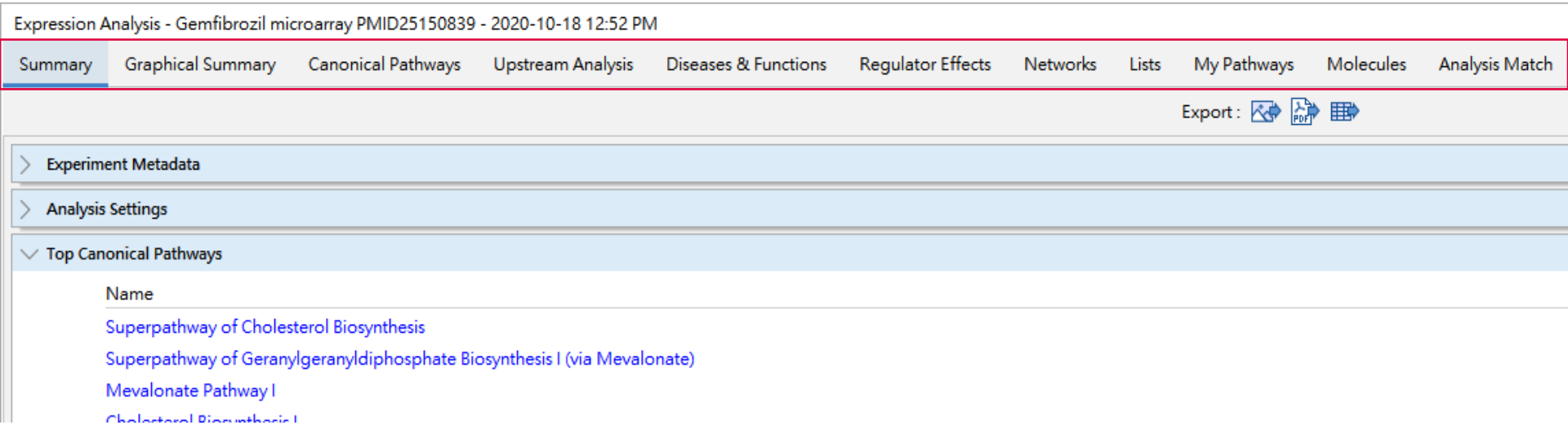

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Diseases and functions

Diseases and functions結果標籤:
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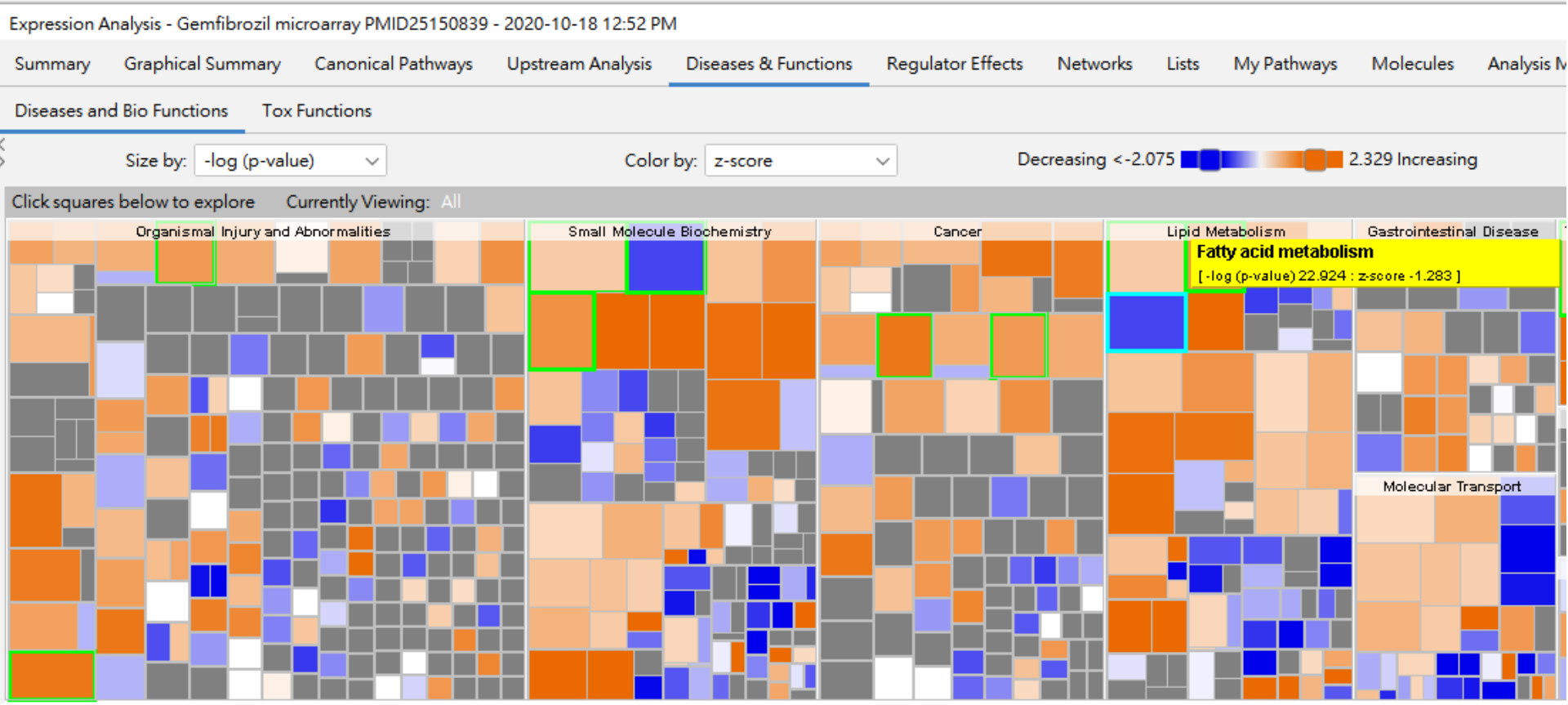

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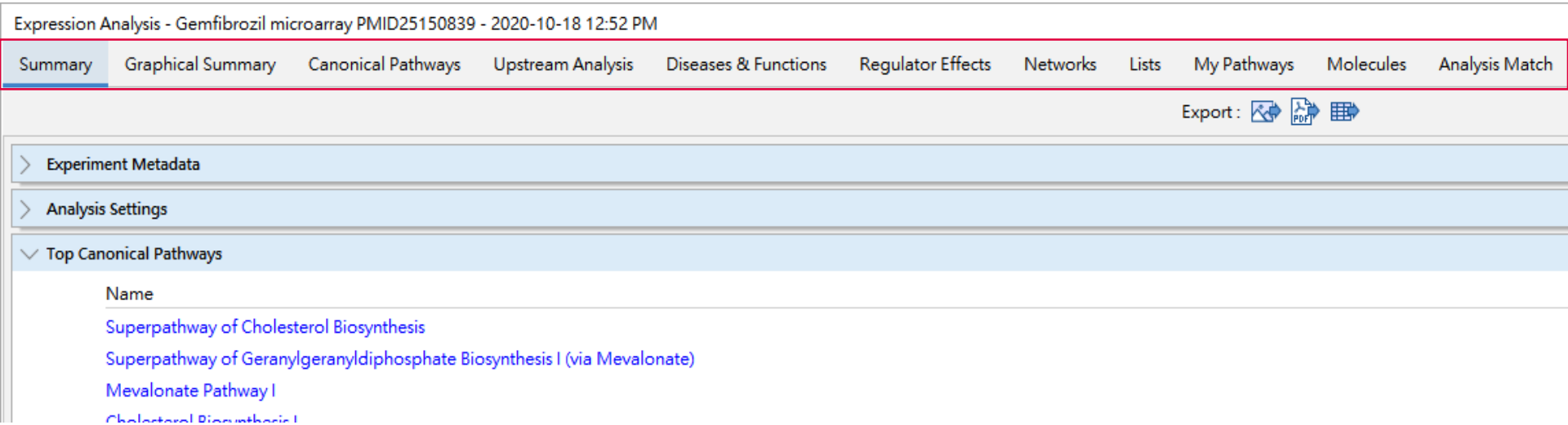

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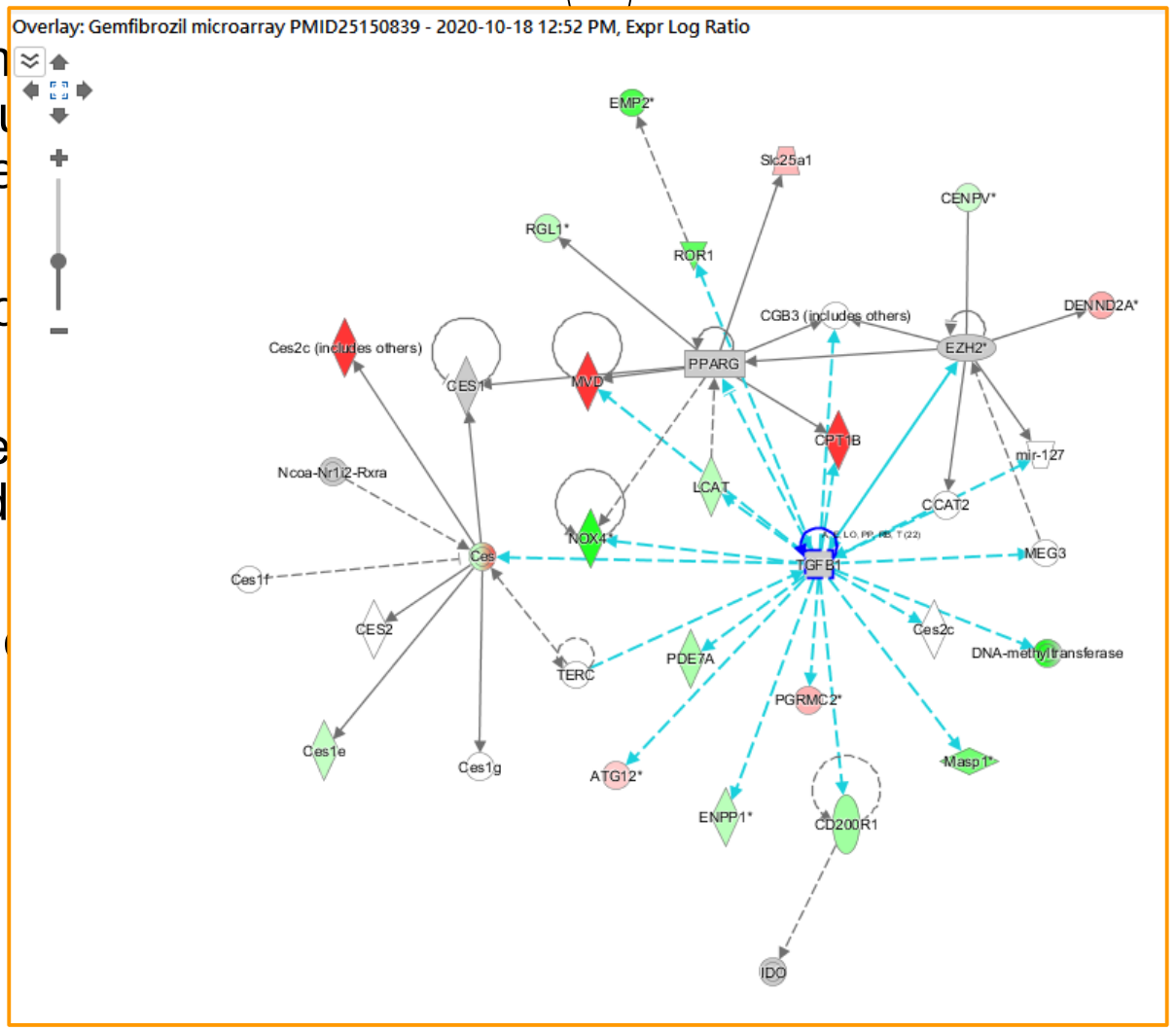
How Networks Are Generated

1. Focus molecules are “seeds”
2. Focus molecules with th
   interactions to other focu
   are then connected toge
   network
3. Non-focus molecules fro
   dataset are then added
4. Molecules from the Inge
   Knowledge Base are ad
5. Resulting Networks are
   then sorted based on th



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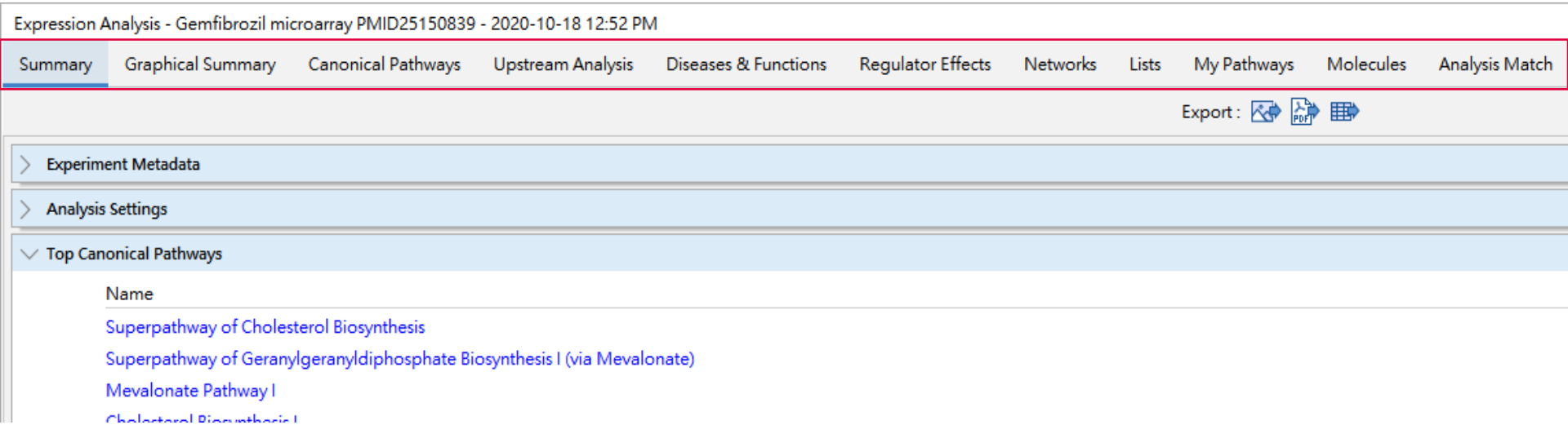

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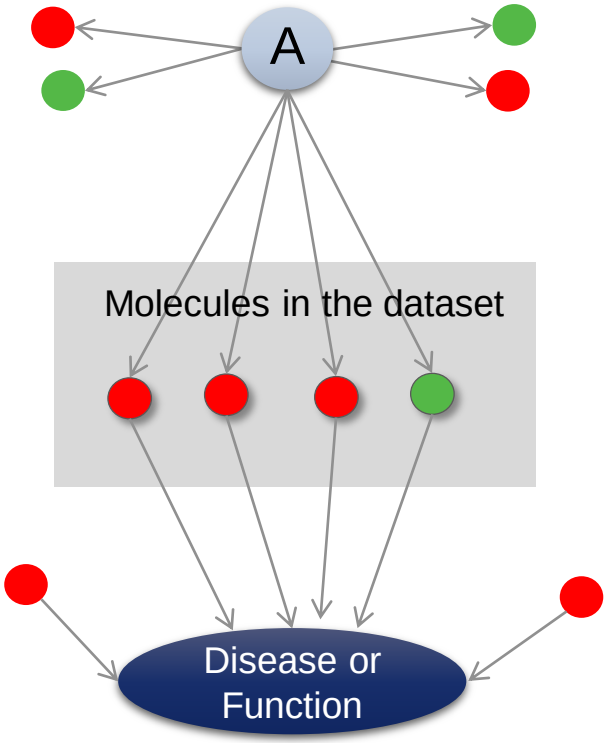
Concept of “Regulator Effects”

Hypotheses for how activated or inhibited upstream regulators cause downstream effects on biology

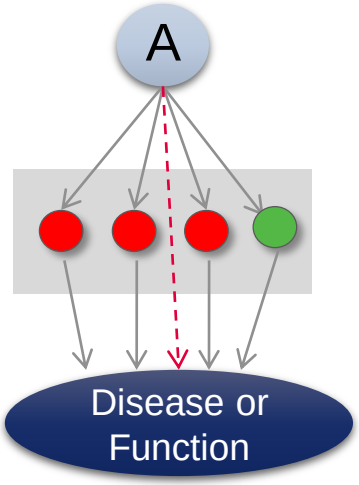
Upstream Regulators



Algorithm

First iteration

Simplest Regulator Effects result



Displays a relationship between the regulator and disease/function if it exists

Downstream Effects Analysis

Causally consistent networks score higher

The algorithm runs iteratively to merge additional regulators with diseases and functions

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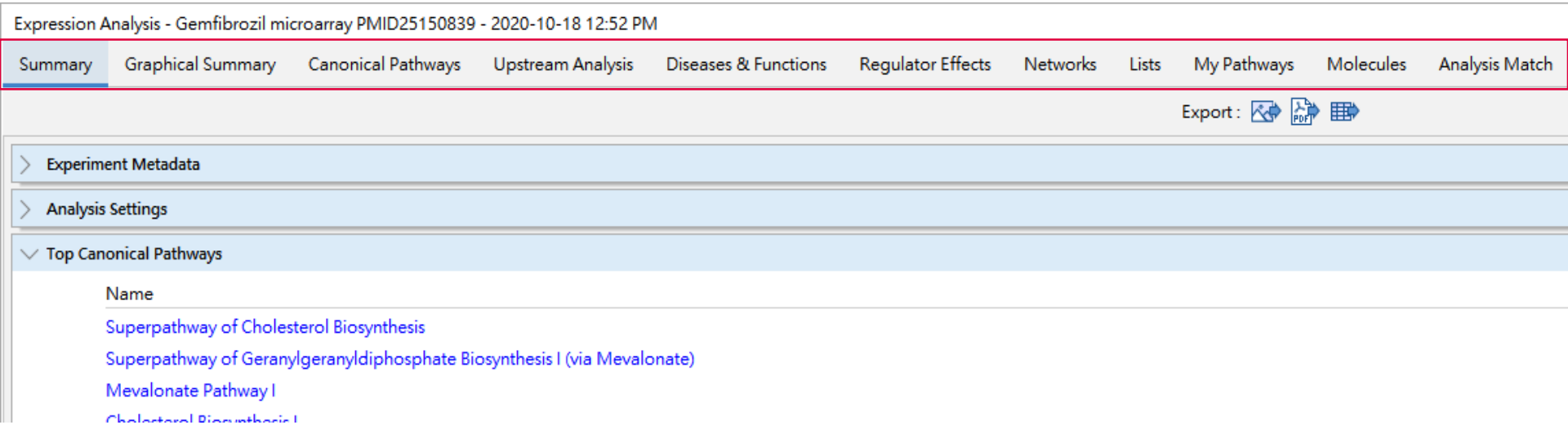

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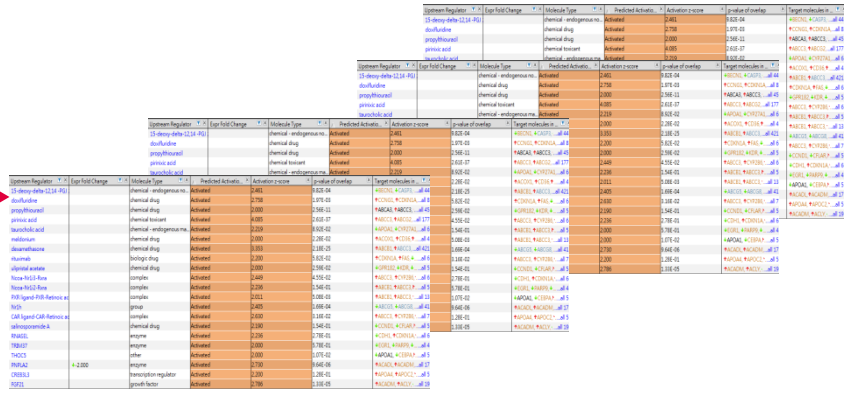
Analysis Match enables you to automatically match your analysis against:

- All your own analysis
- Analyses of 8100+ expression datasets processed and curated from public sources by Omicsoft (QIAGEN)

- Build confidence in your analysis results
- Discover unexpected insights into mechanisms shared between studies
- Gain insight from ‘anti-matches’

Upstream Regulator	Expr Fold Change	Molecule Type	Predicted Activatio...	Activation z-score	p-value of overlap	Target molecules in ...
15-deoxy-delta-12,14 -PGJ...		chemical - endogenous no...	Activated	2.461	9.82E-04	↓BECN1, ↓CASP3, ...all 44
doxifluridine		chemical drug	Activated	2.758	1.97E-03	↑CCNG1, ↑CDKN1A, ...all 8
propylthiouracil		chemical drug	Activated	2.000	2.56E-11	↑ABCA3, ↑ABCC3, ...all 45
pirinixic acid		chemical toxicant	Activated	4.085	2.61E-37	↑ABCC3, ↑ABCG2, ...all 177
taurocholic acid		chemical - endogenous ma...	Activated	2.219	8.92E-02	↓APOA1, ↓CYP27A1, ...all 6
meldonium		chemical drug	Activated	2.000	2.28E-02	↑ACOX1, ↑CD36, ↑...all 4
dexamethasone		chemical drug	Activated	3.353	2.18E-25	↑ABCB1, ↑ABCC3, ...all 421
rituximab		biologic drug	Activated	2.200	5.82E-02	↑CDKN1A, ↑FAS, ↓...all 6
ulipristal acetate		chemical drug	Activated	2.000	2.59E-02	↓GPR182, ↓KDR, ↓...all 5
Ncoa-Nr1i3-Rxra		complex	Activated	2.449	4.55E-02	↑ABCC3, ↑CYP2B6, ↑...all 6
Ncoa-Nr1i2-Rxra		complex	Activated	2.236	1.54E-01	↑ABCB1, ↑ABCC3, ↑...all 5
PXR ligand-PXR-Retinoic ac...		complex	Activated	2.011	5.08E-03	↑ABCB1, ↑ABCC3, ↑...all 13
Nr1h		group	Activated	2.405	1.69E-04	↓ABCG5, ↓ABCG8, ...all 41
CAR ligand-CAR-Retinoic ac...		complex	Activated	2.630	3.16E-02	↑ABCC3, ↑CYP2B6, ↑...all 7
salinosporamide A		chemical drug	Activated	2.190	1.54E-01	↓CCND1, ↓CFLAR, ↑...all 5
RNASEL		enzyme	Activated	2.236	2.78E-01	↓CDH1, ↑CDKN1A, ↑...all 6
TRIM37		enzyme	Activated	2.000	5.78E-01	↓EGR1, ↓PARP9, ↓...all 4
THOC5		other	Activated	2.000	1.07E-02	↓APOA1, ↓CEBPA, ↑...all 5
PNPLA2	↓-2.000	enzyme	Activated	2.730	9.64E-06	↑ACADL, ↑ACADM, ...all 17
CREB3L3		transcription regulator	Activated	2.200	1.28E-01	↑APOA4, ↑APOC2, ↑...all 5
FGF21		growth factor	Activated	2.786	1.33E-05	↑ACADM, ↑ACLY, ...all 19



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Live Demo

Case Study

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Explore key target molecules and disease indications

Construct networks based on key targets and predict molecule activity

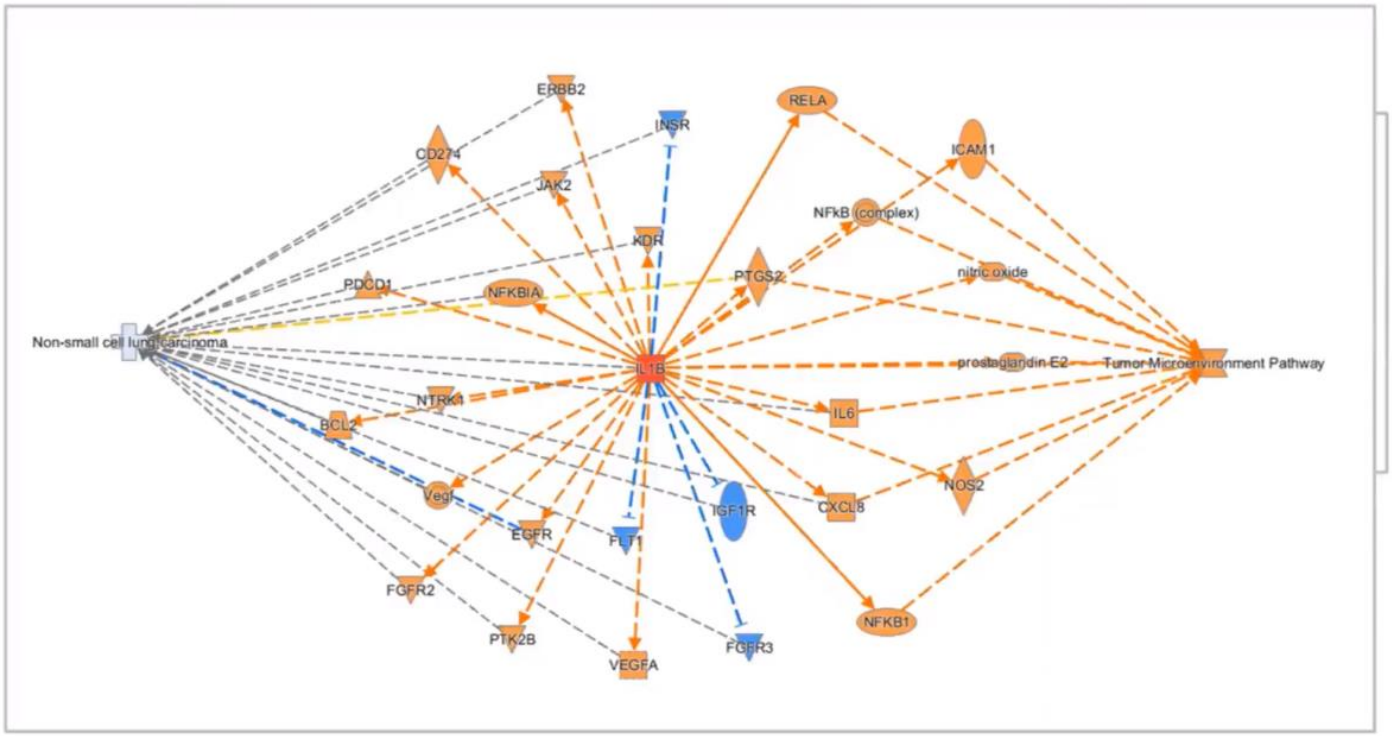
Review > Curr Pharm Des. 2017;23(32):4893-4905. doi: 10.2174/1381612823666170613080919.

Targeting the Tumor Microenvironment by Intervention in Interleukin-1 Biology

Elena Voronov [1], Ron N Apte [1]

Affiliations + expand

PMID: 28606052 DOI: 10.21



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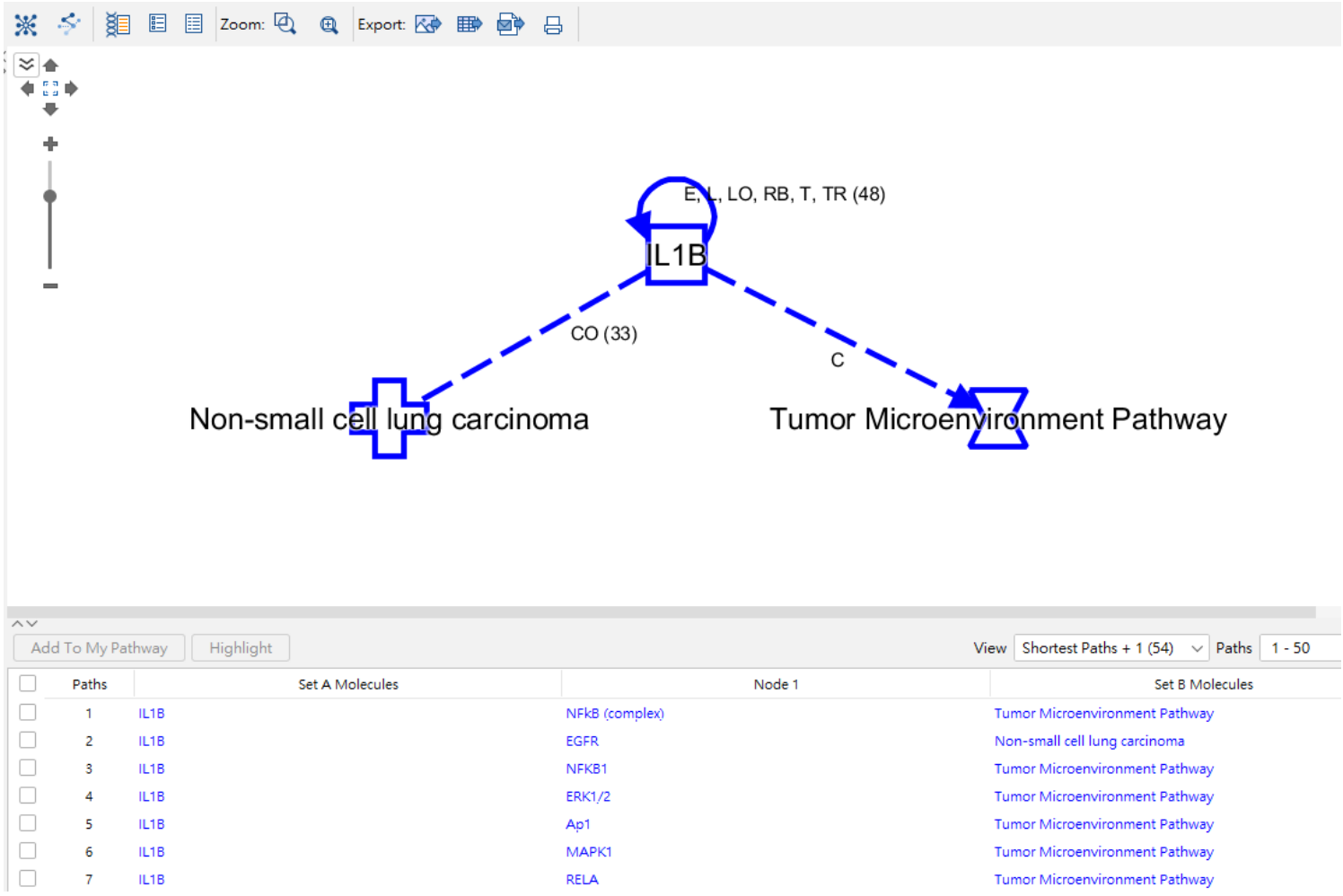
Build networks linking molecules to the TME and disease endpoints

- Search: IL1B、Non-small cell lung carcinoma、Tumor Microenvironment Pathway
- Path Explore: activation、causation、inhibition



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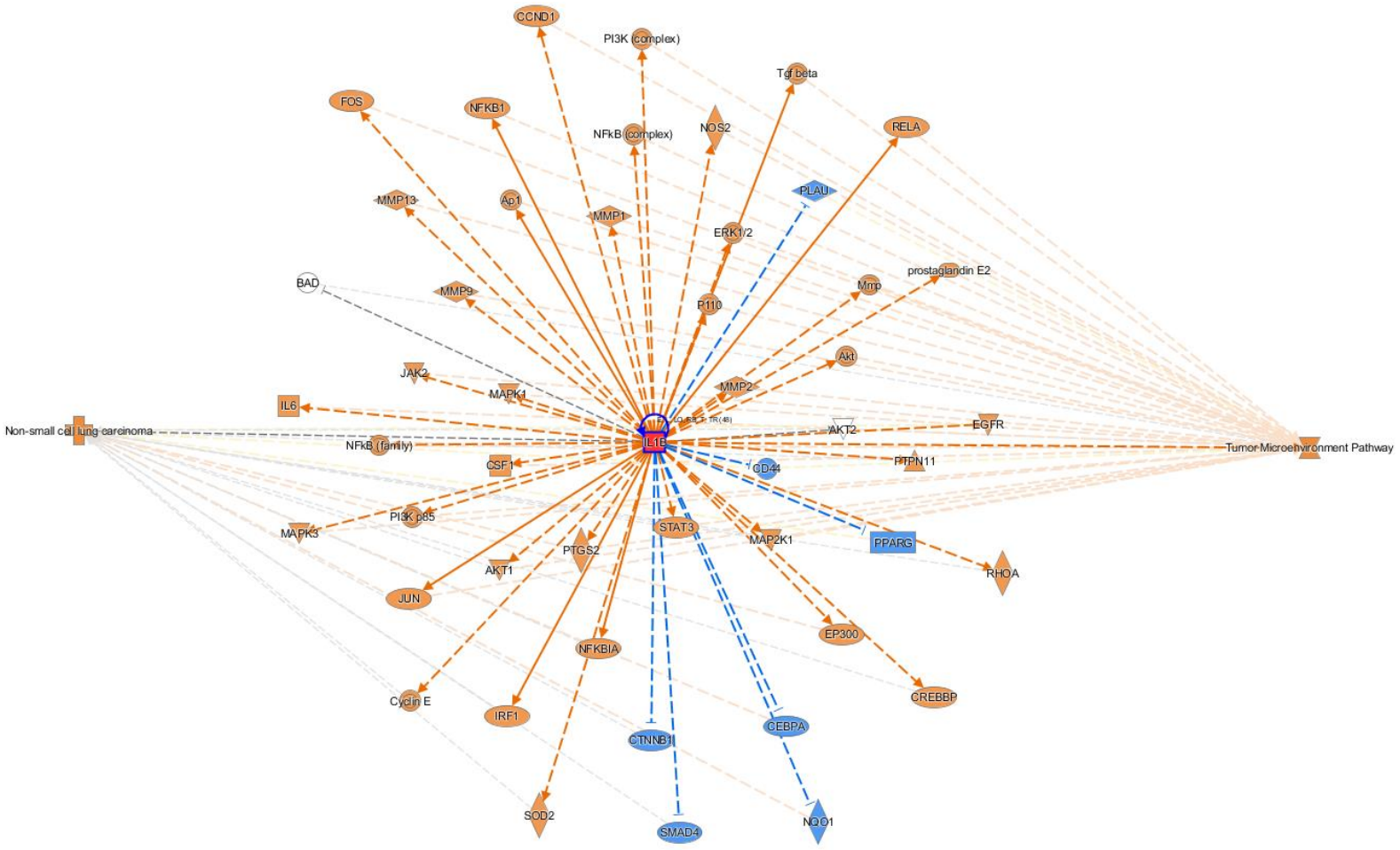
Predict molecule activity of IL1B

- MAP: IL1B Increased
- Lead to Tumor Microenvironment Pathway activation
- Correlation Non-small cell lung carcinoma activation



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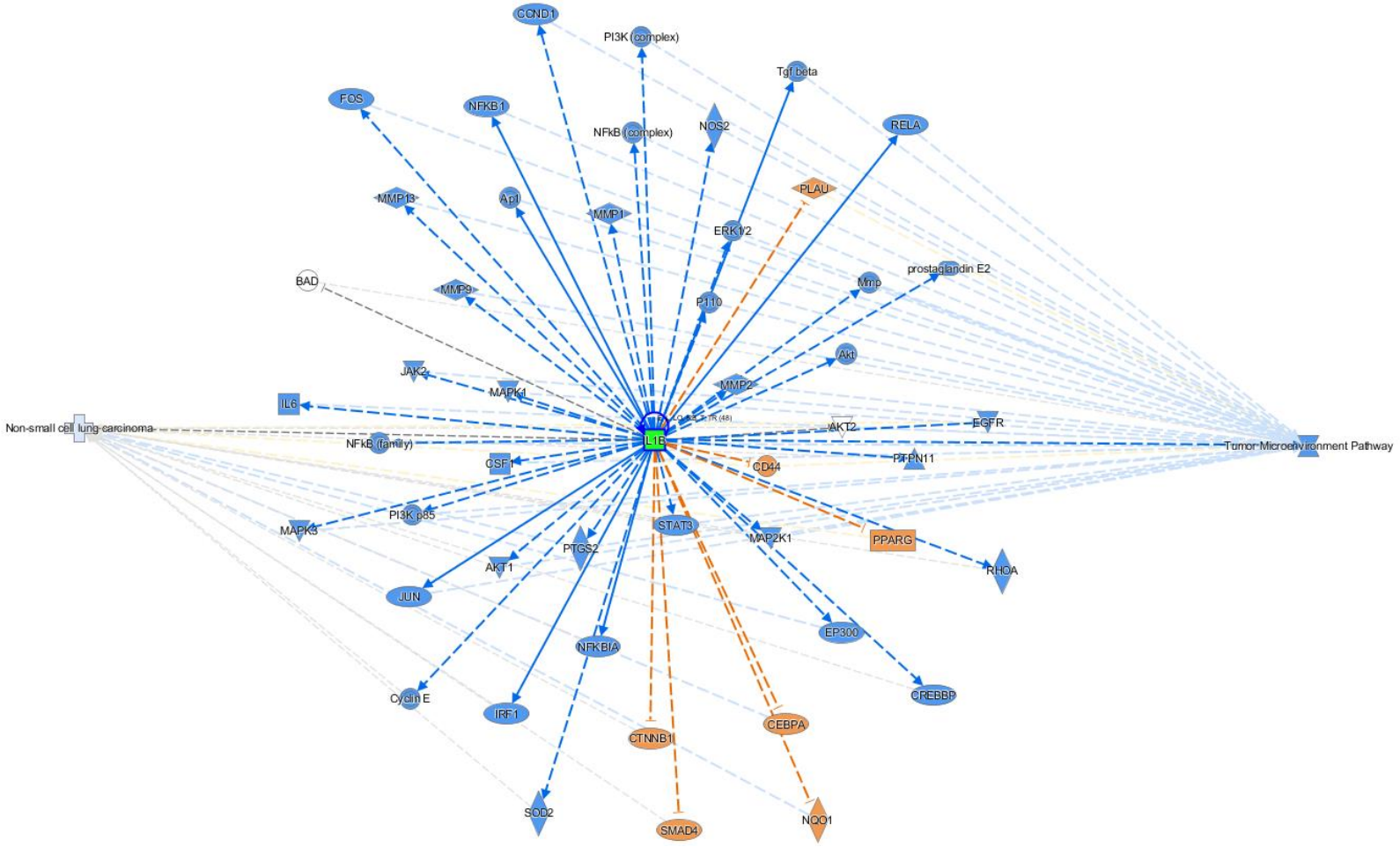
Predict molecule activity of IL1B

- MAP: IL1B Decreased
- Lead to Tumor Microenvironment Pathway inhibition
- Correlation Non-small cell lung carcinoma inhibition



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Profile key immune molecules in the context of cancer

- Search: Non-small cell lung carcinoma
- BioProfiler: Cytokine

BioProfiler

Add To My Pathway | Add To My List | Display as Network | Create Dataset | Limit to Dataset

Molecule		Disease or Function Evidence						
Symbol	Molecule Type	Molecule Activity	Effect on Disease ...	Disease or Function	Mutation evidence	Biomarker Applic...	Species Evidence
AIMP1	cytokine	unknown change in activity	affects	Lung squamous cell c... all 1	unclassified mutation	not applicable	Human
▶CXCL2	cytokine	decreased activity	affects	Lung adenocarcinoma all 2	wild type	not applicable	Human
CXCL8	cytokine	increased activity	affects	Non-small cell lung carc all 1	wild type	efficacy	Human
IFNA10	cytokine	unknown change in activity	affects	Lung squamous cell c... all 1	missense	not applicable	Human
IFNA8	cytokine	unknown change in activity	affects	Lung adenocarcinoma all 1	missense	not applicable	Human
▶IFNG	cytokine	decreased activity,increase...	affects,increases	Lung adenocarcinoma all 2	homozygous,knockout,wil...	not applicable	Human,Mouse
▶IL10	cytokine	increased activity,unknown...	affects	Lung adenocarcinoma all 2	heterozygous,nonsense,wil...	not applicable	Human
IL1A	cytokine	increased activity	affects	Non-small cell lung carc all 1	wild type	efficacy	Human
▶IL1B	cytokine	increased activity	affects	Advanced non-small... all 24	wild type	not applicable	Human
IL36G	cytokine	unknown change in activity	affects	Lung adenocarcinoma all 1	missense	not applicable	Human
IL5	cytokine	unknown change in activity	affects	Lung adenocarcinoma all 1	unclassified mutation	not applicable	Human
▶IL6	cytokine	increased activity,unknown...	affects	Lung adenocarcinoma all 3	unclassified mutation,wild ...	efficacy,not applicable	Human
NAMPT	cytokine	unknown change in activity	affects	Adenocarcinoma in ri... all 1	missense	not applicable	Human
PF4V1	cytokine	unknown change in activity	affects	Lung adenocarcinoma all 1	missense	not applicable	Human
SCG2	cytokine	unknown change in activity	affects	Adenocarcinoma in ri... all 1	missense	not applicable	Human
▶SPP1	cytokine	increased activity,unknown...	affects	Lung adenocarcinoma all 2	missense,wild type	not applicable	Human,Mouse
▶TIMP1	cytokine	increased activity	affects	Lung squamous cell c... all 2	wild type	unspecified application	Human
▶TNF	cytokine	decreased activity	affects	Advanced non-small c... all 3	wild type	not applicable	Human
TNFSF11	cytokine	increased activity	affects	ALK rearrangement n... all 4	wild type	not applicable	Human
TNFSF13	cytokine	increased activity	affects	Non-small cell lung carc all 1	wild type	not applicable	Human
WNT2	cytokine	increased activity	affects	Non-small cell lung carc all 1	wild type	not applicable	Human
WNT7A	cytokine	increased activity	decreases	Development of non-... all 1	wild type	not applicable	Uncategorized

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Explore key target molecules and disease indications

Interrogate immunological mechanisms and the TME with internal or public data

Nat Med. 2018 Jul;24(7):994-1004. doi: 10.1038/s41591-018-0057-z. Epub 2018 Jun 11.

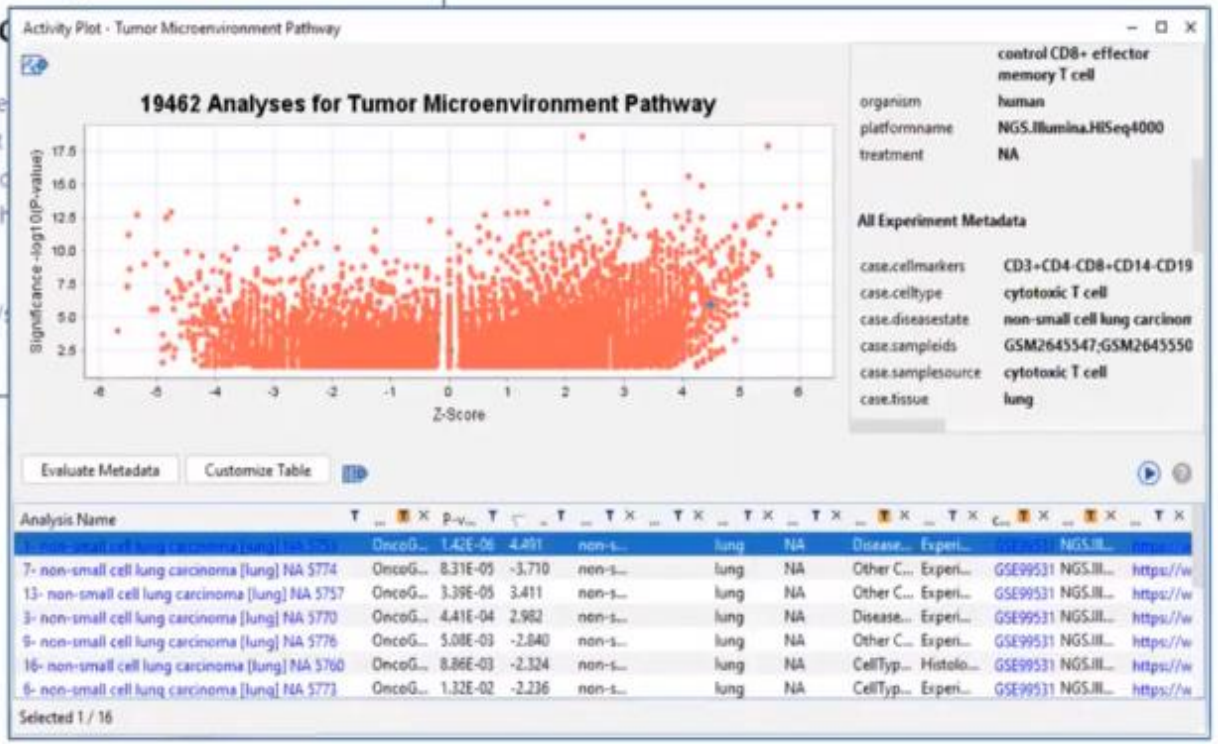
A transcriptionally and functionally distinct PD-1 + CD8 + T cell pool with predictive potential in non-small-cell lung cancer treate

Daniela S Thommen [1 2], Viktor H Koelzer [3 4], Petra He
, Sarah Dimeloe [7], Anna Kiialainen [6], Jonathan Hanhart
, Spasenija Savic Prince [9], Mark Wiese [10], Didier Lardinc
, Vaios Karanikas [12], Kirsten D Mertz [3], Ton N Schumach

Affiliations + expand

PMID: 29892065 PMCID: PMC6110381 DOI: 10.1038/

Free PMC article



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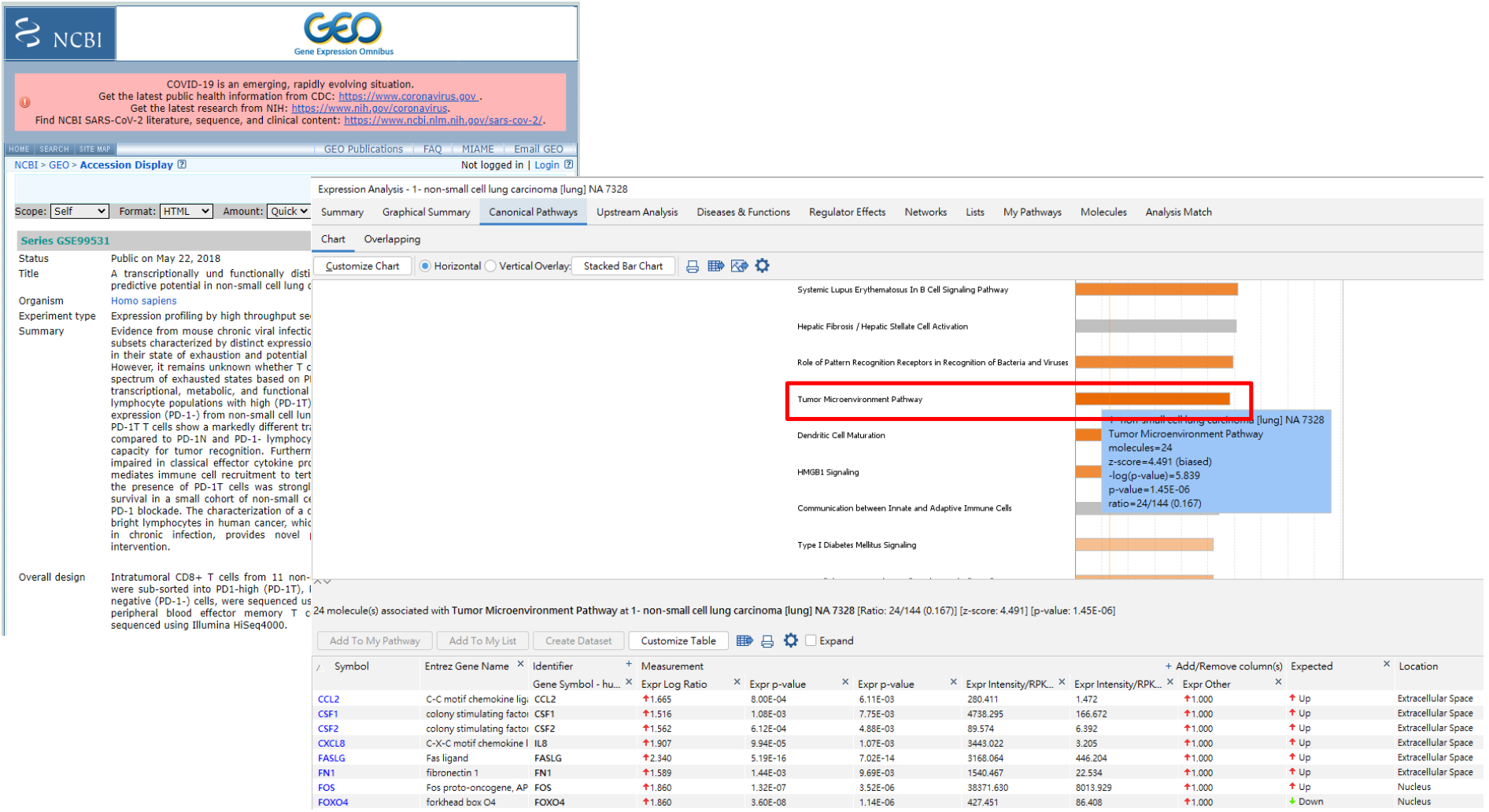
Analyze the impact of expression changes

Use Activity Plot and Omicsoft within the TME pathway (GSE99531)



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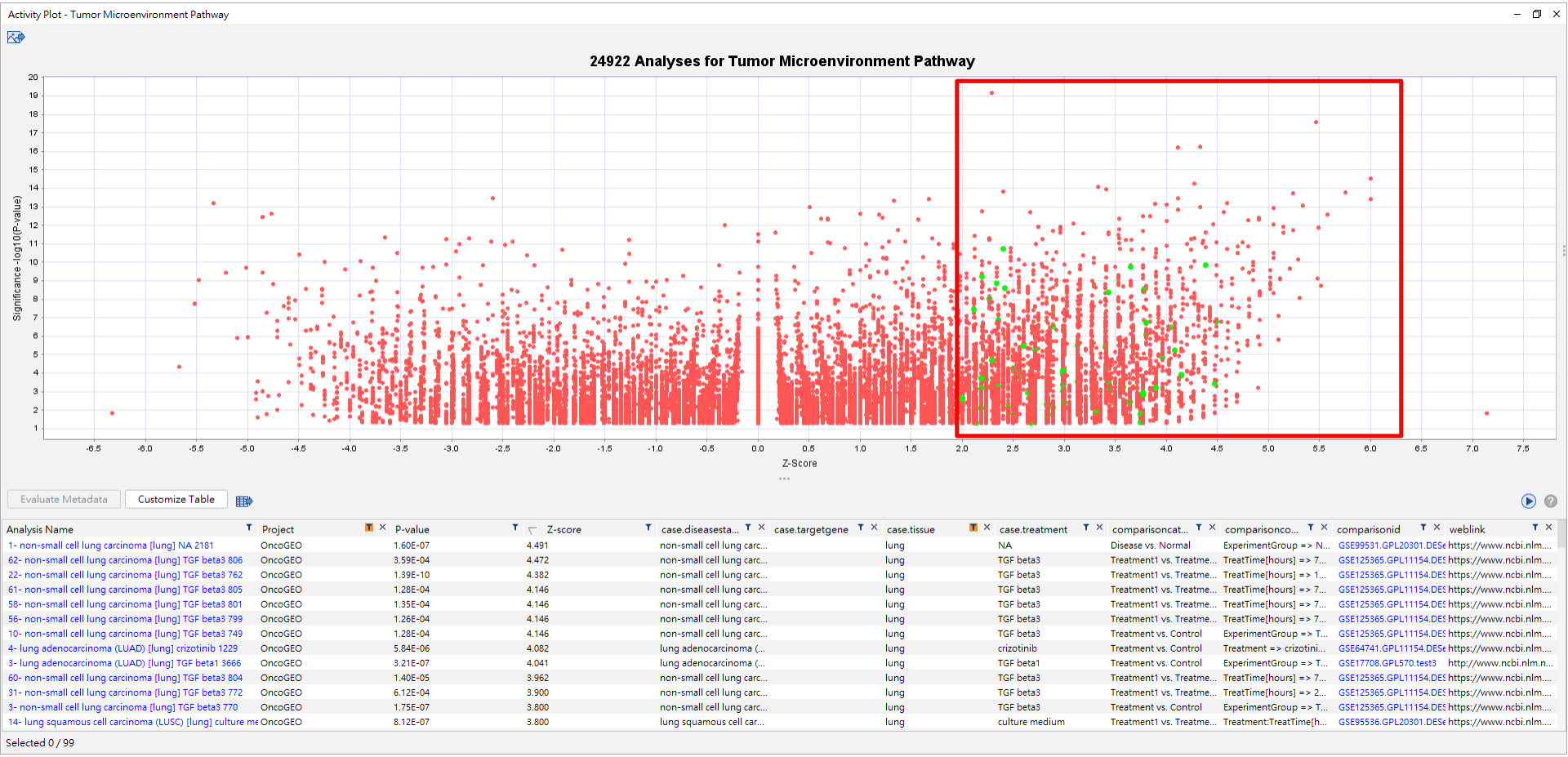
Analyze the impact of expression changes

Use Activity Plot and Omicsoft within the TME pathway

- Z-Score > 2
- OncoGEO、Lung



Analysis Name	Project	P-value	Z-score	case.diseasesta...	case.targetgene	case.tissue	case.treatment	comparisoncat...	comparisonco...	comparisonid	weblink
1- non-small cell lung carcinoma [lung] NA 2181	OncoGEO	1.60E-07	4.491	non-small cell lung carc...		lung	NA	Disease vs. Normal	ExperimentGroup => N...	GSE99531.GPL20301.DES	https://www.ncbi.nlm....
62- non-small cell lung carcinoma [lung] TGF beta3 806	OncoGEO	3.59E-04	4.472	non-small cell lung carc...		lung	TGF beta3	Treatment1 vs. Treatme...	TreatTime[hours] => 7...	GSE125365.GPL11154.DES	https://www.ncbi.nlm....
22- non-small cell lung carcinoma [lung] TGF beta3 762	OncoGEO	1.39E-10	4.382	non-small cell lung carc...		lung	TGF beta3	Treatment1 vs. Treatme...	TreatTime[hours] => 1...	GSE125365.GPL11154.DES	https://www.ncbi.nlm....
61- non-small cell lung carcinoma [lung] TGF beta3 805	OncoGEO	1.28E-04	4.146	non-small cell lung carc...		lung	TGF beta3	Treatment1 vs. Treatme...	TreatTime[hours] => 7...	GSE125365.GPL11154.DES	https://www.ncbi.nlm....
58- non-small cell lung carcinoma [lung] TGF beta3 801	OncoGEO	1.35E-04	4.146	non-small cell lung carc...		lung	TGF beta3	Treatment1 vs. Treatme...	TreatTime[hours] => 7...	GSE125365.GPL11154.DES	https://www.ncbi.nlm....
56- non-small cell lung carcinoma [lung] TGF beta3 799	OncoGEO	1.26E-04	4.146	non-small cell lung carc...		lung	TGF beta3	Treatment1 vs. Treatme...	TreatTime[hours] => 7...	GSE125365.GPL11154.DES	https://www.ncbi.nlm....
10- non-small cell lung carcinoma [lung] TGF beta3 749	OncoGEO	1.28E-04	4.146	non-small cell lung carc...		lung	TGF beta3	Treatment vs. Control	ExperimentGroup => T...	GSE125365.GPL11154.DES	https://www.ncbi.nlm....
4- lung adenocarcinoma (LUAD) [lung] crizotinib 1229	OncoGEO	5.84E-06	4.082	lung adenocarcinoma (...		lung	crizotinib	Treatment vs. Control	Treatment => crizotini...	GSE64741.GPL11154.DES	https://www.ncbi.nlm....
3- lung adenocarcinoma (LUAD) [lung] TGF beta1 3666	OncoGEO	3.21E-07	4.041	lung adenocarcinoma (...		lung	TGF beta1	Treatment vs. Control	ExperimentGroup => T...	GSE17708.GPL570.test3	http://www.ncbi.nlm.n...
60- non-small cell lung carcinoma [lung] TGF beta3 804	OncoGEO	1.40E-05	3.962	non-small cell lung carc...		lung	TGF beta3	Treatment1 vs. Treatme...	TreatTime[hours] => 7...	GSE125365.GPL11154.DES	https://www.ncbi.nlm....
31- non-small cell lung carcinoma [lung] TGF beta3 772	OncoGEO	6.12E-04	3.900	non-small cell lung carc...		lung	TGF beta3	Treatment1 vs. Treatme...	TreatTime[hours] => 2...	GSE125365.GPL11154.DES	https://www.ncbi.nlm....
3- non-small cell lung carcinoma [lung] TGF beta3 770	OncoGEO	1.75E-07	3.800	non-small cell lung carc...		lung	TGF beta3	Treatment vs. Control	ExperimentGroup => T...	GSE125365.GPL11154.DES	https://www.ncbi.nlm....
14- lung squamous cell carcinoma (LUSC) [lung] culture me	OncoGEO	8.12E-07	3.800	lung squamous cell car...		lung	culture medium	Treatment1 vs. Treatme...	Treatment:TreatTime[h...	GSE95536.GPL20301.DES	https://www.ncbi.nlm....

Selected 0 / 99

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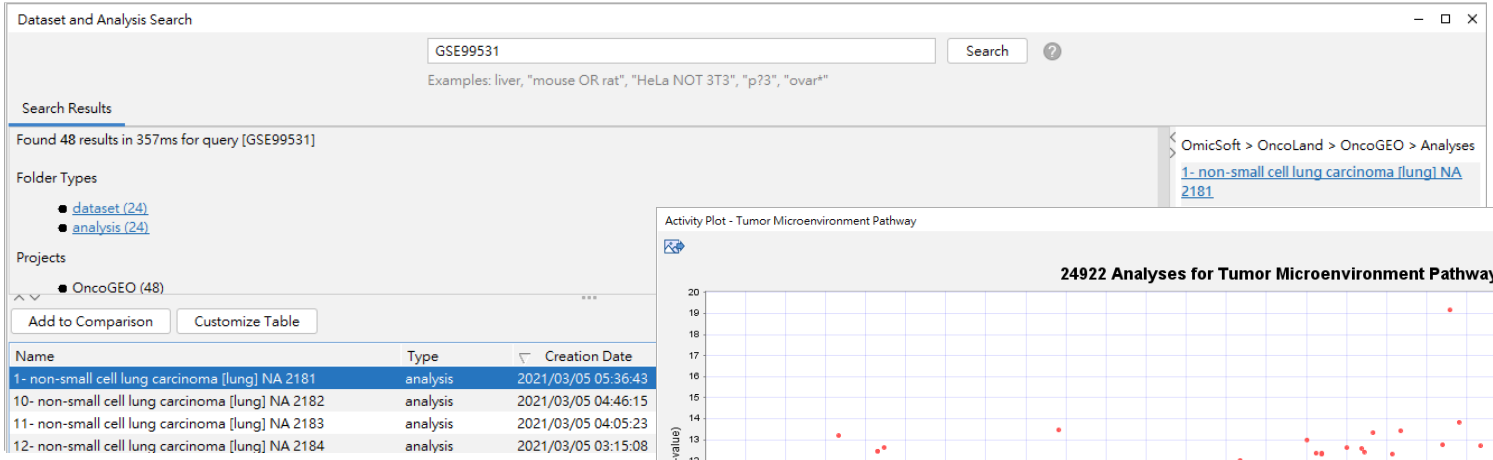
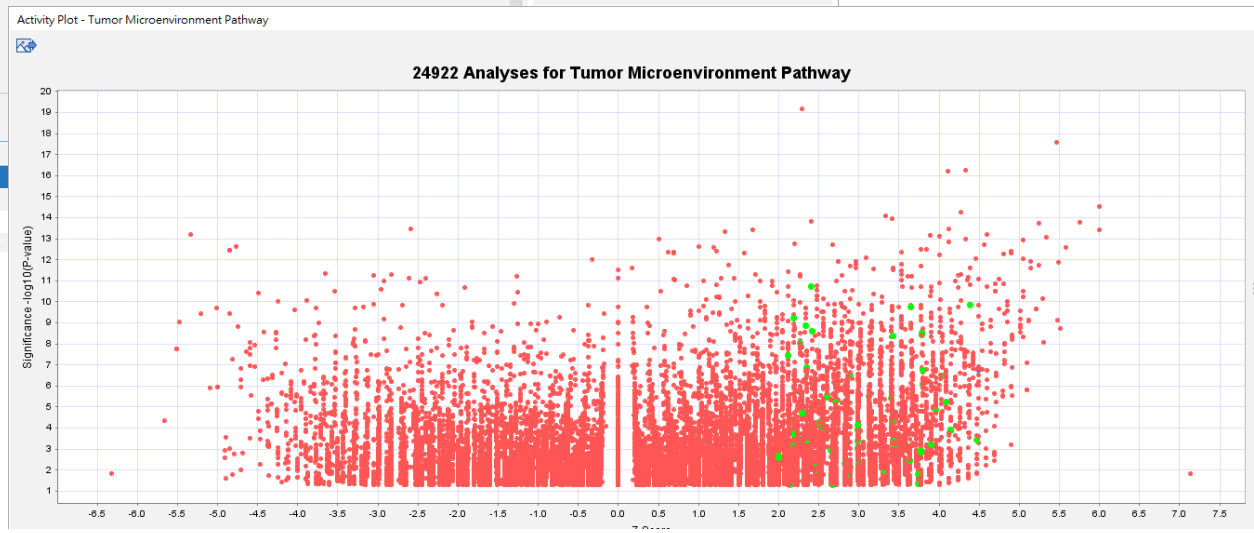
Analyze the impact of expression changes

How to find out Expression Analysis of “1-non small cell lung carcinoma [lung] NA 2181?

1. Project Manager -> Search -> “Key word” (GSE99531) -> Filter

2. Search Pathway -> Activity Plot -> Condition screening (score、project、tissue…)





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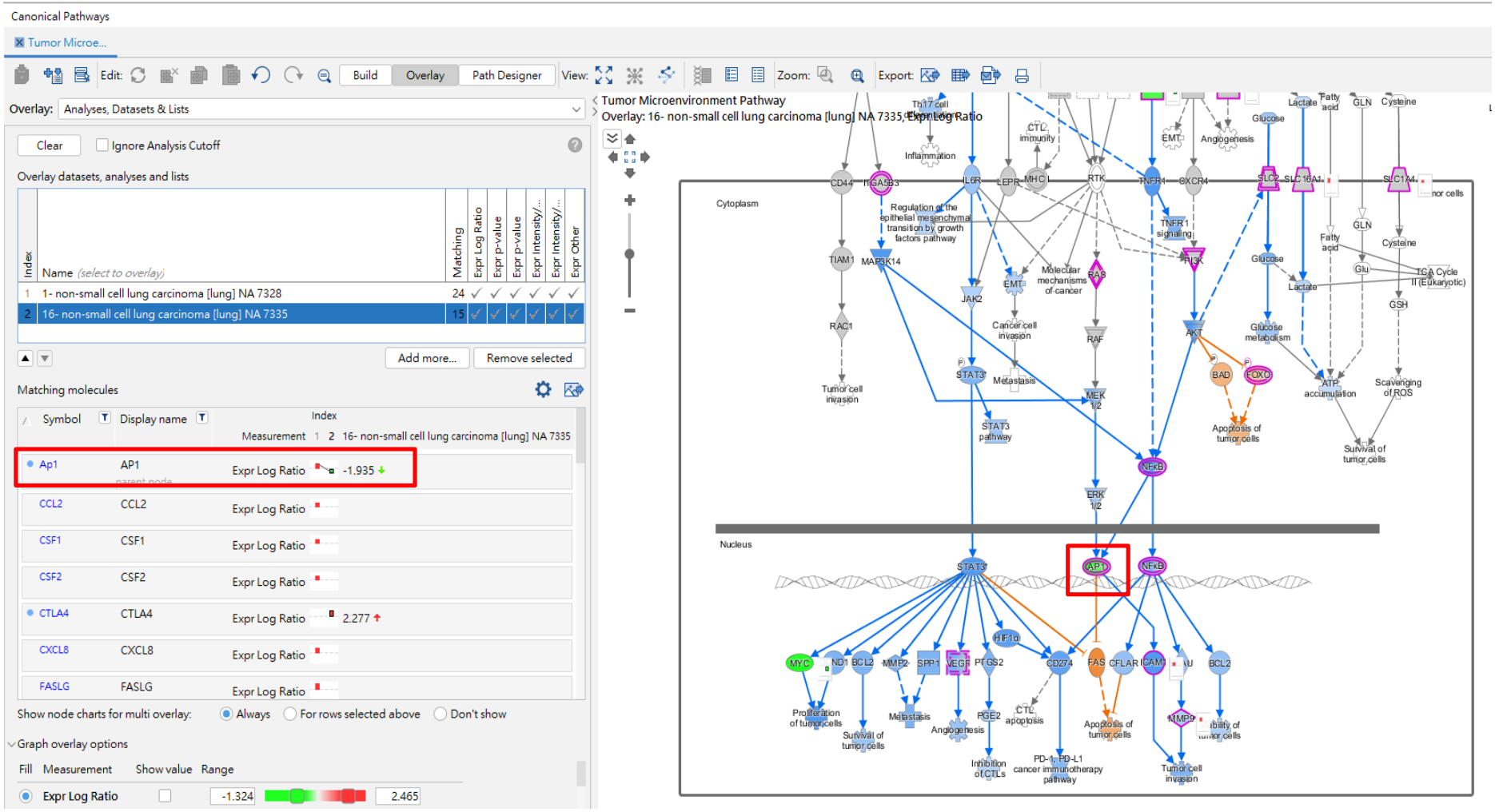
Analyze the impact of expression changes

Compare GSE99531 dataset of 1- LC and 16 - LC in TME pathway



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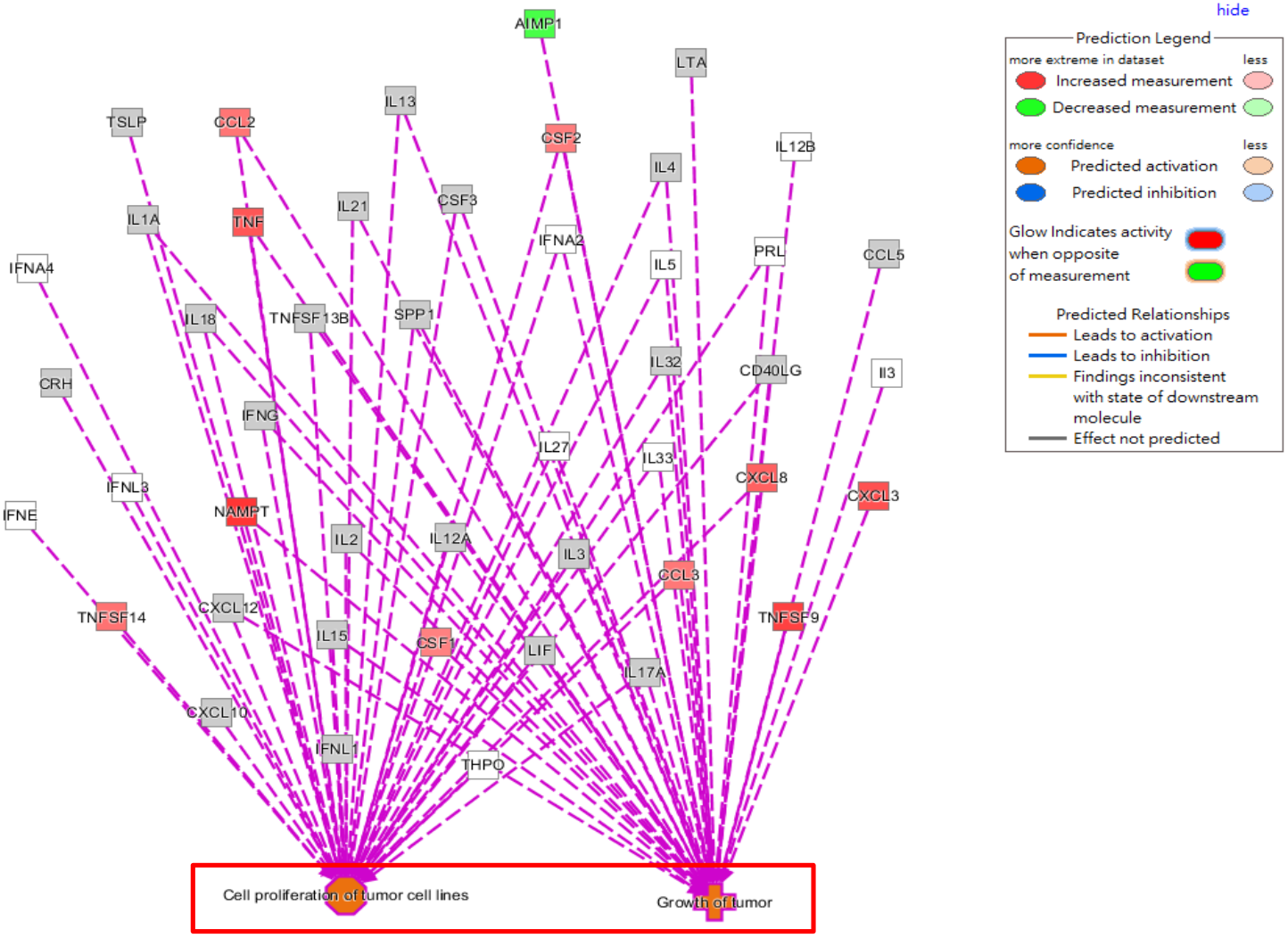
Establish a regulatory profile relevant to immune response

- Upstream regulator of “cytokine”
- Function of “Cell proliferation of tumor cell lines 、 Growth of tumor”



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QIAGEN IPA provides numerous ways to evaluate the tumor microenvironment

1. Utilize key target molecules to construct networks and predict activity of network
2. Profile of molecules associated with cancer and immune system.
3. Utilize OmicSoft to explore key target and pathway in context.
4. Compare multiple data expression changes and activity predictions in TME pathway.
5. Predicted upstream regulatory of immune related with molecules (e.g. cytokines) and how to influence biological function.

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Live Demo

Analysis Match

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Unprecedented discovery, together

Array Express
GEO
TCGA
SRA
Etc.

Journal articles

Clinical Trials
COSMIC
MGD
OMIM
Etc.

Curation, Processing, & QA

Curation & QA

Datasets integrated into OmicSoft Lands

Curated Findings

OmicSoft Array Suite

OncoLand
DiseaseLand

8100+ Expression comparison datasets

INGENUITY PATHWAY ANALYSIS

- Biological analyses of each dataset
- Compare your analysis to all OmicSoft analyses

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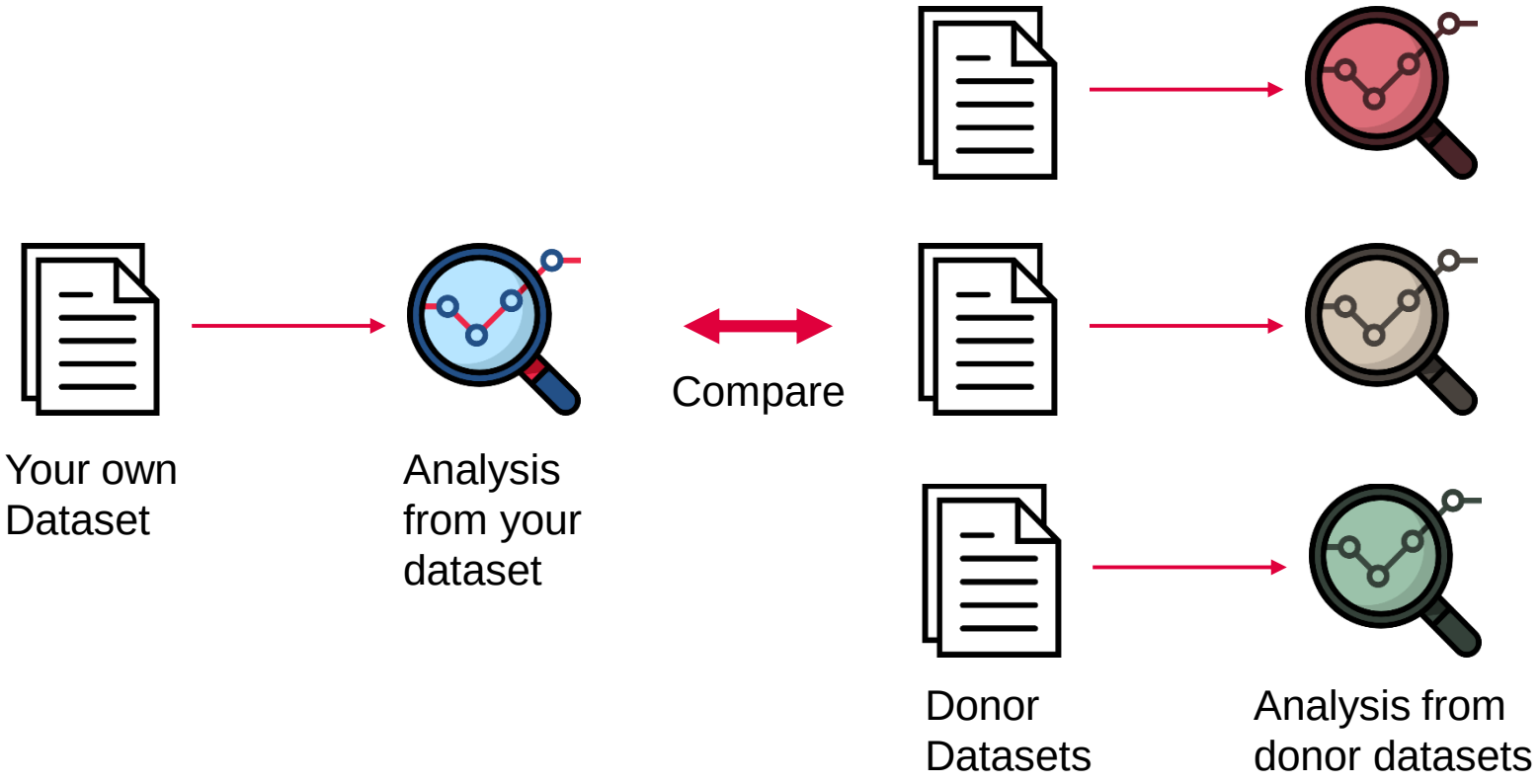
Analysis Match

截至今日，本次更新增加了19,000組分析完成的數據至Analysis Match分析功能中，您可以在Analysis Match分析模組當中，比較您的實驗資料與外部資料庫如TCGA、LINCS等，在不同的癌症類型，疾病類型與實驗組中分析其相似及相異關係度。

並自**LINCS（NIH Library of Integrated Network-Based Cellular Signatures）**再添加大約**28,000**個分析組，總數將超過**73,000**個



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Analysis Match

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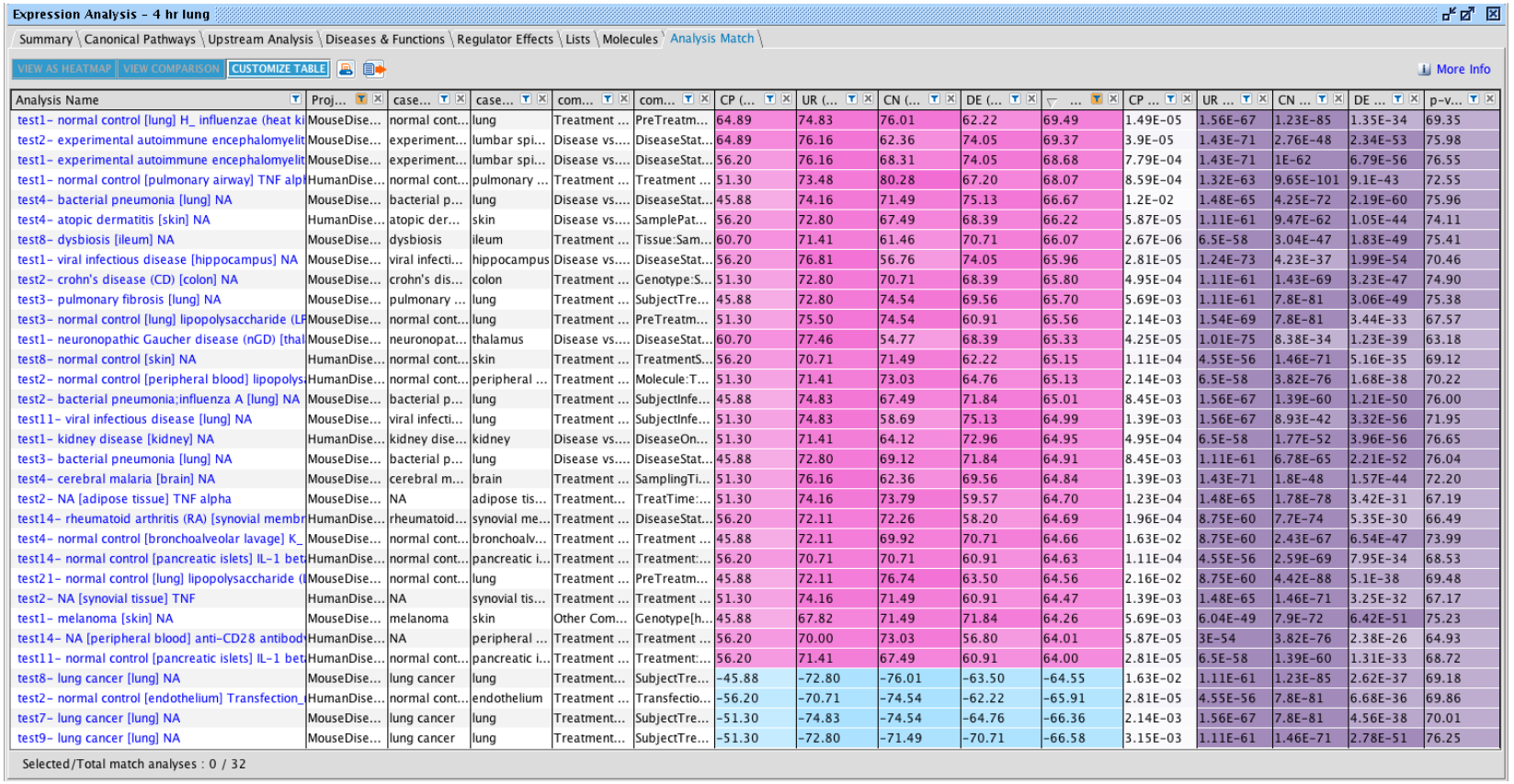
並自**DiseaseLand & OncoLand**再添加大約**6,900**個分析組，總數將超過**80,000**個!



Analysis Name	Proj...	case...	case...	com...	com...	CP (...	UR (...	CN (...	DE (...	...	CP ...	UR ...	CN ...	DE ...	p-v...
test1- normal control [lung] H_ influenzae (heat ki	MouseDise...	normal cont...	lung	Treatment ...	PreTreatm...	64.89	74.83	76.01	62.22	69.49	1.49E-05	1.56E-67	1.23E-85	1.35E-34	69.35
test2- experimental autoimmune encephalomyelit	MouseDise...	experiment...	lumbar spi...	Disease vs....	DiseaseStat...	64.89	76.16	62.36	74.05	69.37	3.9E-05	1.43E-71	2.76E-48	2.34E-53	75.98
test1- experimental autoimmune encephalomyelit	MouseDise...	experiment...	lumbar spi...	Disease vs....	DiseaseStat...	56.20	76.16	68.31	74.05	68.68	7.79E-04	1.43E-71	1E-62	6.79E-56	76.55
test1- normal control [pulmonary airway] TNF alpl	HumanDise...	normal cont...	pulmonary ...	Treatment ...	Treatment ...	51.30	73.48	80.28	67.20	68.07	8.59E-04	1.32E-63	9.65E-101	9.1E-43	72.55
test4- bacterial pneumonia [lung] NA	MouseDise...	bacterial p...	lung	Disease vs....	DiseaseStat...	45.88	74.16	71.49	75.13	66.67	1.2E-02	1.48E-65	4.25E-72	2.19E-60	75.96
test4- atopic dermatitis [skin] NA	HumanDise...	atopic der...	skin	Disease vs....	SamplePat...	56.20	72.80	67.49	68.39	66.22	5.87E-05	1.11E-61	9.47E-62	1.05E-44	74.11
test8- dysbiosis [ileum] NA	MouseDise...	dysbiosis	ileum	Treatment ...	Tissue:Sam...	60.70	71.41	61.46	70.71	66.07	2.67E-06	6.5E-58	3.04E-47	1.83E-49	75.41
test1- viral infectious disease [hippocampus] NA	MouseDise...	viral infecti...	hippocampus	Disease vs....	DiseaseStat...	56.20	76.81	56.76	74.05	65.96	2.81E-05	1.24E-73	4.23E-37	1.99E-54	70.46
test2- crohn's disease (CD) [colon] NA	MouseDise...	crohn's dis...	colon	Treatment ...	Genotype:S...	51.30	72.80	70.71	68.39	65.80	4.95E-04	1.11E-61	1.43E-69	3.23E-47	74.90
test3- pulmonary fibrosis [lung] NA	MouseDise...	pulmonary ...	lung	Treatment ...	SubjectTre...	45.88	72.80	74.54	69.56	65.70	5.69E-03	1.11E-61	7.8E-81	3.06E-49	75.38
test3- normal control [lung] lipopolysaccharide (LF	MouseDise...	normal cont...	lung	Treatment ...	PreTreatm...	51.30	75.50	74.54	60.91	65.56	2.14E-03	1.54E-69	7.8E-81	3.44E-33	67.57
test1- neuronopathic Gaucher disease (nGD) [thal	MouseDise...	neuronopat...	thalamus	Disease vs....	DiseaseStat...	60.70	77.46	54.77	68.39	65.33	4.25E-05	1.01E-75	8.38E-34	1.23E-39	63.18
test8- normal control [skin] NA	HumanDise...	normal cont...	skin	Treatment ...	TreatmentS...	56.20	70.71	71.49	62.22	65.15	1.11E-04	4.55E-56	1.46E-71	5.16E-35	69.12
test2- normal control [peripheral blood] lipopolys	HumanDise...	normal cont...	peripheral ...	Treatment ...	Molecule:T...	51.30	71.41	73.03	64.76	65.13	2.14E-03	6.5E-58	3.82E-76	1.68E-38	70.22
test2- bacterial pneumonia;influenza A [lung] NA	MouseDise...	bacterial p...	lung	Treatment ...	SubjectInfe...	45.88	74.83	67.49	71.84	65.01	8.45E-03	1.56E-67	1.39E-60	1.21E-50	76.00
test11- viral infectious disease [lung] NA	MouseDise...	viral infecti...	lung	Treatment ...	SubjectInfe...	51.30	74.83	58.69	75.13	64.99	1.39E-03	1.56E-67	8.93E-42	3.32E-56	71.95
test1- kidney disease [kidney] NA	HumanDise...	kidney dise...	kidney	Disease vs....	DiseaseOn...	51.30	71.41	64.12	72.96	64.95	4.95E-04	6.5E-58	1.77E-52	3.96E-56	76.65
test3- bacterial pneumonia [lung] NA	MouseDise...	bacterial p...	lung	Disease vs....	DiseaseStat...	45.88	72.80	69.12	71.84	64.91	8.45E-03	1.11E-61	6.78E-65	2.21E-52	76.04
test4- cerebral malaria [brain] NA	MouseDise...	cerebral m...	brain	Treatment ...	SamplingTi...	51.30	76.16	62.36	69.56	64.84	1.39E-03	1.43E-71	1.8E-48	1.57E-44	72.20
test2- NA [adipose tissue] TNF alpha	MouseDise...	NA	adipose tis...	Treatment...	TreatTime:...	51.30	74.16	73.79	59.57	64.70	1.23E-04	1.48E-65	1.78E-78	3.42E-31	67.19
test14- rheumatoid arthritis (RA) [synovial membr	HumanDise...	rheumatoid...	synovial me...	Treatment ...	DiseaseStat...	56.20	72.11	72.26	58.20	64.69	1.96E-04	8.75E-60	7.7E-74	5.35E-30	66.49
test4- normal control [bronchoalveolar lavage] K_	MouseDise...	normal cont...	bronchoalv...	Treatment ...	Treatment ...	45.88	72.11	69.92	70.71	64.66	1.63E-02	8.75E-60	2.43E-67	6.54E-47	73.99
test14- normal control [pancreatic islets] IL-1 bet	HumanDise...	normal cont...	pancreatic i...	Treatment ...	Treatment:...	56.20	70.71	70.71	60.91	64.63	1.11E-04	4.55E-56	2.59E-69	7.95E-34	68.53
test21- normal control [lung] lipopolysaccharide (I	MouseDise...	normal cont...	lung	Treatment ...	PreTreatm...	45.88	72.11	76.74	63.50	64.56	2.16E-02	8.75E-60	4.42E-88	5.1E-38	69.48
test2- NA [synovial tissue] TNF	HumanDise...	NA	synovial tis...	Treatment ...	Treatment ...	51.30	74.16	71.49	60.91	64.47	1.39E-03	1.48E-65	1.46E-71	3.25E-32	67.17
test1- melanoma [skin] NA	MouseDise...	melanoma	skin	Other Com...	Genotype[h...	45.88	67.82	71.49	71.84	64.26	5.69E-03	6.04E-49	7.9E-72	6.42E-51	75.23
test14- NA [peripheral blood] anti-CD28 antibod	HumanDise...	NA	peripheral ...	Treatment ...	Treatment ...	56.20	70.00	73.03	56.80	64.01	5.87E-05	3E-54	3.82E-76	2.38E-26	64.93
test11- normal control [pancreatic islets] IL-1 bet	HumanDise...	normal cont...	pancreatic i...	Treatment ...	Treatment:...	56.20	71.41	67.49	60.91	64.00	2.81E-05	6.5E-58	1.39E-60	1.31E-33	68.72
test8- lung cancer [lung] NA	MouseDise...	lung cancer	lung	Treatment...	SubjectTre...	-45.88	-72.80	-76.01	-63.50	-64.55	1.63E-02	1.11E-61	1.23E-85	2.62E-37	69.18
test2- normal control [endothelium] Transfection_	HumanDise...	normal cont...	endothelium	Treatment ...	Transfectio...	-56.20	-70.71	-74.54	-62.22	-65.91	2.81E-05	4.55E-56	7.8E-81	6.68E-36	69.86
test7- lung cancer [lung] NA	MouseDise...	lung cancer	lung	Treatment...	SubjectTre...	-51.30	-74.83	-74.54	-64.76	-66.36	2.14E-03	1.56E-67	7.8E-81	4.56E-38	70.01
test9- lung cancer [lung] NA	MouseDise...	lung cancer	lung	Treatment...	SubjectTre...	-51.30	-72.80	-71.49	-70.71	-66.58	3.15E-03	1.11E-61	1.46E-71	2.78E-51	76.25

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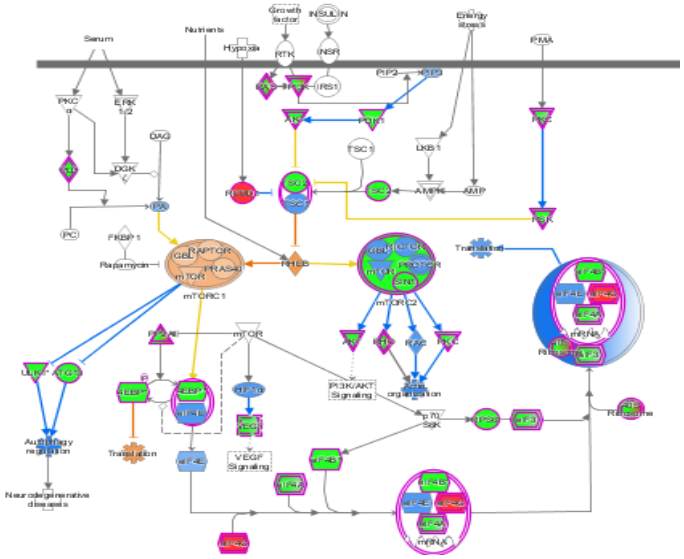
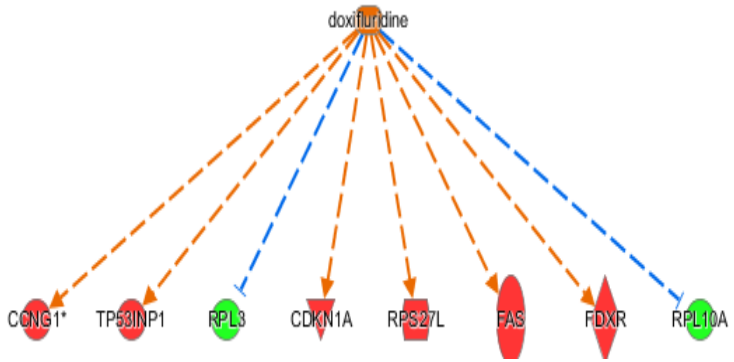
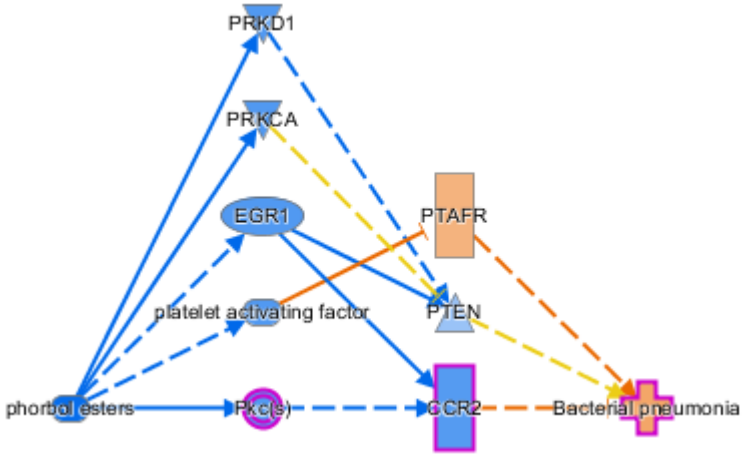
Canonical pathways (CP)



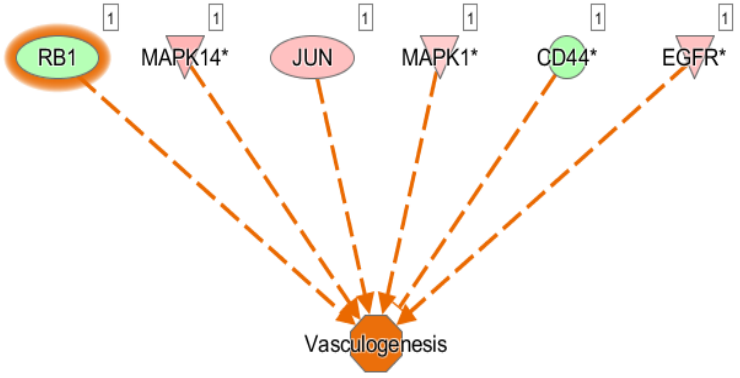
Upstream regulators (UR)



Causal networks (CN ‘master’ regulator)



Disease and functions (DE)



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>80,000 OmicSoft Analyses available in Analysis Match and Activity Plot

Land	Repository	Datasets Q3 2020	Datasets Q4 2020	Increase
DiseaseLand	HumanDisease	15,146	16,290	1144
	MouseDisease	12,698	14,563	1865
	RatDisease	3948	5480	1532
	LINCS	28,234	28,234	
OncoLand	OncoGEO	6364	7379	1015
	OncoMouse	501	933	432
	TCGA	4789	4789	
	MetastaticCancer	81	81	
	Hematology	1512	2511	999
	Pediatrics	444	444	

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Live Demo

microRNA target filter

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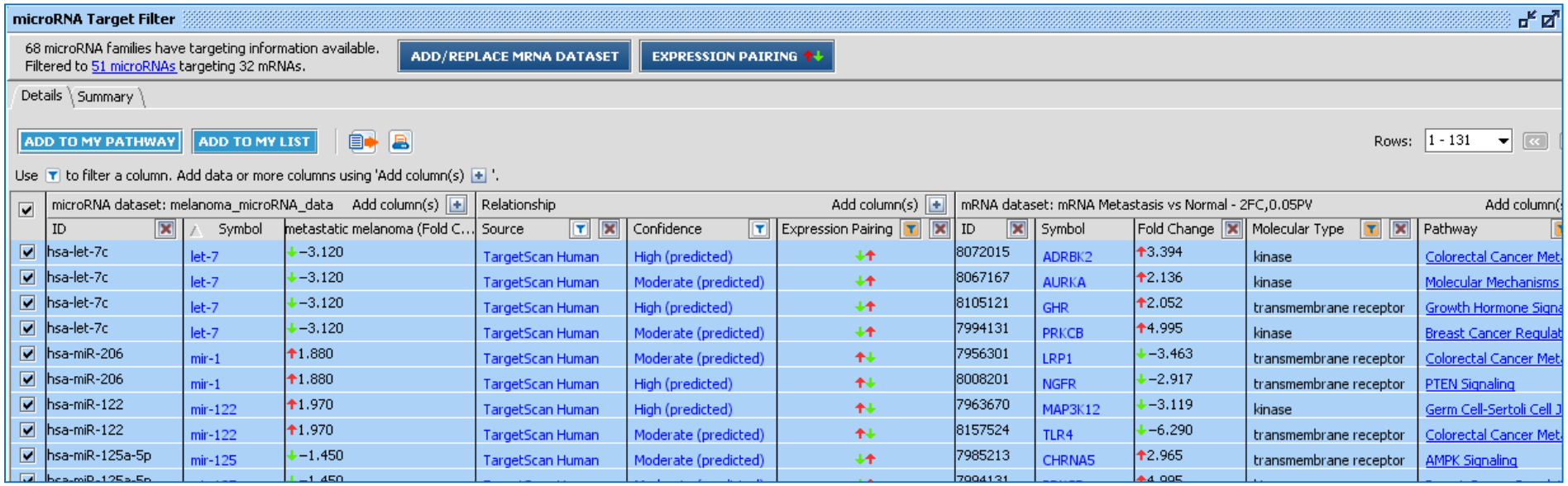
Filter Datasets for Biomarkers or miRNA Targets



microRNA dataset: melanoma_microRNA_data			Relationship			mRNA dataset: mRNA Metastasis vs Normal - 2FC,0.05PV				
ID	Symbol	metastatic melanoma (Fold C...	Source	Confidence	Expression Pairing	ID	Symbol	Fold Change	Molecular Type	Pathway
hsa-let-7c	let-7	↓−3.120	TargetScan Human	High (predicted)	↓↑	8072015	ADRBK2	↑3.394	kinase	Colorectal Cancer Met
hsa-let-7c	let-7	↓−3.120	TargetScan Human	Moderate (predicted)	↓↑	8067167	AURKA	↑2.136	kinase	Molecular Mechanisms
hsa-let-7c	let-7	↓−3.120	TargetScan Human	High (predicted)	↓↑	8105121	GHR	↑2.052	transmembrane receptor	Growth Hormone Signa
hsa-let-7c	let-7	↓−3.120	TargetScan Human	Moderate (predicted)	↓↑	7994131	PRKCB	↑4.995	kinase	Breast Cancer Regulat
hsa-miR-206	mir-1	↑1.880	TargetScan Human	Moderate (predicted)	↑↓	7956301	LRP1	↓−3.463	transmembrane receptor	Colorectal Cancer Met
hsa-miR-206	mir-1	↑1.880	TargetScan Human	High (predicted)	↑↓	8008201	NGFR	↓−2.917	transmembrane receptor	PTEN Signaling
hsa-miR-122	mir-122	↑1.970	TargetScan Human	High (predicted)	↑↓	7963670	MAP3K12	↓−3.119	kinase	Germ Cell-Sertoli Cell J
hsa-miR-122	mir-122	↑1.970	TargetScan Human	Moderate (predicted)	↑↓	8157524	TLR4	↓−6.290	transmembrane receptor	Colorectal Cancer Met
hsa-miR-125a-5p	mir-125	↓−1.450	TargetScan Human	Moderate (predicted)	↓↑	7985213	CHRNA5	↑2.965	transmembrane receptor	AMPK Signaling

miRNA Data	miRNA Target Filter	Molecule Type	Pathways (Cancer/ Growth)	mRNA	↑↓ ↓↑	?
88 data points	13,690 targets	1,090 targets	333 targets	39 targets	32 targets	

Use Pathway tools to build hypothesis for microRNA to mRNA target association

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TargetScanHuman

Prediction of microRNA targets

Release 5.1: April 2009

Human | miR-25/32/92/92ab/363/367

692 conserved targets, with a total of **764** conserved sites and **151** poorly conserved sites.

Table sorted by total context score [Sort table by aggregate P_{CT}]

Genes with only poorly conserved sites are not shown [View top predicted targets, irrespective of site conservation]

Target gene	Gene name	Conserved sites				Poorly conserved sites				Repre-sentative miRNA
		total	8mer	7mer-m8	7mer-1A	total	8mer	7mer-m8	7mer-1A	
CD69	CD69 molecule	**3**	3	0	0	**0**	0	0	0	hsa-miR-3E
SLC12A5	solute carrier family 12, (potassium-chloride transporter) member 5	**3**	2	0	1	**1**	0	0	1	hsa-miR-25
FNIP1	folliculin interacting protein 1	**2**	2	0	0	**0**	0	0	0	hsa-miR-3E
ACTC1	actin, alpha, cardiac muscle 1	**1**	0	1	0	**3**	1	1	1	hsa-miR-32
MAN2A1	mannosidase, alpha, class 2A, member 1	**2**	1	1	0	**1**	0	1	0	hsa-miR-3E
FBXW7	F-box and WD repeat domain containing 7	**2**	1	1	0	**1**	0	0	1	hsa-miR-3E
PTAR1	protein prenyltransferase alpha subunit repeat containing 1	**1**	1	0	0	**2**	0	1	1	hsa-miR-3E
RBM47	RNA binding motif protein 47	**3**	1	2	0	**0**	0	0	0	hsa-miR-3E
IQWD1	IQ motif and WD repeats 1	**1**	1	0	0	**1**	0	1	0	hsa-miR-3E
PCDH11X	protocadherin 11 X-linked	**2**	2	0	0	**0**	0	0	0	hsa-miR-25
PCDH11Y	protocadherin 11 Y-linked	**1**	1	0	0	**1**	1	0	0	hsa-miR-25

(1 Target Scan search) x (each microRNA in your data set) =
A LOT of targets

2006-2009 Whitehead Institute for Biomedical Research

Questions: wibr-bioinformatics@wi.mit.edu

Compatibility

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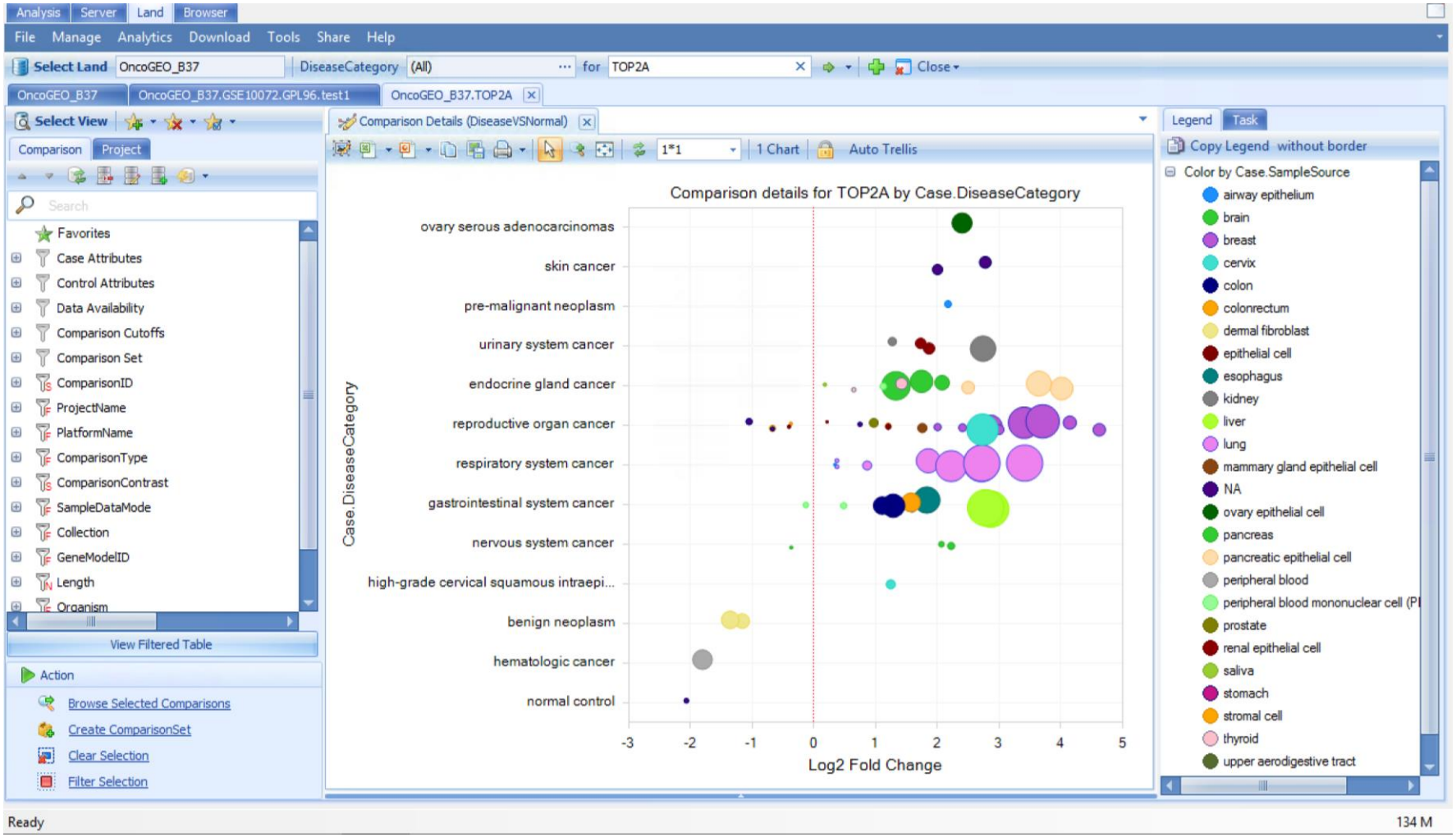
Visualizing an individual gene across comparisons



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Live Demo

Causal Network

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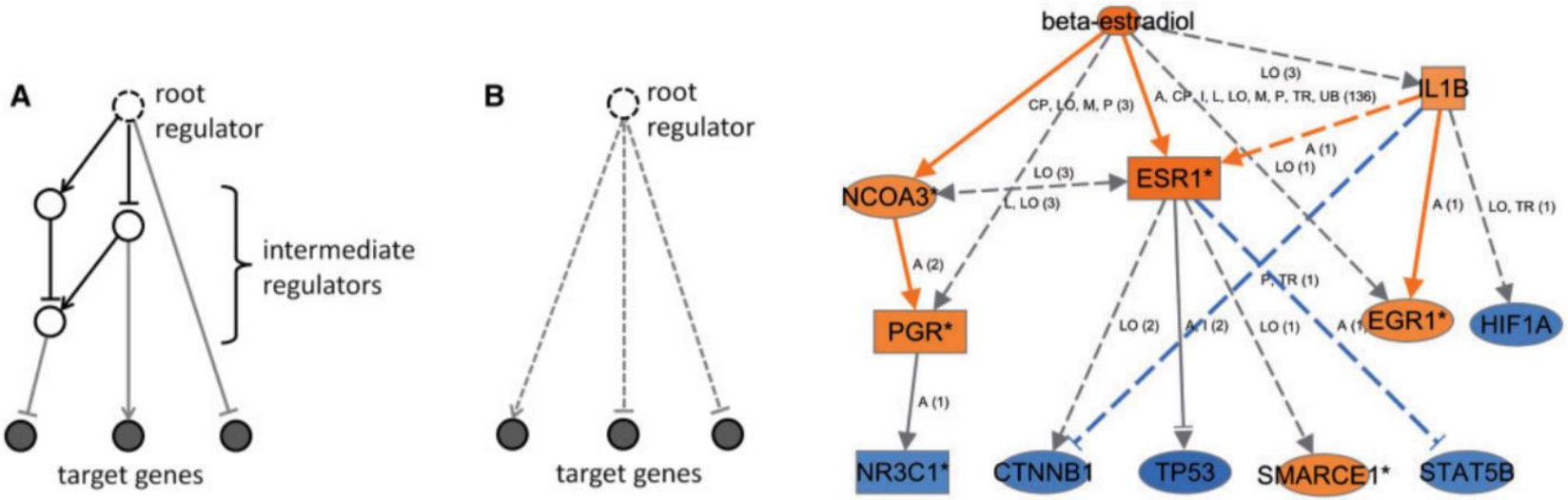
The enhanced Causal Network Analysis (CNA) provides a comprehensive approach to identifying upstream molecules that control the expression of the genes in your datasets. You can now, in a single click, visualize the diseases and functions you are scoring against, understand the effect of the master regulator on that disease or function, and drill-down to the evidence supporting those relationships. In addition, increase the predictive power by allowing intervening molecules or functions, up to three steps or 'hops', to connect a hypothesis to the scoring criteria.



Causal analysis approaches in Ingenuity Pathway Analysis. 2014 *Bioinformatics*

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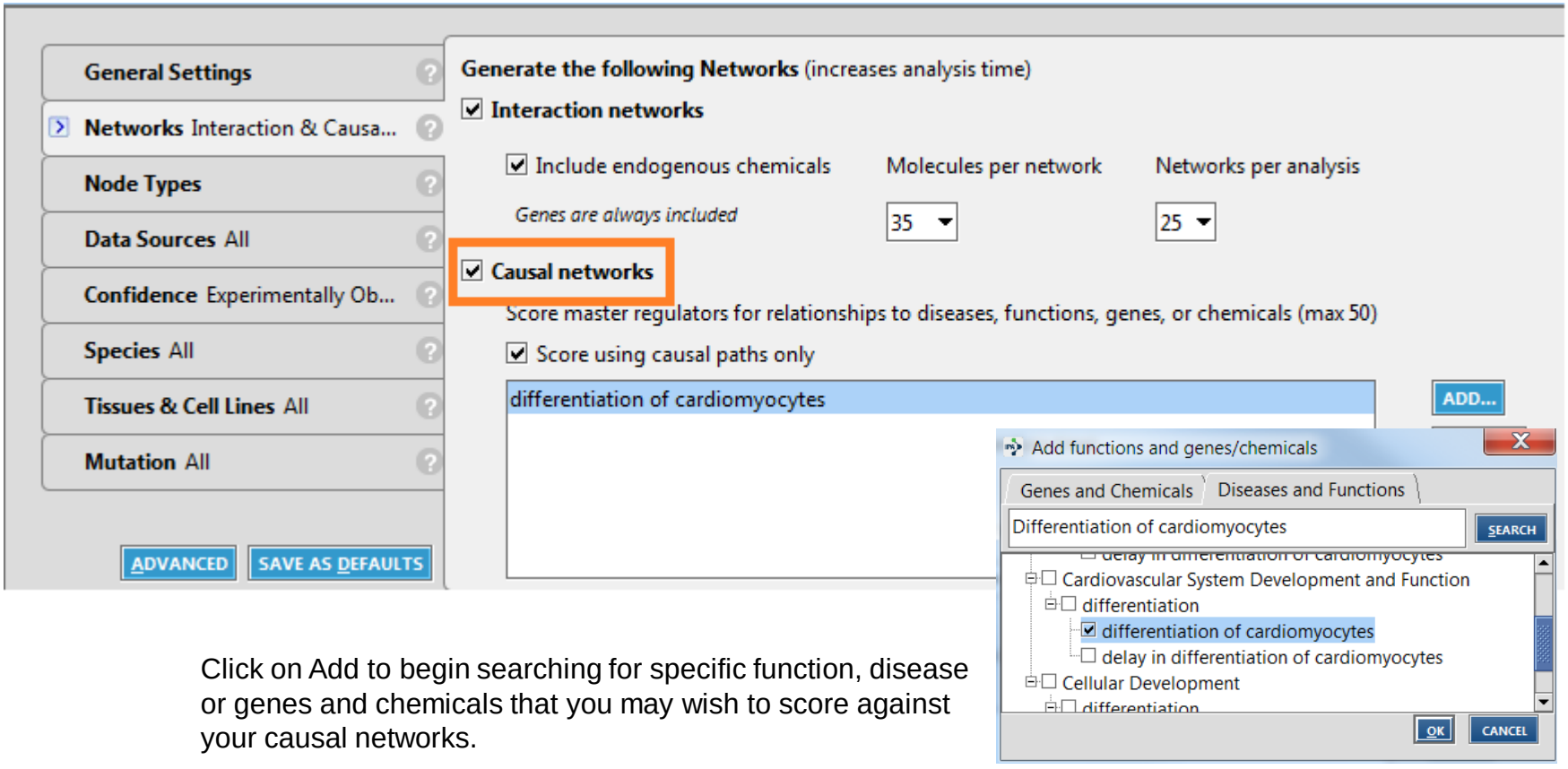
How to Create Causal networks?

The option to build causal networks is available in IPA on the Create Analysis page. Select the check box for Causal network under General Settings > Networks to include Casual Analysis in your analysis results.



Click on Add to begin searching for specific function, disease or genes and chemicals that you may wish to score against your causal networks.

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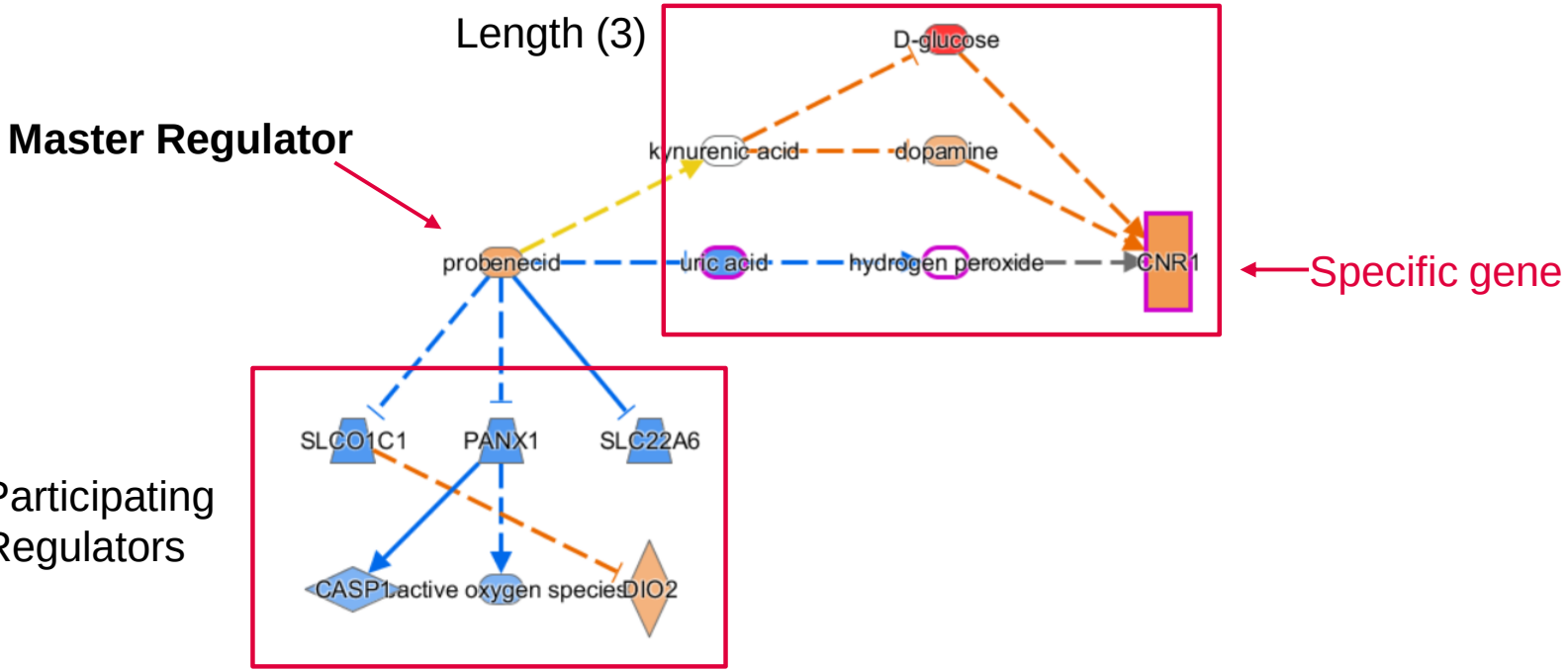
Result

Master Regulator and Networks

Specific function, disease or genes and chemicals that you wish to score against your causal networks.

							Add/Remove column(s)		CNR1		Diabetes mellitus [diabetes]		Insulin		Relationships Between M...		
Master ...	Expr...	Mol...	Participating regulators	Depth	Pre...	Acti...	p-va...	Length l...	Path ...	Length l...	Path ...	Length l...	Path ...	Incr...	Decr...
ICMT		enzyme	ICMT ...all 1	1	Activated	2.000	1.31E-08	3 | 8	DU(3),	2 | 1	DU(1)	3 | 23	DD(2),		
G6PC		phosphatase	↑D-glucose, G6PC ...all 2	2	Activated	2.000	9.99E-03	2 | 12	DD(6),	3 | 51	DU(23),	1 | 1	DD(1)	GC... ...all 9	7alp.....all 8
afatinib		chemical drug	afatinib ...all 1	1		-1.667	8.47E-16	2 | 1	DU(1)	2 | 3	DU(2),	2 | 3	IU(3)		
UCP2		transporter	UCP2 ...all 1	1		-1.633	6.82E-13	2 | 7	DD(4),	1 | 1	IU(1)	1 | 1	DD(1)	sirol.....all 1	PLI... ...all 5
propylthiourac		chemical drug	propylthiouracil ...all 1	1		-1.134	8.83E-13	2 | 1	IU(1)	2 | 3	DU(3)	2 | 1	IU(1)		
sirolimus		chemical drug	sirolimus ...all 1	1		-1.265	3.23E-09	2 | 2	DU(2)	1 | 1	IU(1)	1 | 1	IU(1)		
methimazole		chemical drug	methimazole ...all 1	1		-1.342	2.62E-08	2 | 2	DU(1),	2 | 1	DU(1)	2 | 2	DU(1),		
probenecid		chemical drug	CASP1, DIO2, PANX1, ...all 7	3		0.816	1.23E-06	3 | 5	DU(5)	3 | 77	DU(36),	3 | 7	DU(2),		
HTT		transcription ...	HTT ...all 1	1		-0.447	2.05E-06	1 | 1	IU(1)	1 | 1	DU(1)	2 | 7	DD(2),		sirol.....all 2



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Live Demo

IsoProfiler

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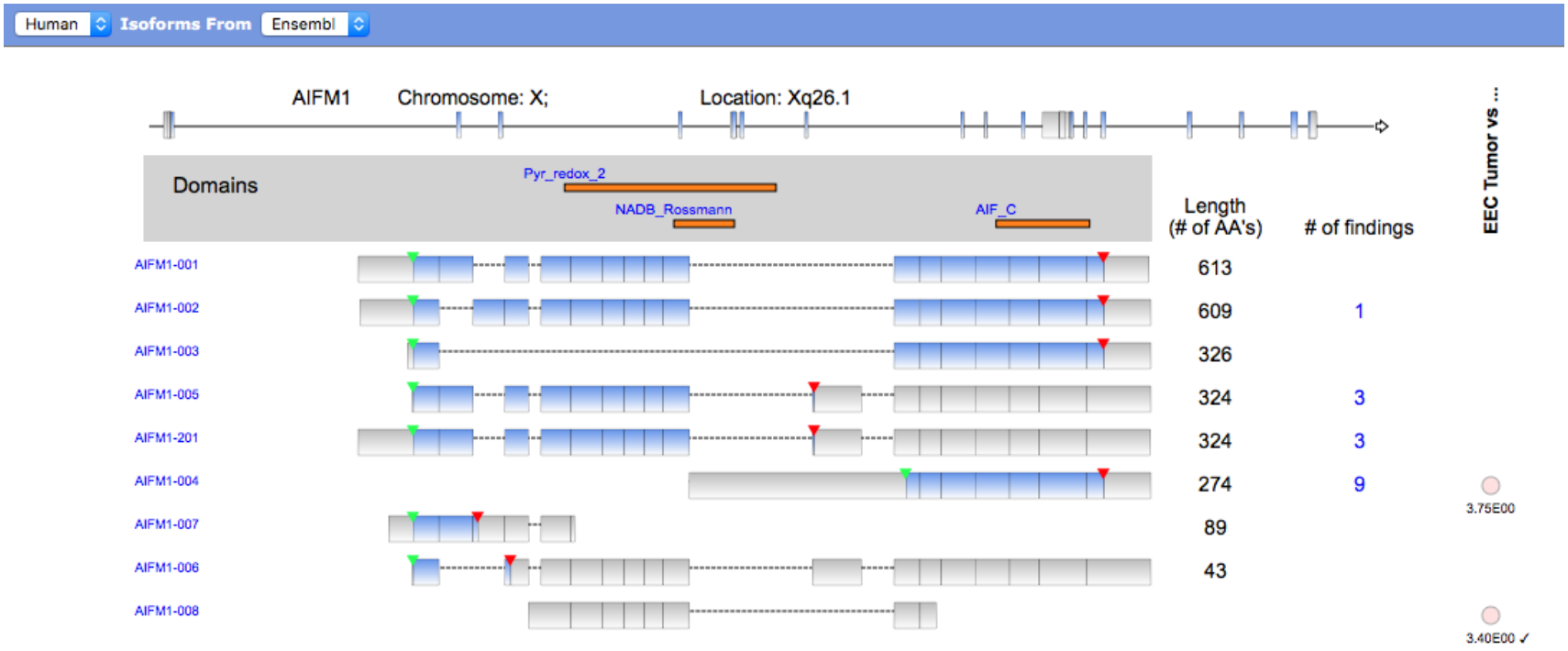
IsoProfiler displays and enables filtering on transcripts & isoforms in your RNA-seq dataset(s)

Your data must be mapped using **RefSeq**, **Ensembl**, or **UCSC** identifiers. You cannot use gene names or gene-level IDs to map your dataset for IsoProfiler, you must use **transcript** IDs.

Furthermore, for IsoProfiler your dataset must consist of a single source for your dataset-- i.e. only Ensembl, or only RefSeq. **You cannot mix sources**.



Ensembl ID with isoform viewer in IPA

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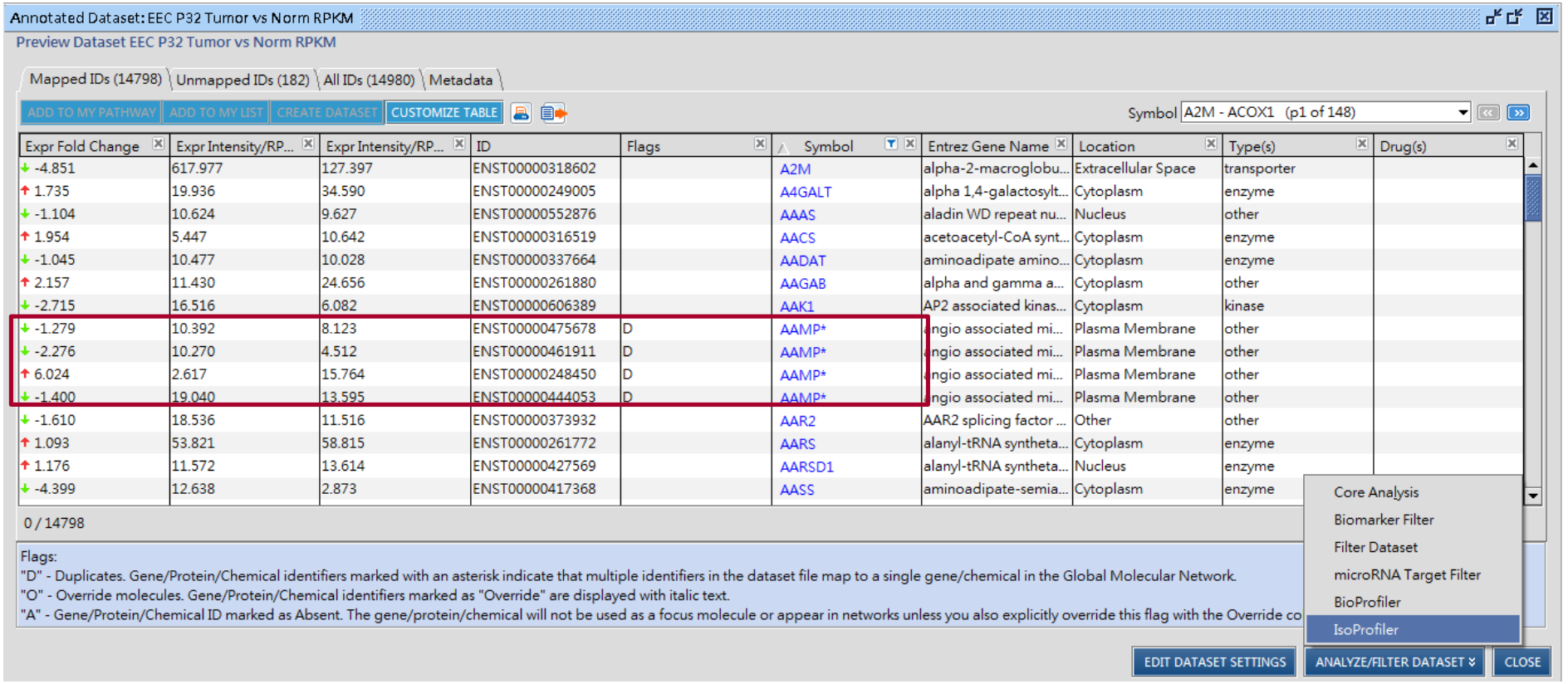
Dataset Analysis with Isoprofiler

Without Isoprofiler Analysis, different treanscript ID with same gene name can only analysis with the one which has the max expression value.



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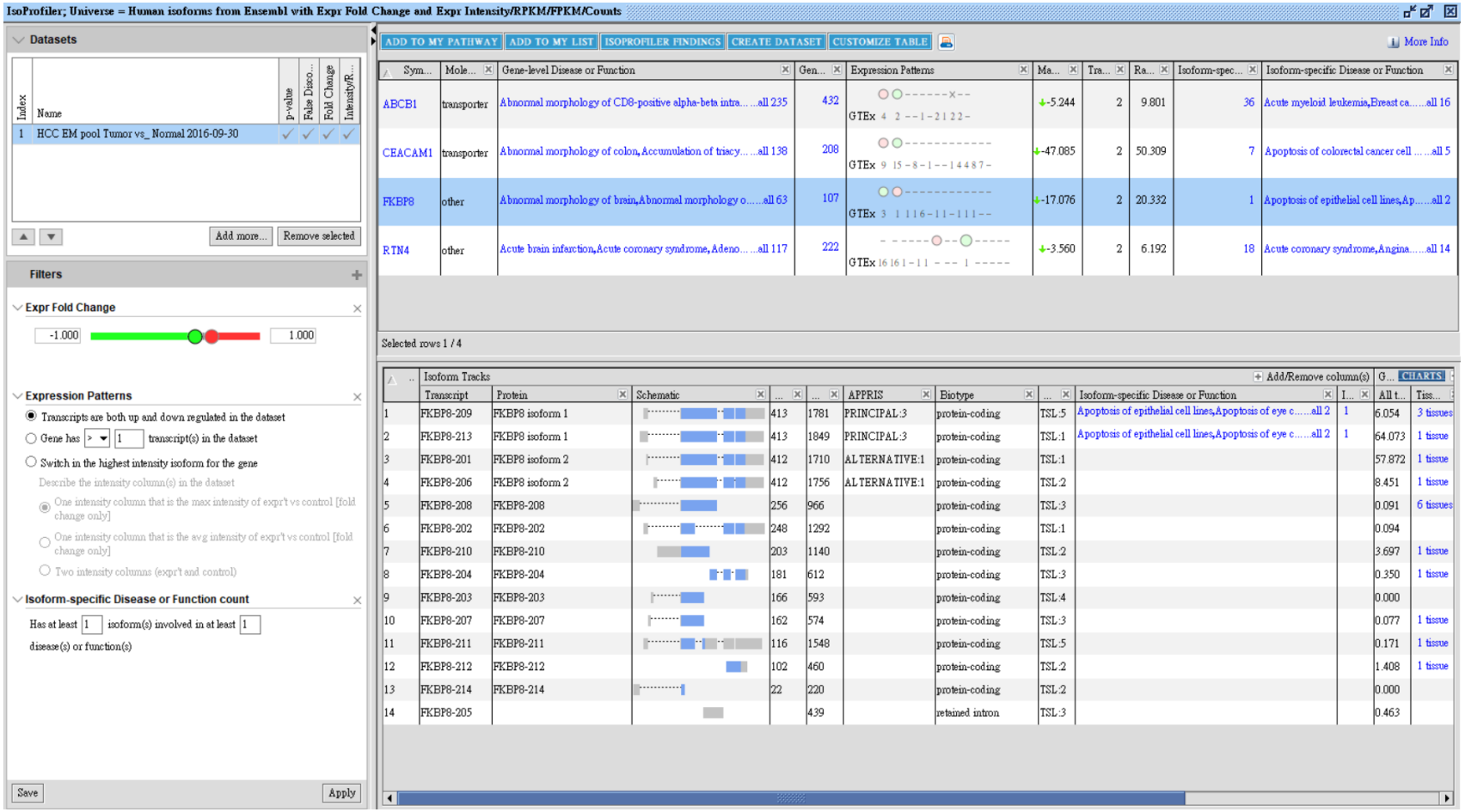
Once IsoProfiler launches, it will display results such as in this example

Dataset Chooser

Genes and their isoforms from the dataset



Isoform filters

Isoform details on the selected gene

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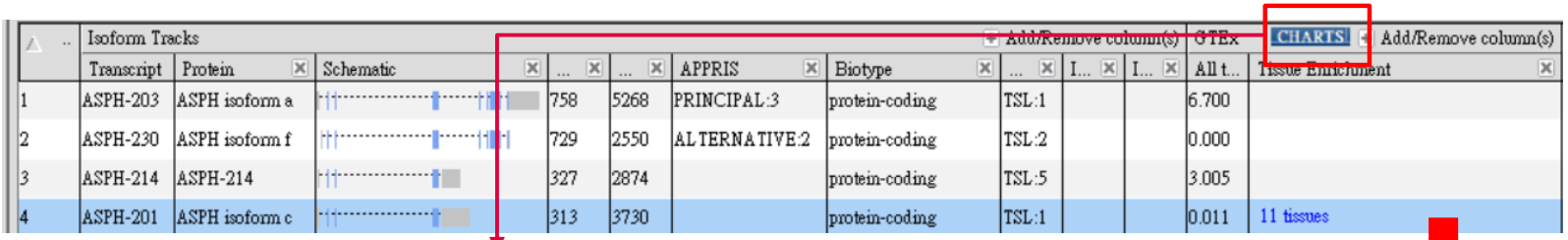
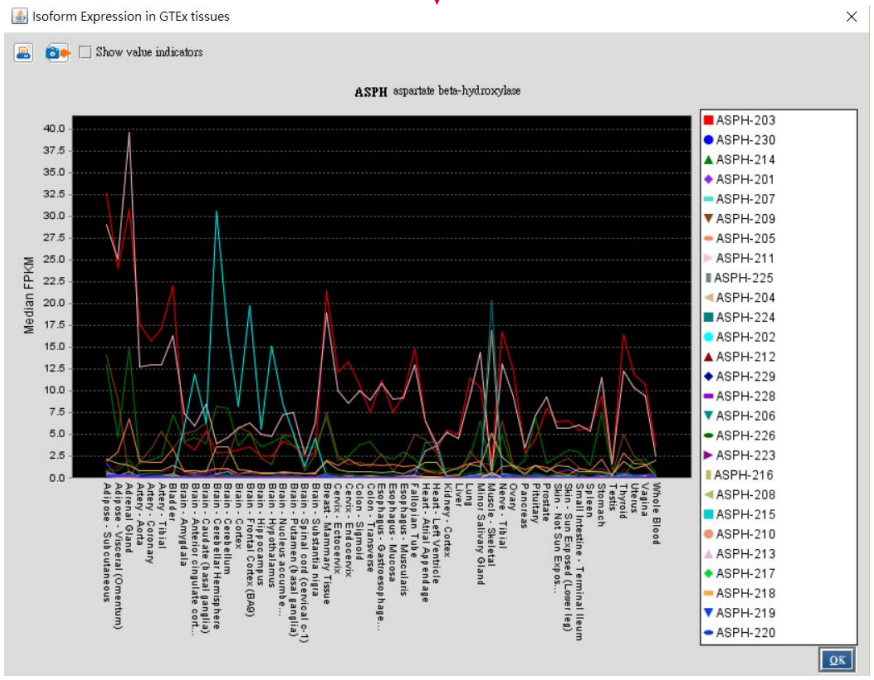
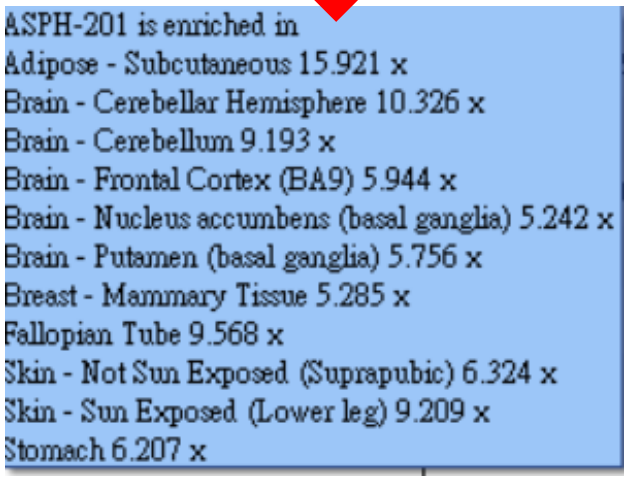
IsoProfiler with **GTEx Tissue Expression**

If your dataset is based on human expression data, additional functionality appears in IsoProfiler to help you explore tissue expression information from the **GTEx consortium**, which profiled **51 tissues** from multiple human tissue donors by RNA-seq.







The GTEx consortium has performed over 9,800 paired-end RNA-Seq experiments across 51 human tissues

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Live Demo

PhosphoProteomics

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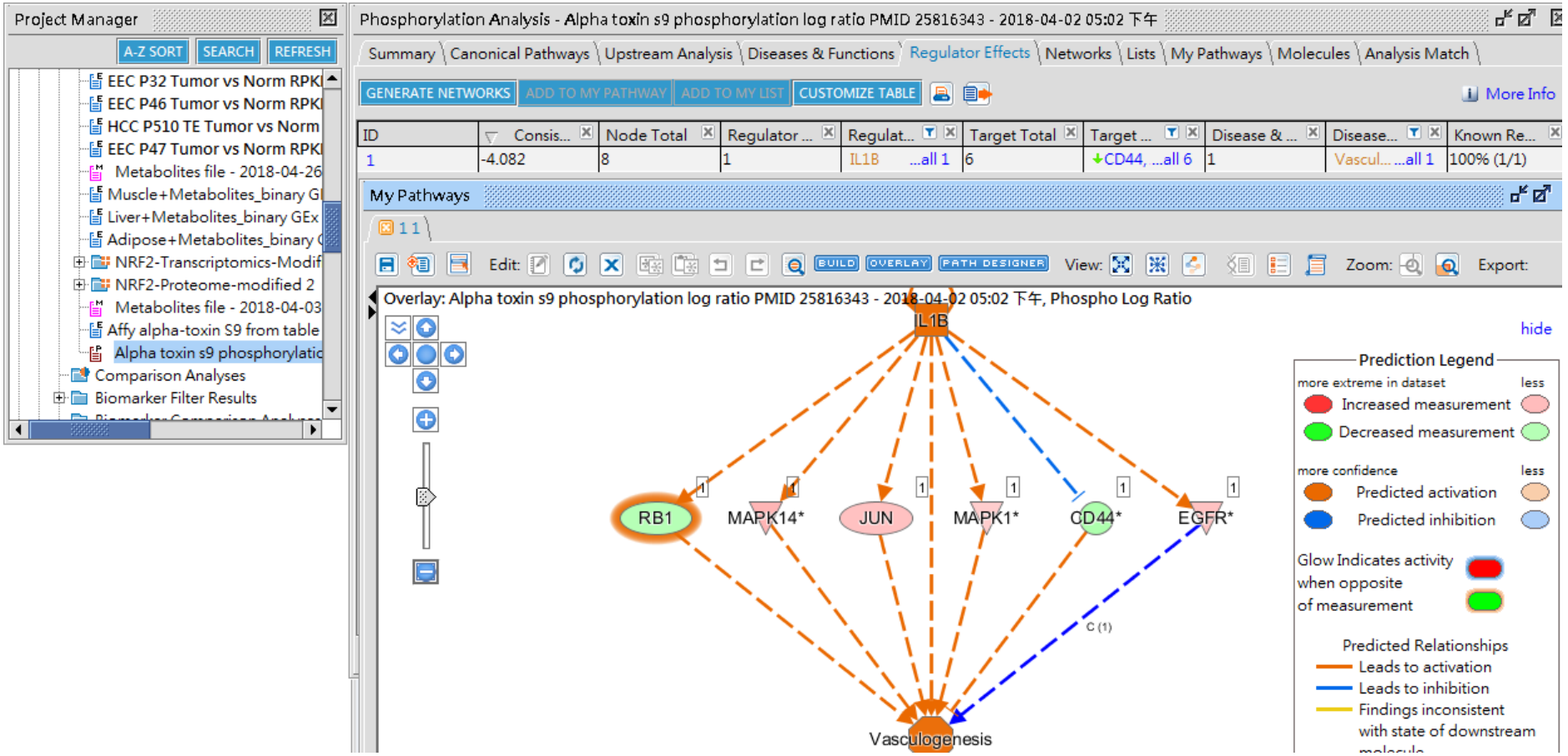
PhosphoProteomics Analysis

Find out how to understand your Phosphoproteomics Analysis and about the multiple ways of relating the molecules in your dataset to the body of information in the Ingenuity Knowledge Base.



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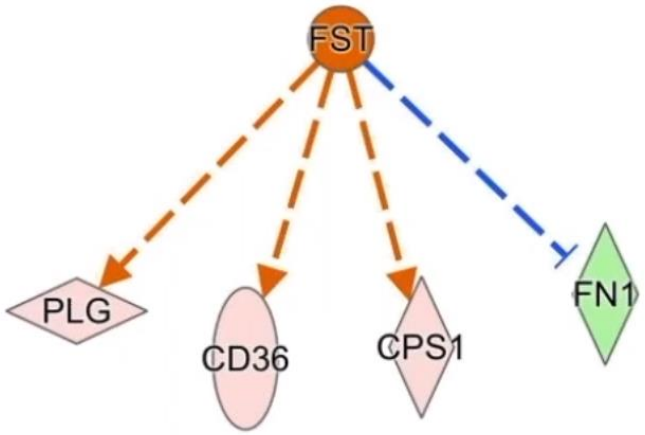
Gene expression data:

FST causes the up-or-down-regulation of target genes

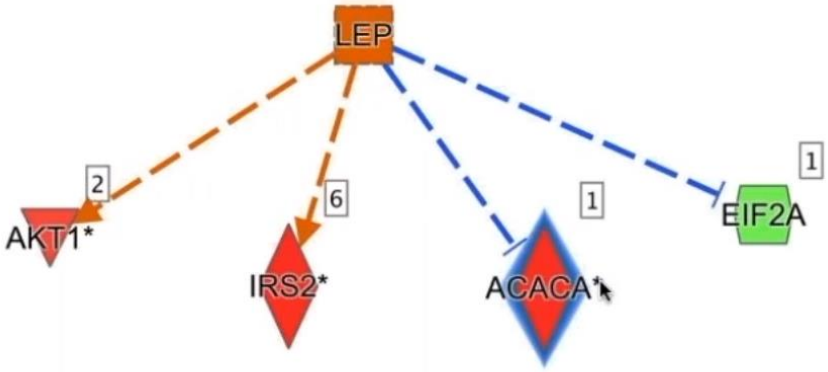


PLG, CD36, CPS1 are *up-regulated* by *activated* PST

FN1 is *down-regulated* by *activated* PST

Phosphorylation data:

LEP causes the up-or-down phosphorylation of target proteins



AKT1, IRS2 are *activated* by *increased* phosphorylation from *activated* LEP

EIF2A's activity is *inhibited* by *decreased* phosphorylation from *activated* LEP

ACACA has *increased* phosphorylation from *activated* LEP

The blue halo indicates that phosphorylation cause *inhibition* of ACACA's activity

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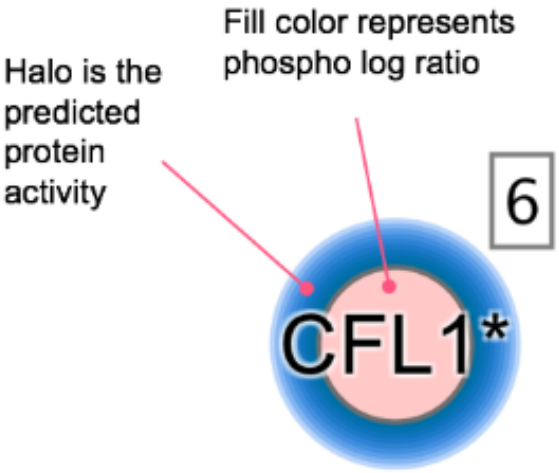
Halos indicate the protein's activity when it is *opposite* of the direction of phosphorylation



CFL1 has *increased* phosphorylation in dataset but prediction of *decreased* protein activity

GSK3B has *decreased* phosphorylation in dataset but prediction of *increased* protein activity

Find out how to understand your Phosphoproteomics Analysis and about the multiple ways of relating the molecules in your dataset to the body of information in the Ingenuity Knowledge Base.

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Q&A

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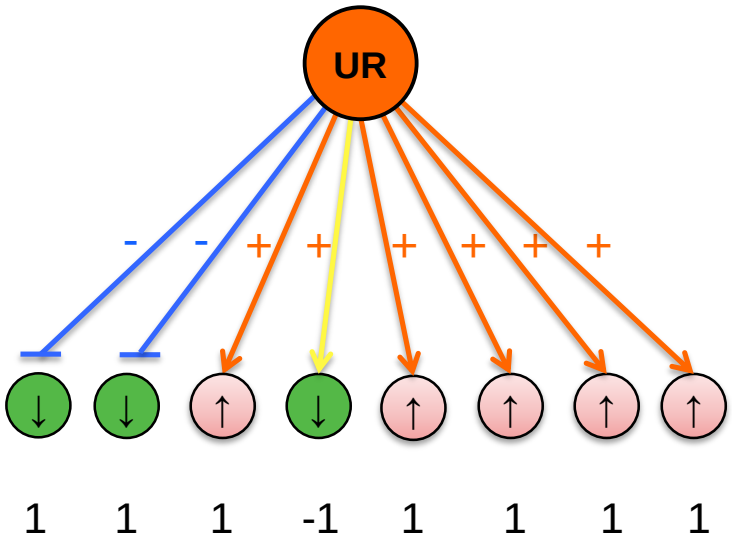
Predicting upstream regulators of a dataset



← Every possible TF & Upstream Regulator in the
Ingenuity Knowledge Base is analyzed

← Literature-based effect TF/UR has on downstream genes

← Differential Gene Expression (Uploaded Data)

← Predicted activation state of TF/UR:
1 = Consistent with activation of UR
-1 = Consistent with inhibition of UR

$$z = \frac{x}{\sigma_x} = \frac{\sum_i x_i}{\sqrt{N}} = \frac{N_+ - N_-}{\sqrt{N}}$$

$= (7\text{-}1)/\sqrt{8} = 2.12$ (=predicted activation)

- z-score is a statistical measure of the match between expected relationship direction and observed gene expression
- z-score > 2 or < -2 is considered significant

Note that the actual z-score is weighted by the underlying findings, the relationship bias, and dataset bias

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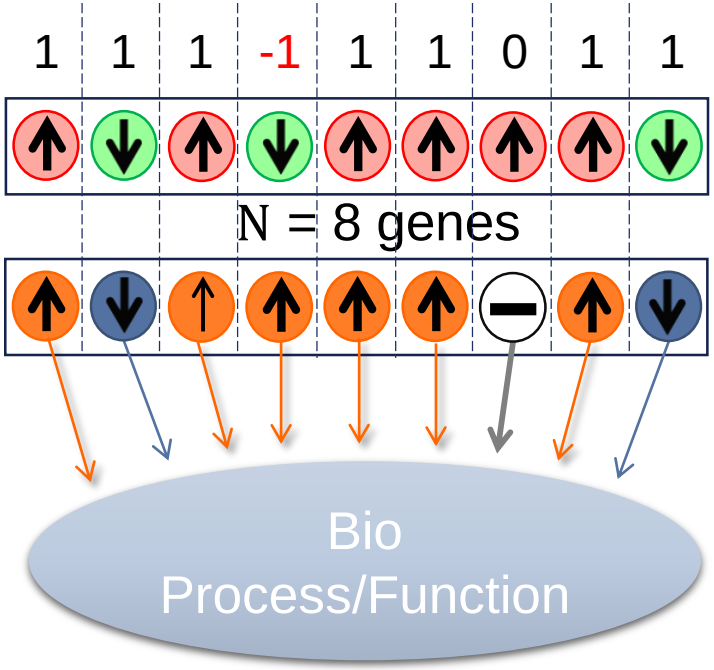
Downstream Effect Activation z–score

Statistical measure of correlation between the relationship direction and resulting gene expression



Differential gene expression
(Uploaded Data)

Effect genes have on a process or function
(Literature)

$$z = \frac{x}{\sigma_x} = \frac{\sum_i x_i}{\sqrt{N}} = \frac{N_+ - N_-}{\sqrt{N}}$$

z-score > 2 or < -2 is considered significant

Actual z-score *can* be weighted by relationship types, relationship bias, data bias

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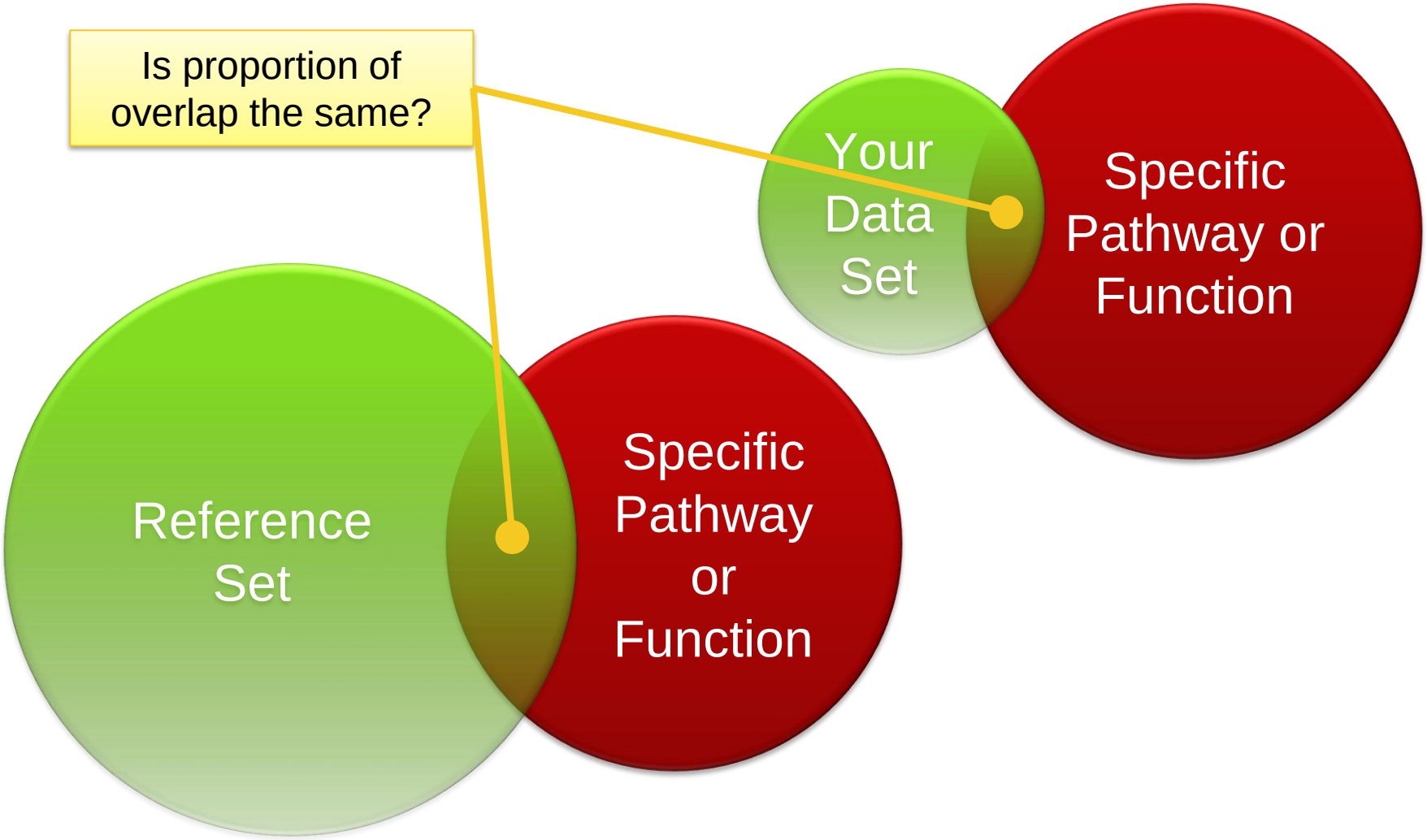
Determining Significance of Your Data to IPA



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Important note: Statistics in Biology

The Fisher's Exact Test

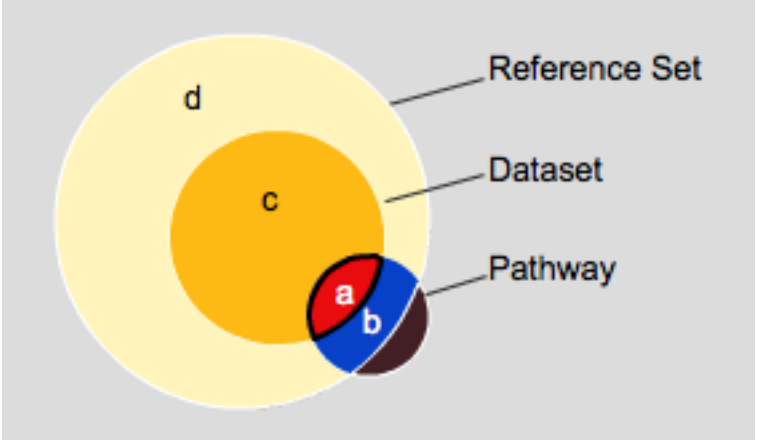
Given a list of differentially expressed genes in a dataset, what is the probability that the overlap with the set of genes on a particular pathway is by random chance?

The null hypothesis is that the association occurs purely by chance.

The Fisher's Exact Test is a way to test for significant associations

The test looks at the **number** of genes

a. That match between pathway and dataset
b. That are in pathway but did not match dataset
c. That are in dataset but did not match pathway
d. That were possible to assay in the experiment but are not in the pathway or dataset (this is usually called the "reference set" and is ~the set of all genes on the array platform)



The calculation returns a **p-value:**
From 0-1, where values <0.05 are generally considered significant)

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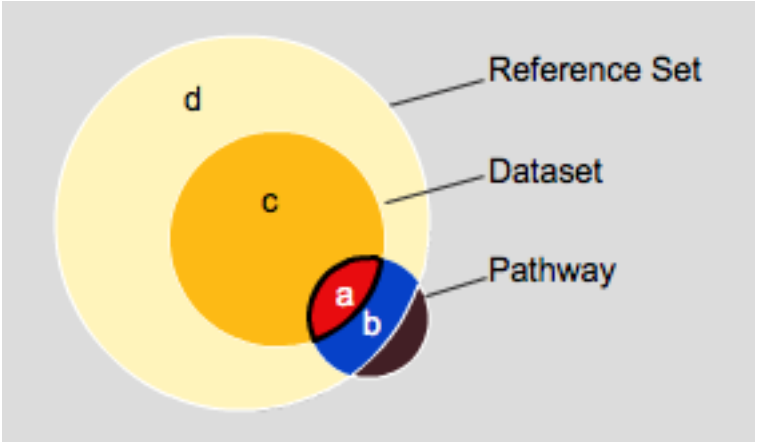
Statistics in Biology: Fisher's Exact, continued

If you had this situation:

- Dataset (significantly differentially expressed) of 286 genes
- Pathway of 81 genes
- Where 5 of the dataset genes overlap those in the pathway
- And the platform measured about 12,000 genes

What is the significance of that overlap?

$$\text{p-value} = \frac{(a+b)!(c+d)!(a+c)!(b+d)!}{(a+b+c+d)!a!b!c!d!}$$



a 5 Observed Overlap	b 76 Genes in pathway but not the dataset
c 281 Genes in dataset but not the pathway	d 11,715 Genes in reference set

$$p = \frac{(5+76)!\,(281+11715)!\,(5+281)!}{(76+11715)!\,(5+76+281+11715)!\,5!\,76!\,281!\,11715!}$$

$$= 0.043$$

Note: "!" is the factorial operator, where for example 3! = 3 x 2 x 1 = 6

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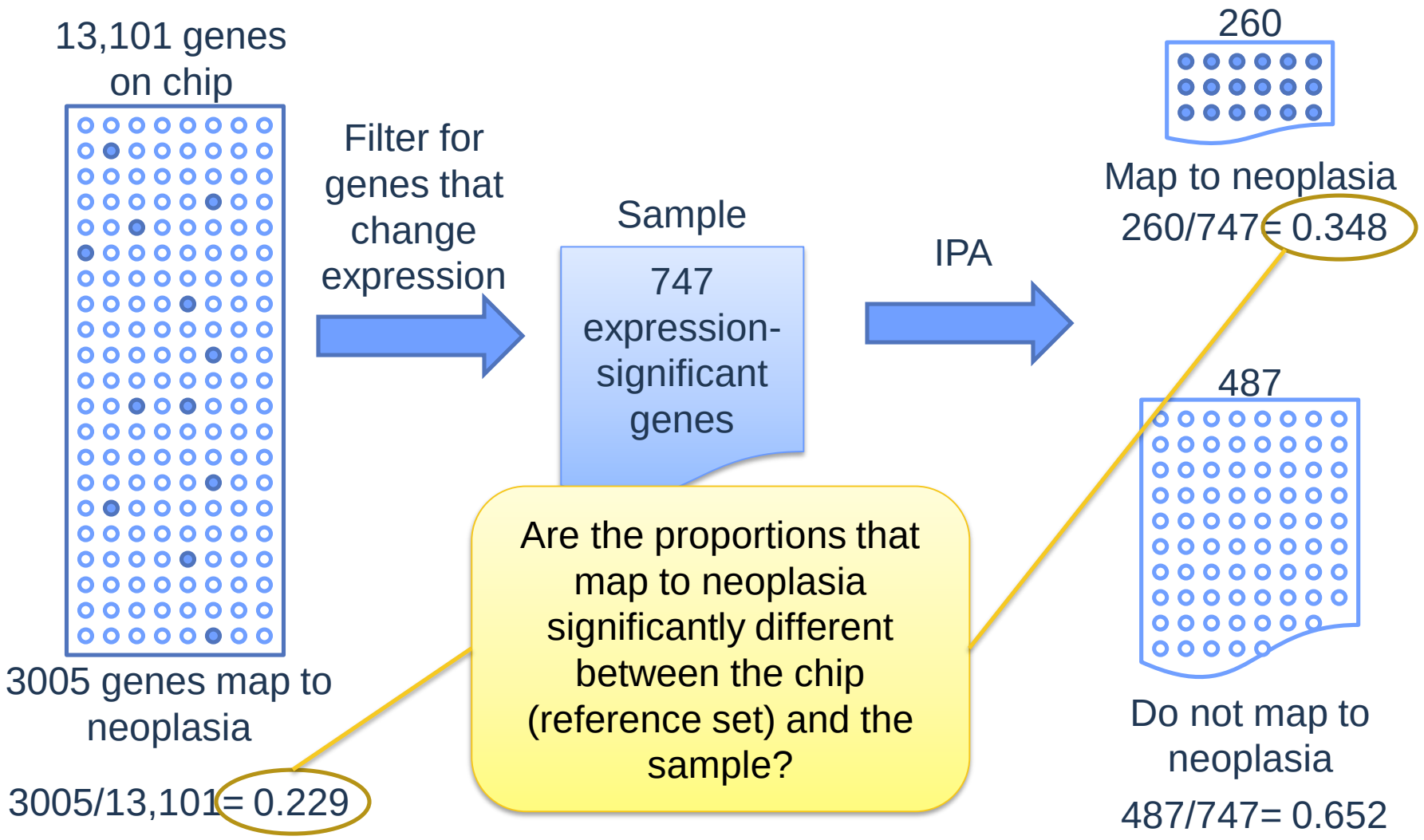
Mapping Colorectal Cancer Expression Data to the Function “Neoplasia”



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Calculating the Fisher's Exact Test

- For IPA, a 2x2 contingency table is created based on the total population, the sample, and how many genes map to the function/pathway. This table is used to calculate the Fisher's exact test.

	Neoplasia	Not Neoplasia	
In Sample	k	n - k	n
Not in Sample	m - k	N + k - n - m	N - n
	m	N - m	N

m= Total that map to function/pathway
N= Total
k= Number that map to function/pathway in sample
n= Total sample

What Does the p-Value Mean?

- The smaller the p-value, the less likely an observed proportion of genes mapping to a function or pathway is a result of chance. We then infer that there is a biological effect.
  - A p-value of 0.05 indicates that you should expect to observe the gene proportion mapping to a function or pathway by chance in one out of 20 (5 out of 100) repeated experiments of the same size

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What is the Fisher's Exact Test

- The Fisher's exact test is a statistical test, similar to the chi-square test, used for categorical data that result from classifying objects in two different ways
- It is used to examine the significance of the association (contingency) between the two kinds of classification
  - In IPA, the two categories are the uploaded dataset and a particular pathway or function
  - A Fisher's exact test is used instead of the chi-square test because the number of genes that map to a function or pathway can be less than five and would cause the chi-square test to be inaccurate

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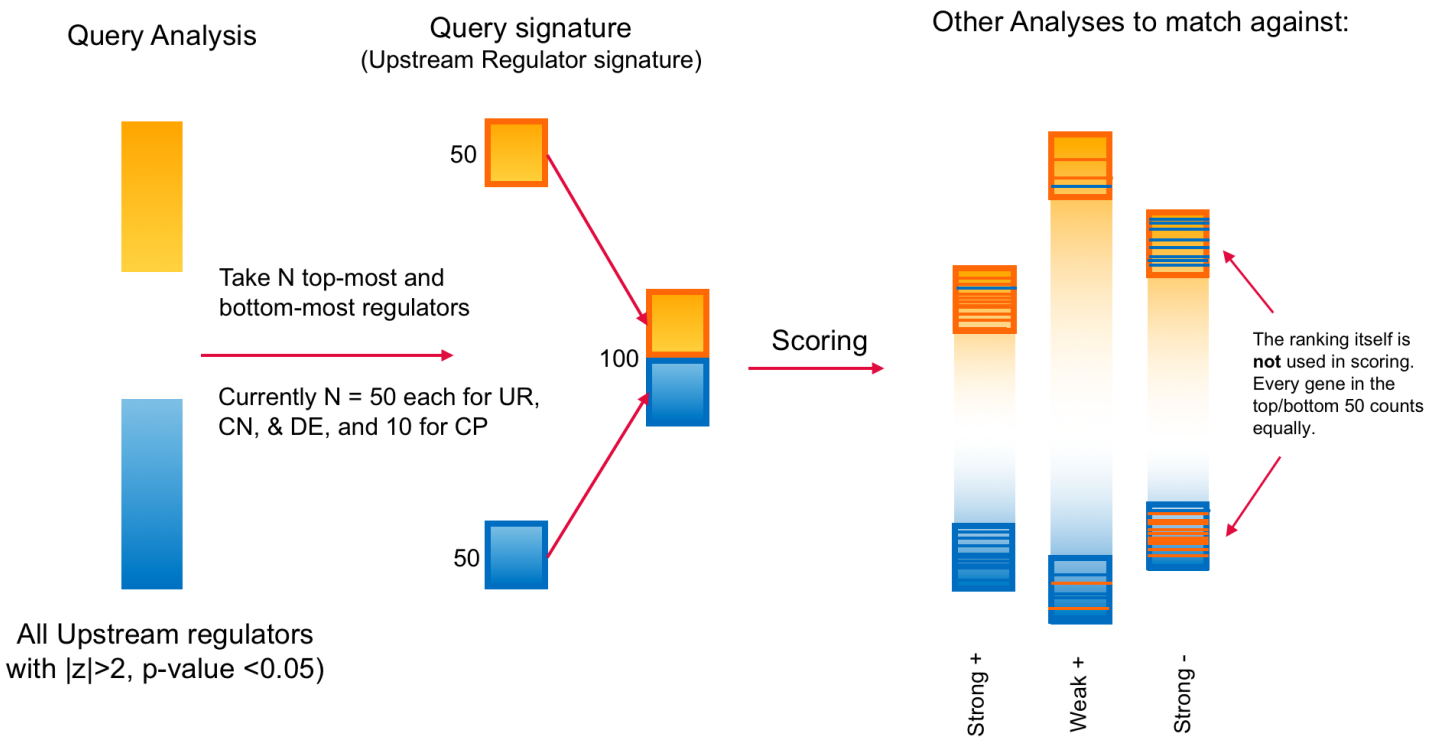
How signatures are created and compared

Canonical Pathways (up to 20 pathways)
Upstream Regulators (up to 100 regulators)
Causal Networks (up to 100 master regulators)
Diseases & Functions (up to 100 diseases or functions)

Example



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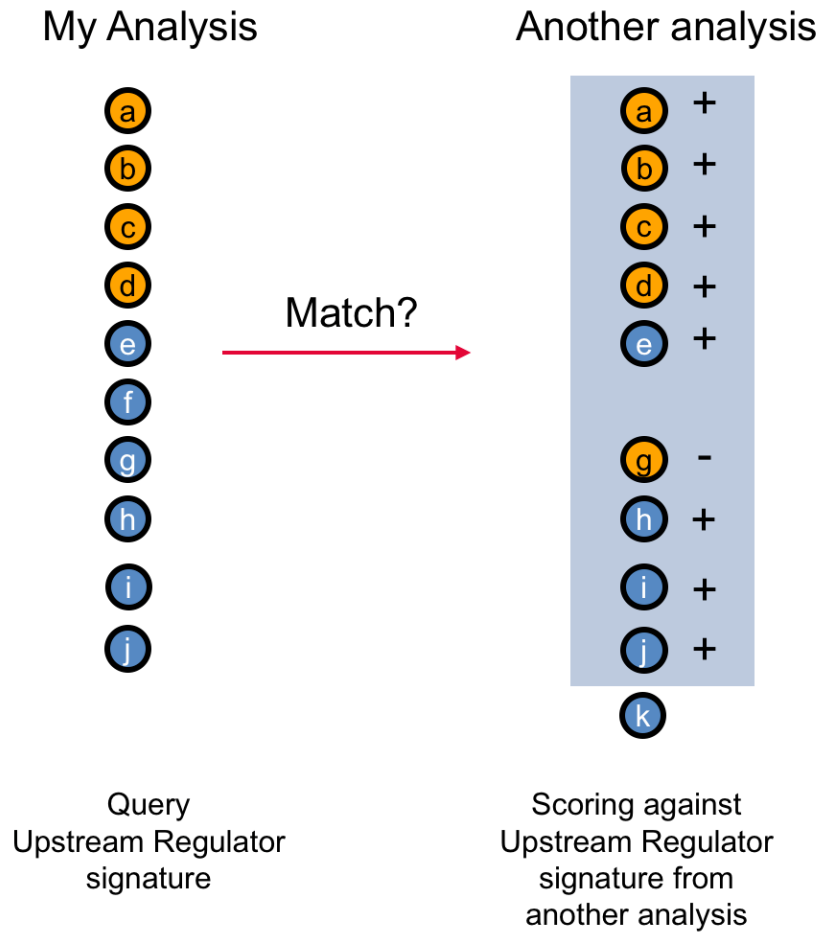
Analysis Match – explanation of z-score

How signatures are created and compared



$$Z = \frac{\text{matches - mismatches}}{\text{Square root of all matches}}$$

- z-score is a measure of the match between two patterns
- Assumes the pattern is created from two sets of entities where the sign of the matching entities is random

$= (8-1)/\sqrt{9} = 2.33$ (raw z-score)

Yes, it matches (because z>2)

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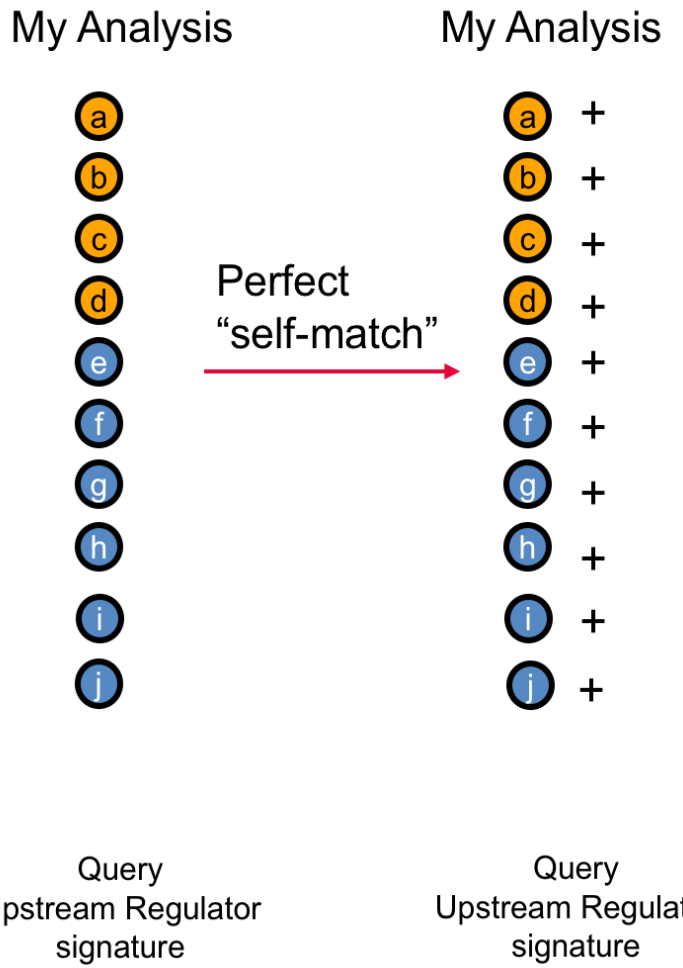
Steps for normalizing the z-score for a match percentage



First, find out the **max** possible z-score for a perfect match for this particular analysis:
= (10-0)/√10 = 3.16 (It’s really just equal to √N)

Then divide the **actual** z-score for the matching analysis by the calculated **max**.

In this example:
Normalized z-score for the matching analysis is 2.33/3.16 = 74%

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How are Overall scores calculated in Analysis match

For z-score

- Simply take average of percentages for all four entities

CP (z-score)	UR (z-score)	CN (z-score)	DE (z-score)	z-score overall score
50.00	60.91	53.85	40.49	51.31

Average of the four percentages

For p-value

- P-value percentage for entities are not reported
- Take the –log 10 of each p-value (if –log 10 of p-value is >50, then just set it to 50)
- Calculate % vs. the maximum possible p-value (self vs. self match)
- Take average of percentages for all four entities

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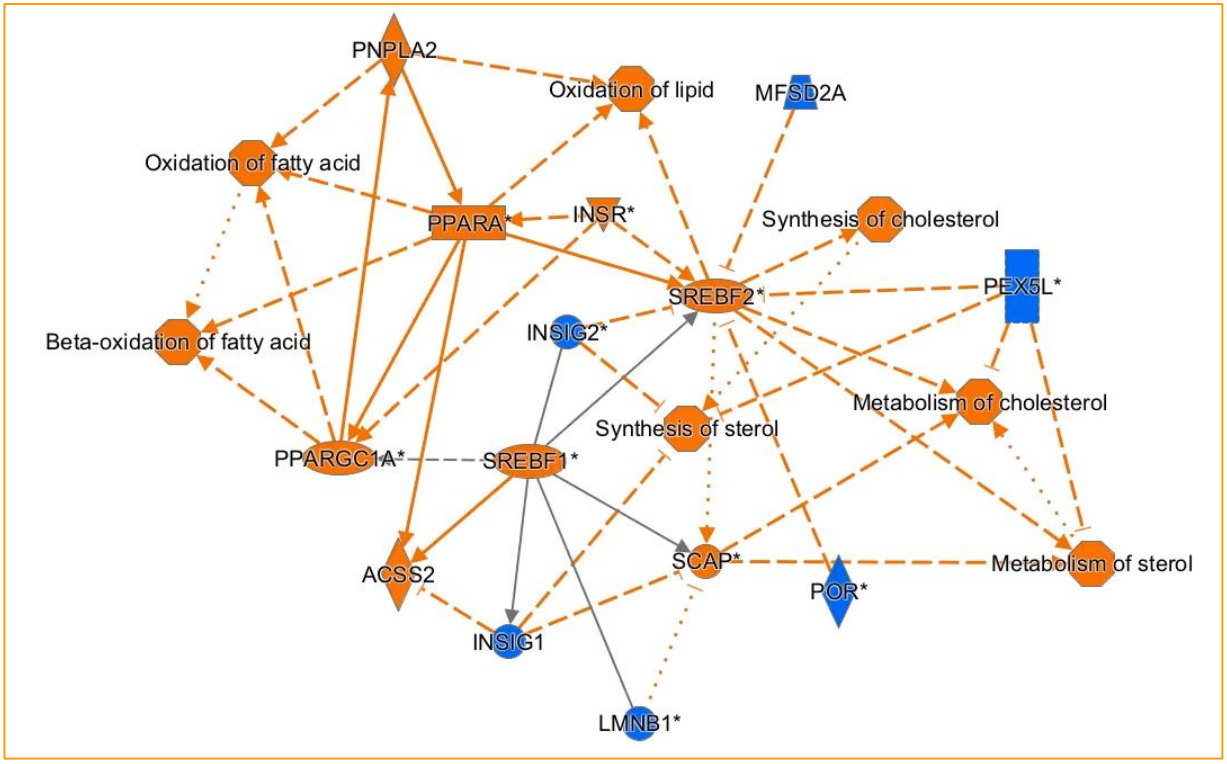
Graphical Summary

Graphical Summary結果:
將資料集最相關的生物主題以網路圖像呈現
(canonical pathways, upstream regulators, causal network master regulators, diseases, and biological functions)



Criteria for selection

- All entities:
  p-value < 0.05
- Diseases、Functions、Upstream regulators:
  z-score ≧ 2
- All molecules types (except chemicals)
- Activated nodes
  z-score ≧ 2
- Inhibited nodes
  z-score ≦ -2

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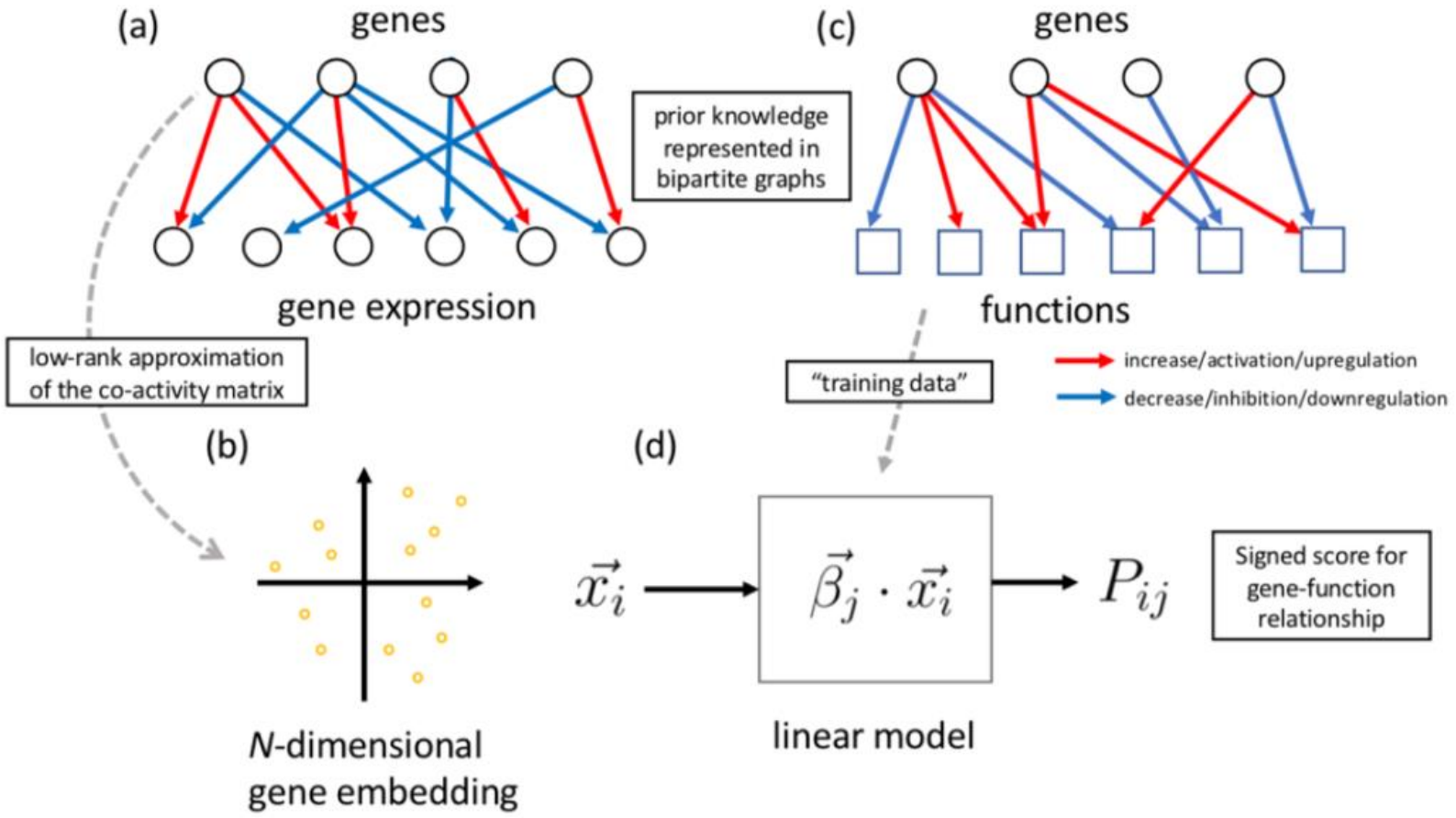
Content-based machine learning



This also applies to inferred **molecule-function relationships**, but in this case the predicted relationships can also be interpreted as being **causal**.

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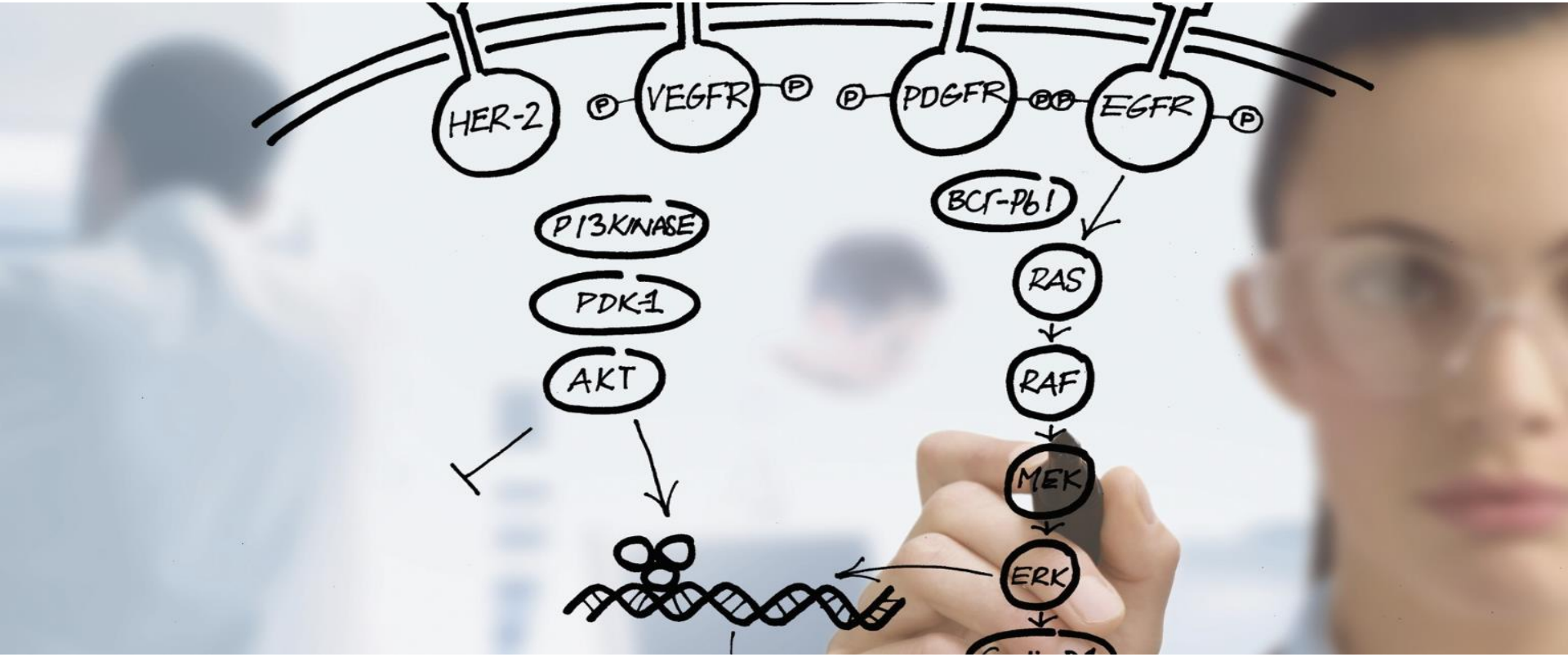

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Sample to Insight

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