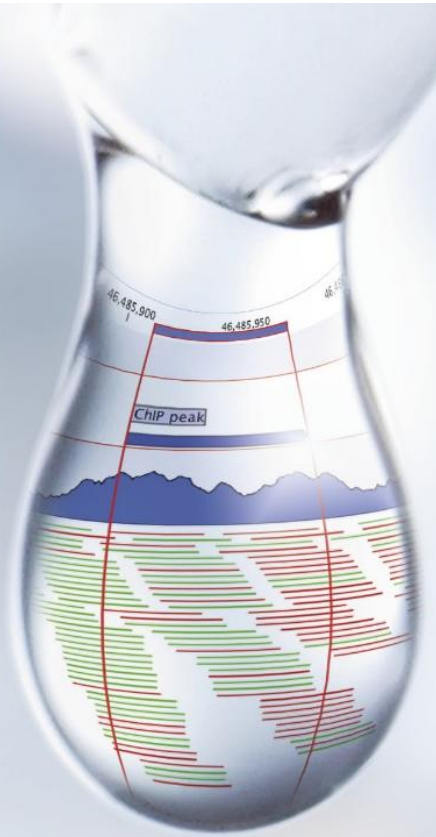
Translating Multi-Omics Data into Target Discovery and Translational Medicine



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System Requirements

Minimum Software Requirements

Windows OS	Windows 11 Windows 10 Windows 8
Browser	Microsoft Edge 94 or later Chrome 110 or later Firefox 91 or later Safari 16 or later
macOS	Sequoia Sonoma Ventura
Java (JRE)	JRE 1.8.0_xx or later

Minimum Hardware Requirements

- PC - 1.25GHz, 2GB RAM (for lightweight usage of IPA)*
- PC - 2GHz, 4GB RAM (Recommended)
- Mac - 1.25GHz, 2GB RAM (for lightweight usage of IPA)*
- Mac - 2GHz, 4GB RAM (Recommended)

Minimum Screen Resolution of 1280 x 800

*Lightweight usage of IPA includes Search, Build/Overlay operations and small dataset upload and analysis creation. For larger analyses and Comparison Analyses, IPA requires more memory.

For Causal Network Analysis, BioProfiler, IsoProfiler, Phosphorylation Analysis, Relationship Export, and Analysis Match-related features:

CoreTM i5 processor or equivalent running at 2 GHz or higher with 64-bit OS and Java, and at least 3 GB RAM free for Java. Screen resolution of at least 1280 x 800.

Notes:

1. We recommend that you install the IPA client on your computer with this installer: https://analysis.ingenuity.com/pa/installer/select. The installed IPA client still requires you to have internet access to launch but does *not require* you to install Java (a JRE) or to launch IPA from a web browser.

2. Alternatively, you can launch IPA using Java Web Start, which requires a recent version of Java installed on your computer. Oracle has changed its licensing terms for Java: https://www.java.com/en/download/. Therefore, please ensure you are following Oracle's terms and conditions for the Java version on your computer should you choose to launch IPA via Web Start, which is available at this link: https://analysis.ingenuity.com. Help on installing and/or launching IPA can be found at the following links:

   i. Mac: https://qiagen.my.salesforce-sites.com/KnowledgeBase/articles/Basic_Technical_Q_A/Running-IPA-on-Mac
   ii. Windows: https://qiagen.my.salesforce-sites.com/KnowledgeBase/articles/Basic_Technical_Q_A/Running-IPA-on-Windows

IPA Installer Download (ingenuity.com)

Agenda

Introduction to pathway analysis

What is QIAGEN Ingenuity Pathway Analysis

- Introduction of Ingenuity Pathway Analysis
- What's new in Ingenuity Pathway Analysis

Module 1 | IPA in Drug Discovery and Translational Medicine

Module 2 | Transcriptomics and Drug Mechanism of Action

- Case Study: BOLD-100 in Colorectal Cancer

Module 3 | miRNA Regulation and Natural Compound Mechanisms

- Case Study: Ugonin V in Chondrosarcoma

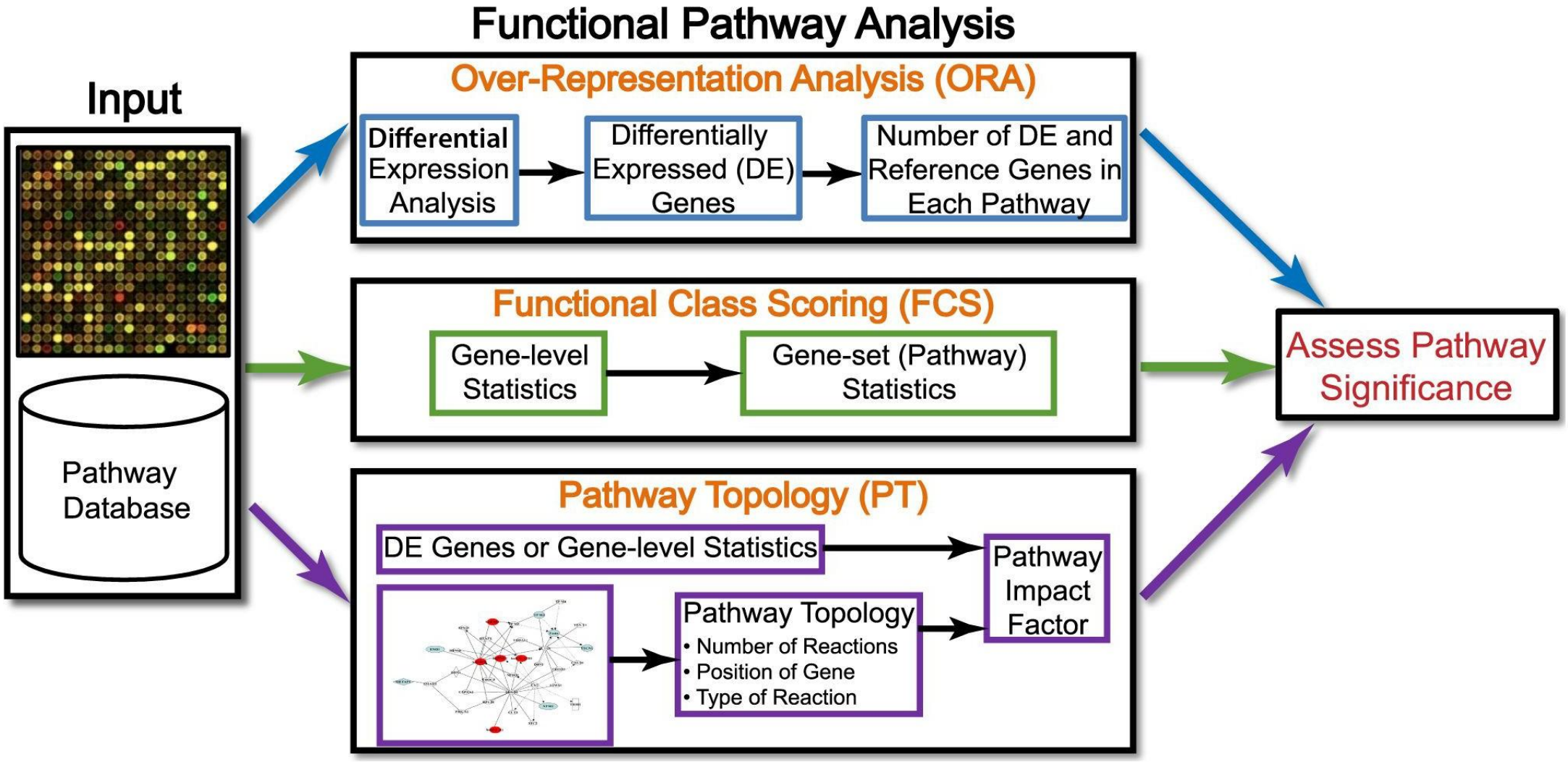
Module 4 | Comparative Analysis and Candidate Target Discovery

- Case Studies: Immunotherapy Resistance and Single-Cell Heterogeneity

Module 5 | Translational Applications: Drug Effect Prediction and Biomarker Discovery

- Case Study: BOLD-100 in Colorectal Cancer

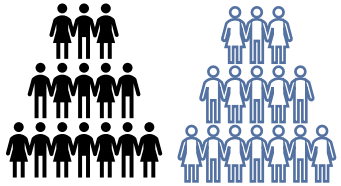
Introduction of pathway analysis

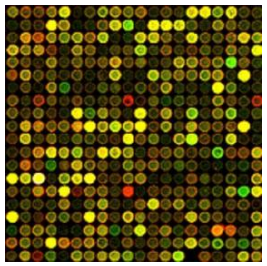


Khatri, Sirota, and Butte. *PLoS Comp Bio*. 2012.

Why are we using Qiagen Ingenuity Pathway analysis?

Your dataset





PDE6A
SLC6A14
LPCAT1
C2
CFB
REG4
CD55
TIMP1
DPP10
PDIA4
PRKG2
NAT8B
SHISA5
LCN2
CDH3
ACAT1
NAALADL1
APOBEC3B
NMT2
KYNU
TMEM63C
S100A11
PI3
CDC25B
CNNM2
CHRNA1
LRRN2
RMDN2
CNTFR
CDC14A
C7orf31
BACE2
CXCL1
SLC36A1
WDR78
PKM

Public /commercial database

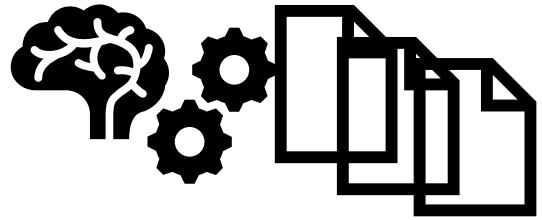
Drugs and chemicals

Pathway

Disease

Function

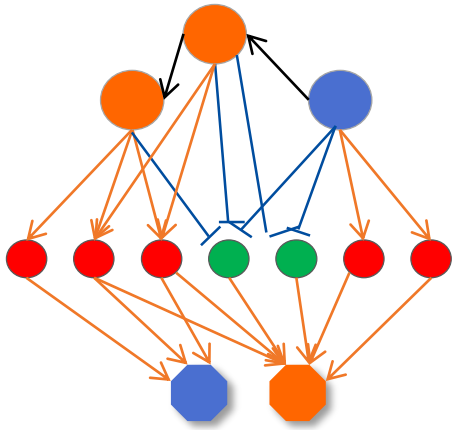
Network



ORA/FCS/Topology Pathway Analysis

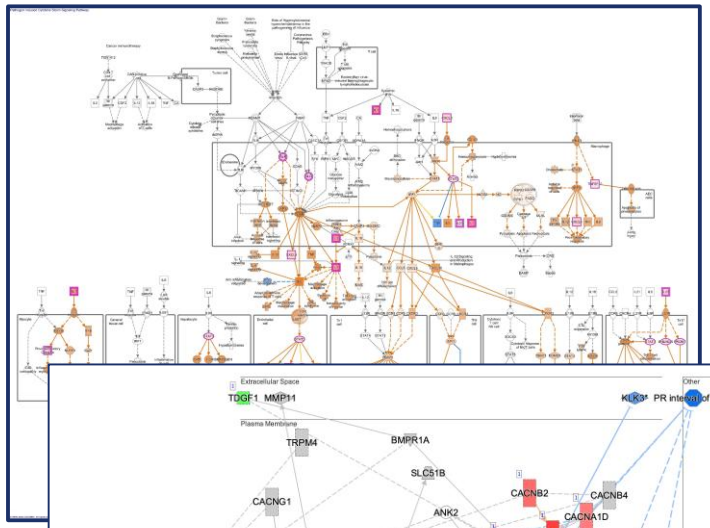
Machine learning

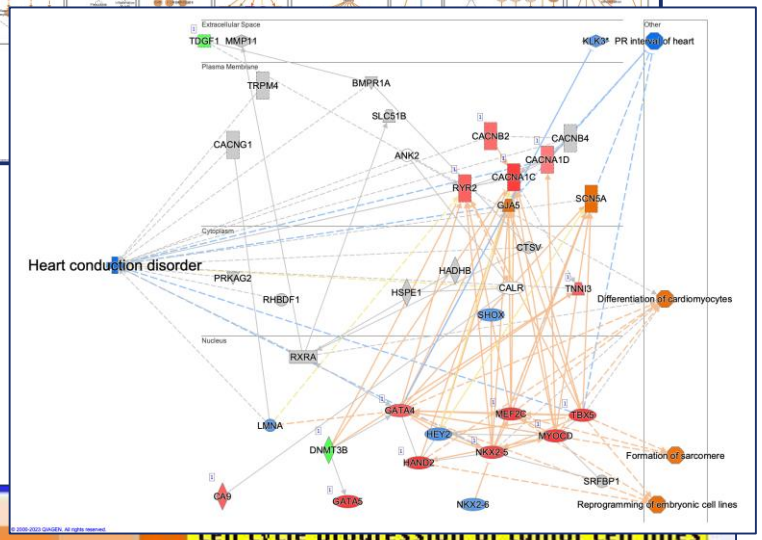
What do they relate to each other?

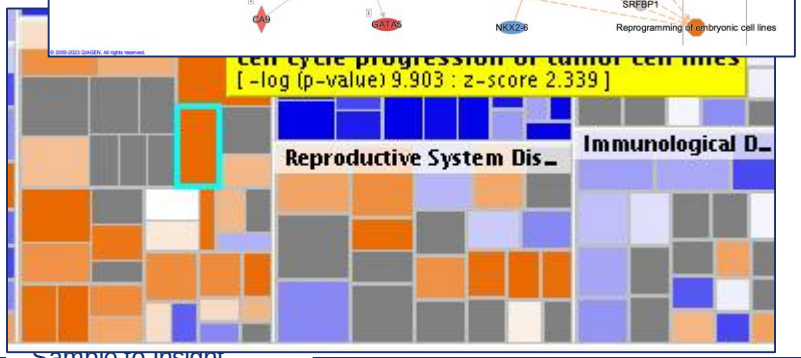


What are the relationship between each molecules?

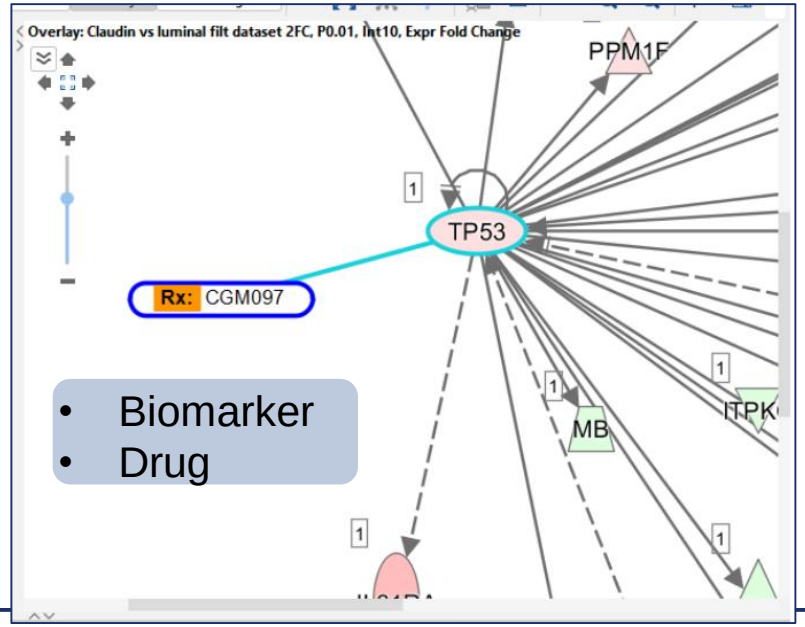
What Can We Achieve with IPA?

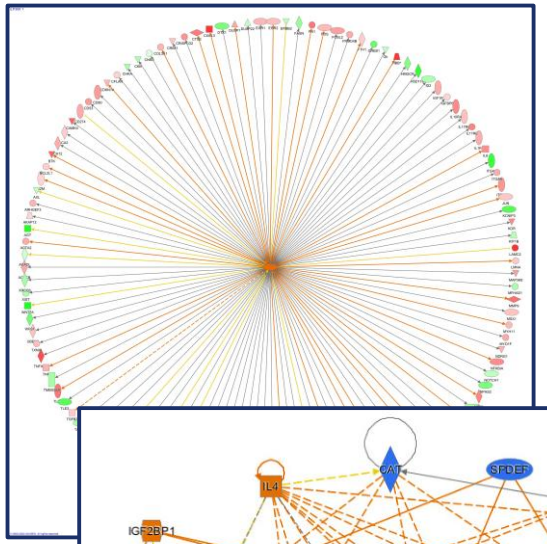


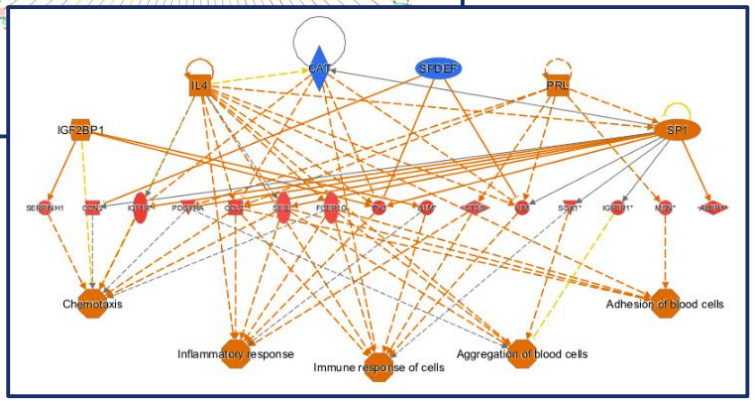


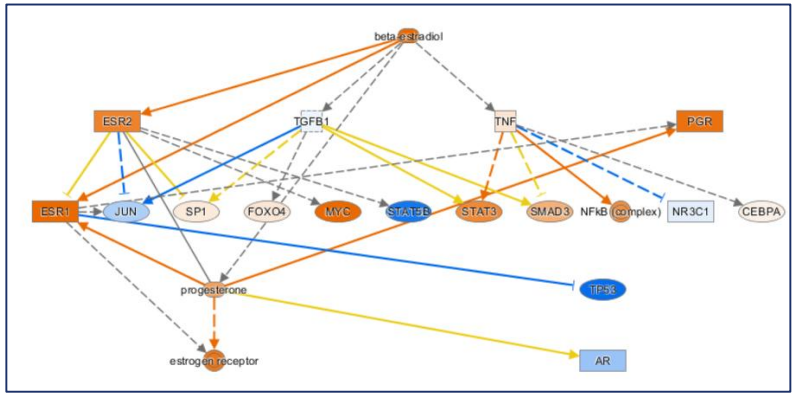


1. Canonical pathway
2. Machine Learning disease pathway
3. Disease and function
4. Upstream regulator
5. Regulate effect
6. Network





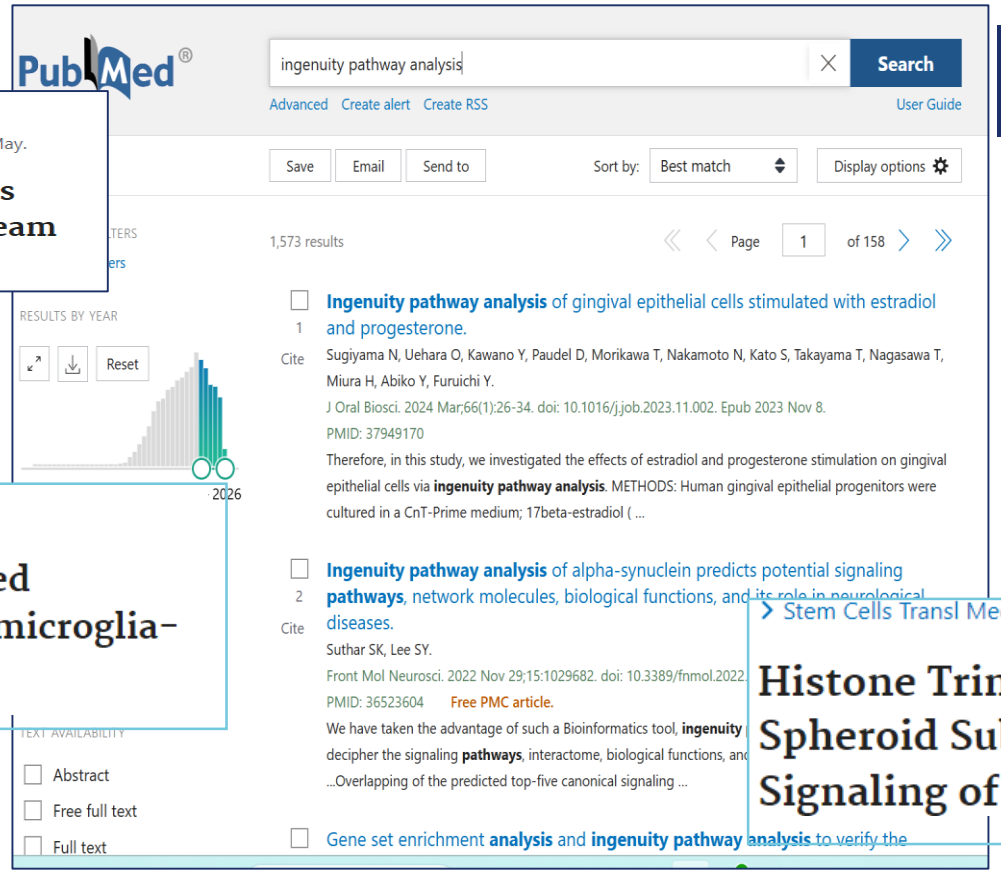




Publication using Qiagen Ingenuity Pathway Analysis

訊聯基因數位

From 2020-2026
1,537literatures



> Hepatol Commun. 2020 Mar 15;4(5):724-738. doi: 10.1002/hep4.1497. eCollection 2020 May.

Integrated GWAS and mRNA Microarray Analysis Identified IFNG and CD40L as the Central Upstream Regulators in Primary Biliary Cholangitis

GWAS

> J Neuroinflammation. 2024 Mar 20;21(1):69. doi: 10.1186/s12974-024-03065-z.

Deletion of Slc9a1 in Cx3cr1^{+} cells stimulated microglial subcluster CREB1 signaling and microglia–oligodendrocyte crosstalk

transcriptomic

> Stem Cells Transl Med. 2024 Mar 15;13(3):293-308. doi: 10.1093/stcltm/szad090.

Histone Trimethylations and HDAC5 Regulate Spheroid Subpopulation and Differentiation Signaling of Human Adipose-Derived Stem Cells

Single-cell RNA-seq

> J Allergy Clin Immunol. 2024 May;153(5):1268-1281. doi: 10.1016/j.jaci.2023.12.030. Epub 2024 Mar 29.

Galectin–10 in serum extracellular vesicles reflects asthma pathophysiology

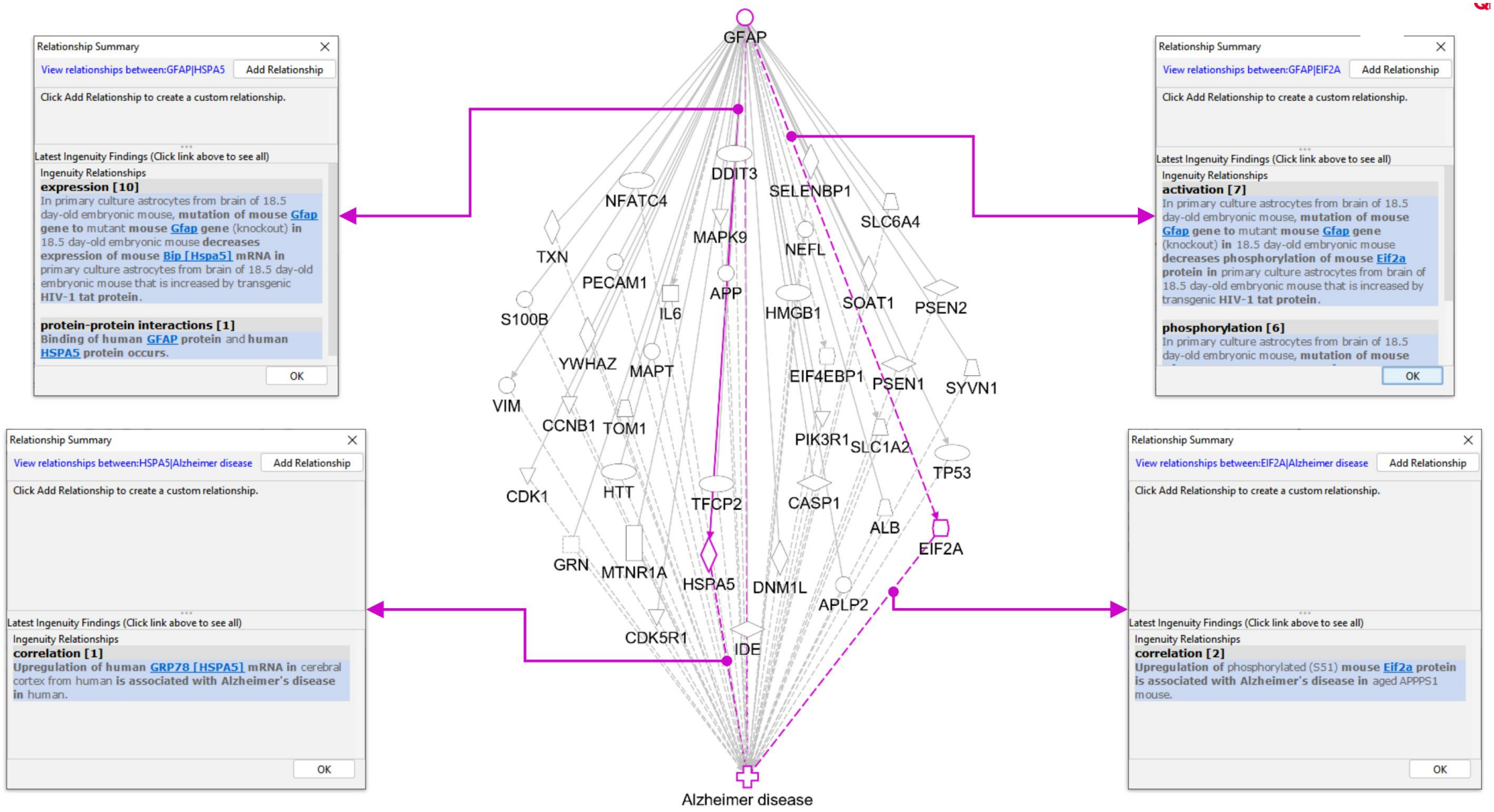
proteinomics

> Chin Med. 2022 Jun 15;17(1):71. doi: 10.1186/s13020-022-00632-5.

Serum metabolomics analysis of deficiency pattern and excess pattern in patients with rheumatoid arthritis

metabolomics

Every connection in IPA is backed by literature findings



Species Support within IPA

Fully supported:

Human

Mouse

Rat

What species identifiers are accepted for analysis by IPA?

- Atlantic Salmon (*Salmo salar*)
- Thale cress (*Arabidopsis thaliana)*
- Bat (Greater horseshoe bat, *Rhinolophus ferrumequinum*)
- Brewer's yeast (*Saccharomyces cerevisiae)*
- Cat (domestic, *Felis catus*)
- Chicken (*Gallus gallus*)
- Chimpanzee (*Pan troglodytes*)
- Chinese hamster (*Cricetulus griseus*)
- Cow (*Bos taurus*)
- Crab-eating macaque (*Macaca fascicularis*)
- Dog (*Canis lupus familiaris*)
- Fission yeast (*Schizosaccharomyces pombe)*
- Fruit fly (*Drosophila melanogaster*)
- Golden hamster (*Mesocricetus auratus*)
- ✓ Guinea pig, domestic (*Cavia porcellus*)
- ✓ Horse (*Equus caballus*)
- ✓ Human (*Homo sapiens*)
- ✓ Mouse (*Mus musculus*)
- ✓ Pig (*Sus scrofa*)
- ✓ Rabbit (*Oryctolagus cuniculus*)
- ✓ Rainbow trout (*Oncorhynchus mykiss*)
- ✓ Rat (*Rattus norvegicus*)
- ✓ Rhesus Monkey (*Macaca mulatta*)
- ✓ Roundworm (*Caenorhabditis elegans)*
- ✓ Sheep (*Ovis aries*)
- ✓ Western clawed frog (*Xenopus tropicalis*)
- ✓ Zebrafish (*Danio rerio*)
- ✓ Domestic goat
- ✓ three-spined stickleback

Orthologs Gene from NCBI Eukaryotic Genome Annotation Pipeline

Supported Identifiers for Data Upload

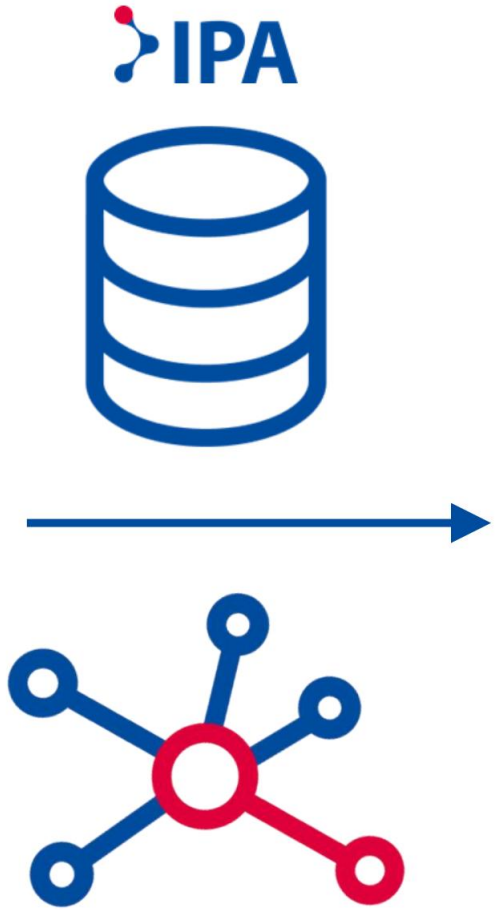
Get more complete mapping during dataset upload!

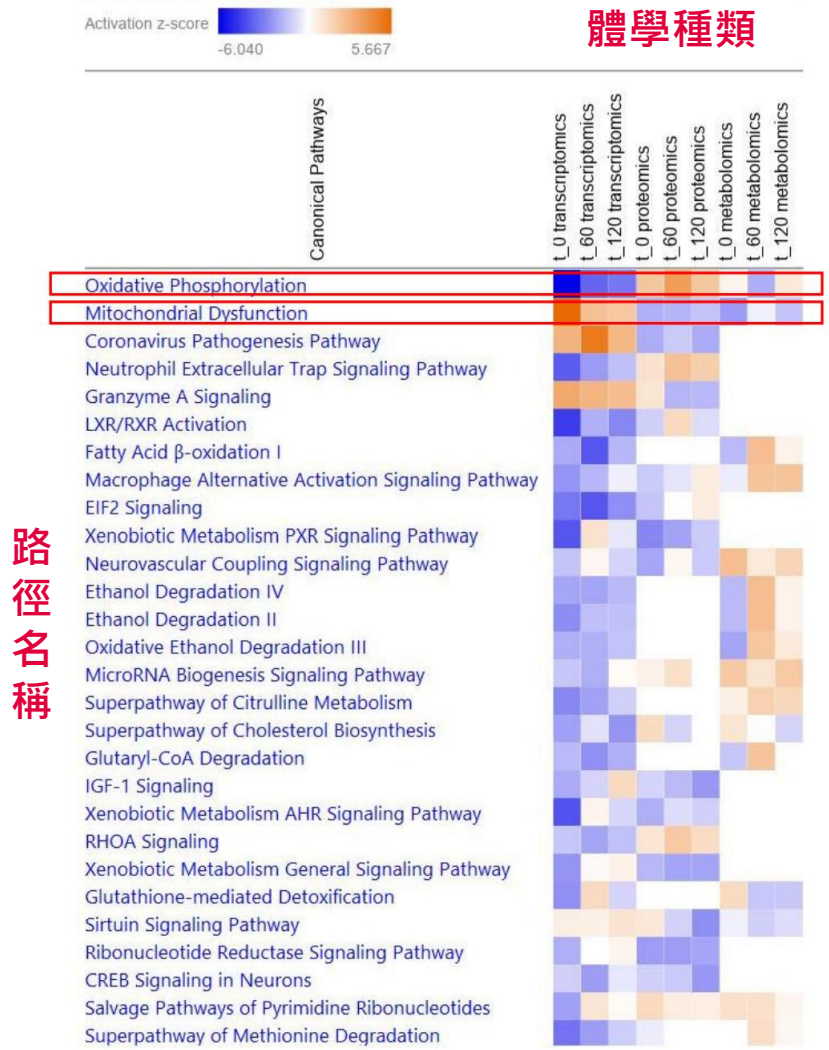
Vendor IDs	Gene	Protein	Transcript	microRNA	SNP	Chemical
Affymetrix (na36)	Entrez Gene (2023/8)	GenPept	Ensembl (110)	miRbase (mature)	Affy SNP IDs	CAS Registry Number
Agilent	GenBank (257)	International Protein Index (IPI)	RefSeq (human、mouse)	miRBase (stemloop)	dbSNP	HMDB
Life Tech (ABI)	Symbol-human (HUGO/ HGNC, EG)	UniProt/ Swiss-Prot Accession (2022_02)	UCSC (hg18)			KEGG
Codelink	Symbol- mouse (EG)		UCSC (hg19)			PubChem CID
Illumina	Symbol- rat (EG)		UCSC (hg38)			
Ingenuity	GI Number					
	UniGene					

Multi-omics data analysis using QIAGEN IPA

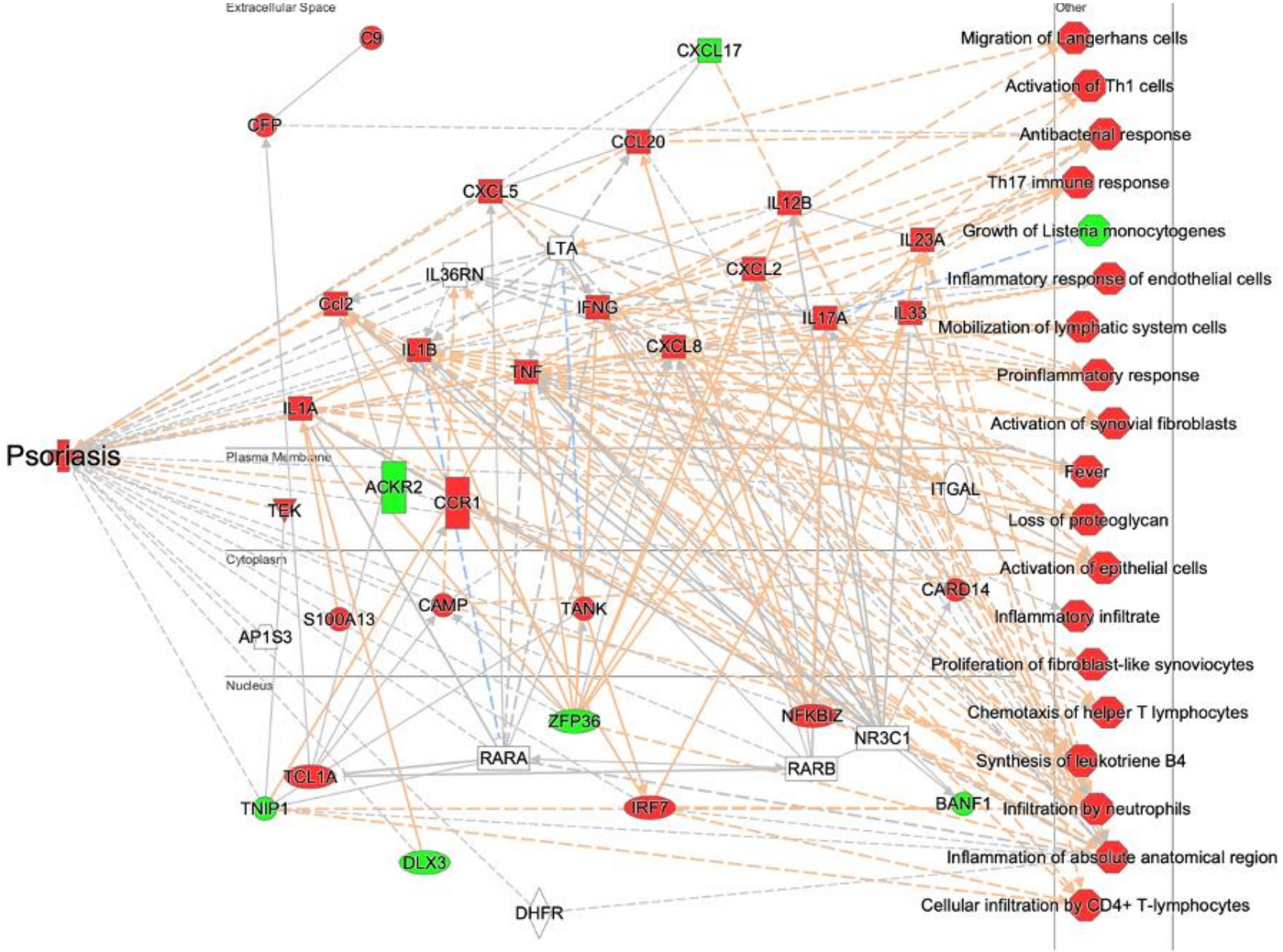
Omics data type

- RNA-seq
- scRNA-seq
- Microarray
- Nanostring
- qPCR
- ChIP-seq
- Proteomics
- Metabolomics
- RNAi
- CRISPR
- WGS/WES etc.

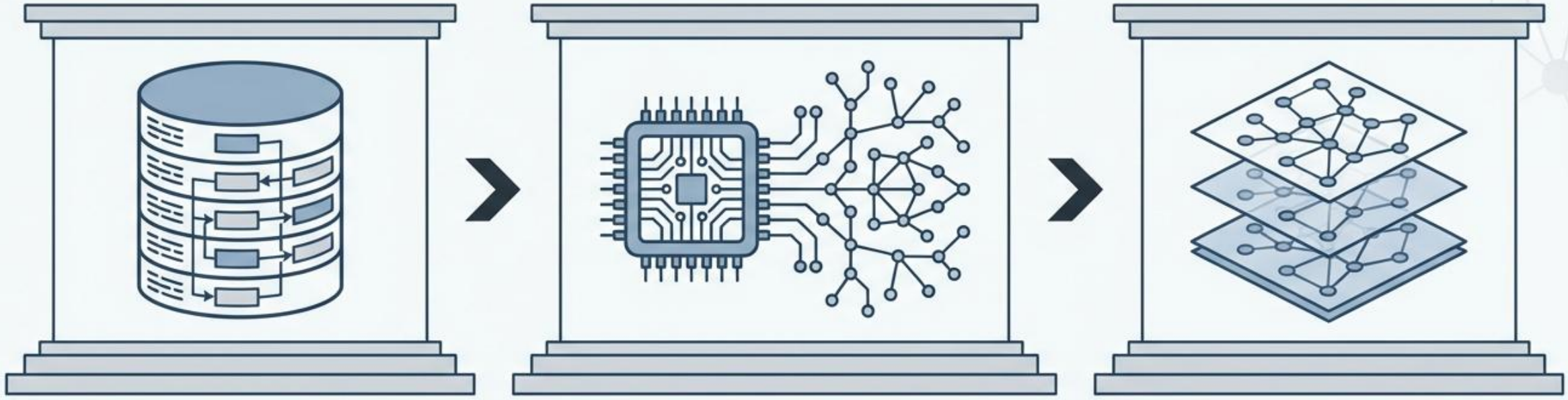




Real-World Application: The Psoriasis Network



Birding Global Literature with Empirical Data



The Source: QIAGEN Knowledge Base

Mining decades of **causal findings.**

The Engine: Machine Learning Generation

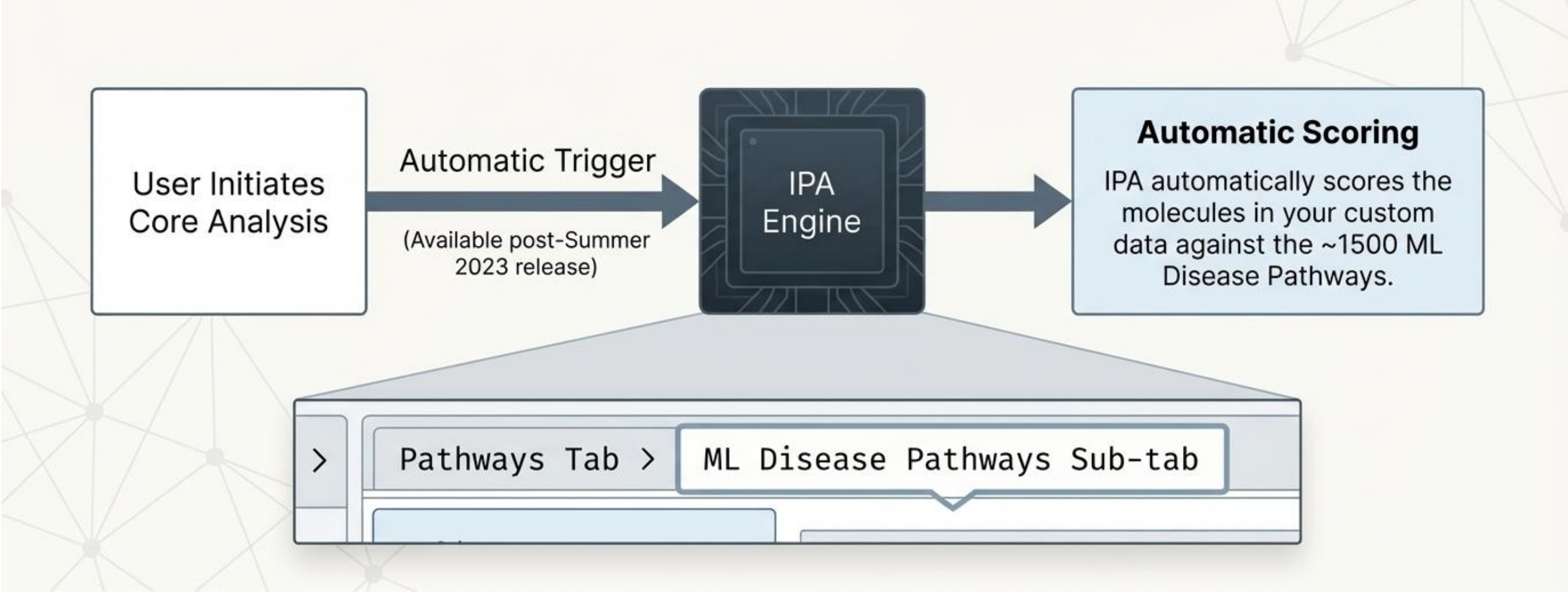
Automated creation of **~1500 disease, phenotype,** and **function pathways** to prioritize **key causal genes.**

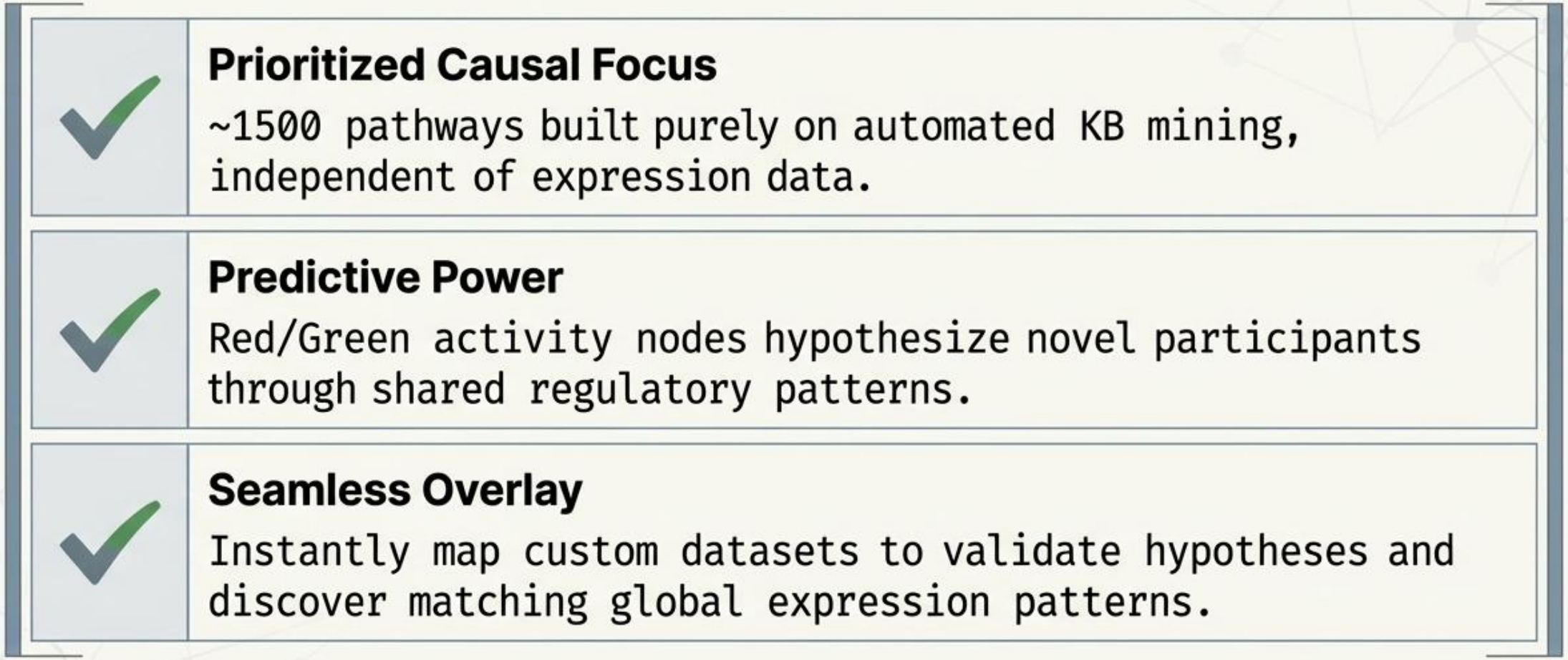
The Application: Data Overlay

Mapping **custom expression datasets** onto **predictive networks** to uncover **novel etiology.**

ML Disease Pathways visualize a **human-readable set** of the most important **causally connected genes**—revealing **known players** and inferring **novel participants.**

Directly through Core analysis





Prioritized Causal Focus

~1500 pathways built purely on automated KB mining, independent of expression data.

Predictive Power

Red/Green activity nodes hypothesize novel participants through shared regulatory patterns.

Seamless Overlay

Instantly map custom datasets to validate hypotheses and discover matching global expression patterns.

Help shape the algorithm. Please use the link at the top of the main IPA window.

QIAGEN IPA Analysis Match and Land Explorer

ArrayExpress, GEO, TCGA, SRA, LINCS, etc.

Processing, curation and QA

Journal articles and databases such as Clinical Trials, COSMIC, MGD,OMIM , etc.

Curated Findings

Land Explorer

- Explore gene expression levels
- Determine where a target is differentially expressed
- Understand how 'omics data influences survival
- Identify mutation status of a target

QIAGEN OmicSoft Studio

141,000+ comparison

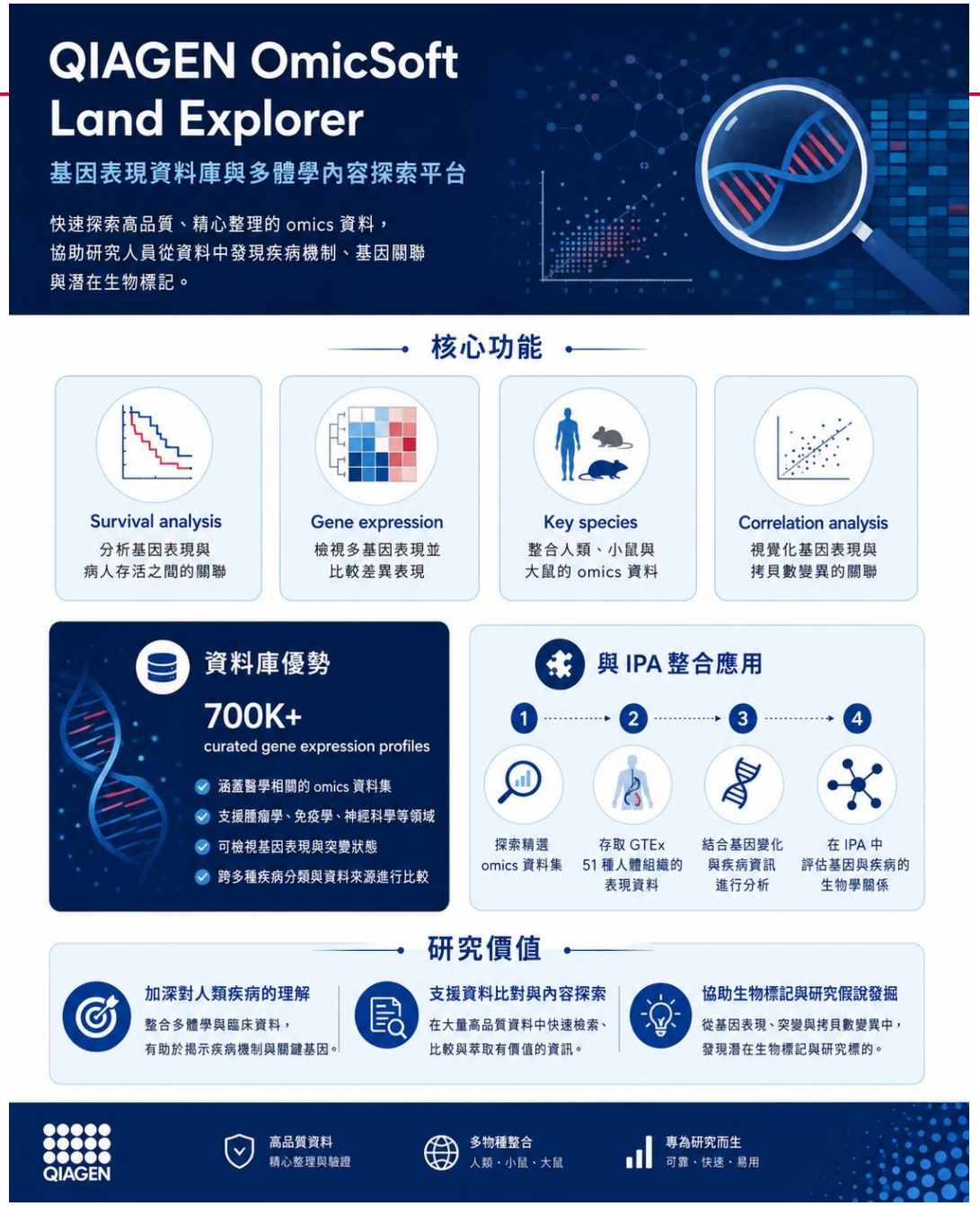
Ingenuity Pathway Analysis

- Explore biological findings in public datasets
- Build confidence in your analysis results
- Make unexpected insights into shared mechanisms between studies
- "Anti-matches" may provide insights

OmicSoft datasets

246,776 total datasets from OmicSoft with 15,001 datasets newly added. A new source called NCI Patient-Derived Models has been added in this release derived from this source: https://pdmr.cancer.gov/ .

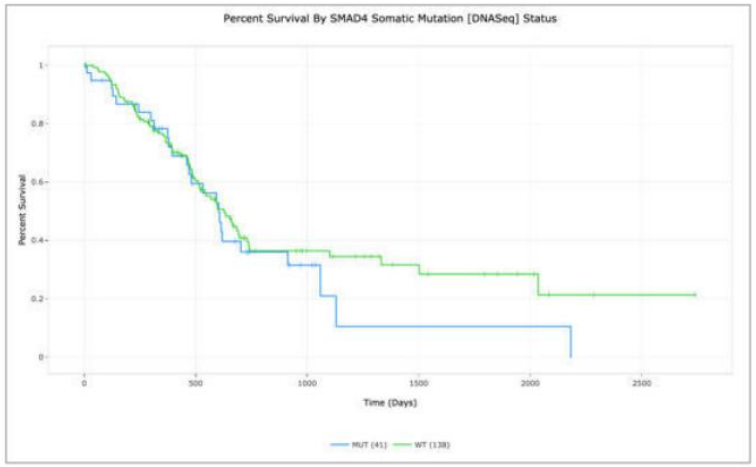
Land	Repository	Datasets Q1 2025	Datasets Q2 2025	Increase
DiseaseLand	HumanDisease	38,710	39,036	326
	MouseDisease	28,784	29,355	571
	RatDisease	10,264	10,269	5
	LINCS	25,880	25,880	
OncoLand	OncoHuman	24,972	25,262	290
	OncoMouse	1,516	1,516	
	TCGA	4,854	4,854	
	ENCODE RNA Binding	486	486	
	ClinicalProteomicTumor	2,978	2,978	
	NCBI Patient-Derived Models		552	552
Single Cell Land	SingleCellHuman	194	194	
	SingleCellHumanUmi	77,140	81,140	4,000
	SingleCellHumanHCL	1,469	1,469	
	SingleCellMouse	81	81	
	SingleCellMouseUmi	13,135	22,392	9,257
Normal Cells and Tissues	Human Tissues (GTEx)	1,312	1,312	


QIAGEN OmicSoft Land Explorer
基因表現資料庫與多體學內容探索平台
快速探索高品質、精心整理的 omics 資料，
協助研究人員從資料中發現疾病機制、基因關聯
與潛在生物標記。
核心功能
Survival analysis
分析基因表現與病人存活之間的關聯
Gene expression
檢視多基因表現並比較差異表現
Key species
整合人類、小鼠與大鼠的 omics 資料
Correlation analysis
視覺化基因表現與拷貝數變異的關聯
資料庫優勢
700K+
curated gene expression profiles
涵蓋醫學相關的 omics 資料集
支援腫瘤學、免疫學、神經科學等領域
可檢視基因表現與突變狀態
跨多種疾病分類與資料來源進行比較
與 IPA 整合應用
1
2
3
4
探索精選 omics 資料集
存取 GTEx 51 種人體組織的表現資料
結合基因變化與疾病資訊進行分析
在 IPA 中評估基因與疾病的生物學關係
研究價值
加深對人類疾病的理解
整合多體學與臨床資料，有助於揭示疾病機制與關鍵基因。
支援資料比對與內容探索
在大量高品質資料中快速檢索、比較與萃取有價值的資訊。
協助生物標記與研究假說發掘
從基因表現、突變與拷貝數變異中，發現潛在生物標記與研究標的。
QIAGEN
高品質資料
精心整理與驗證
多物種整合
人類、小鼠、大鼠
專為研究而生
可靠、快速、易用

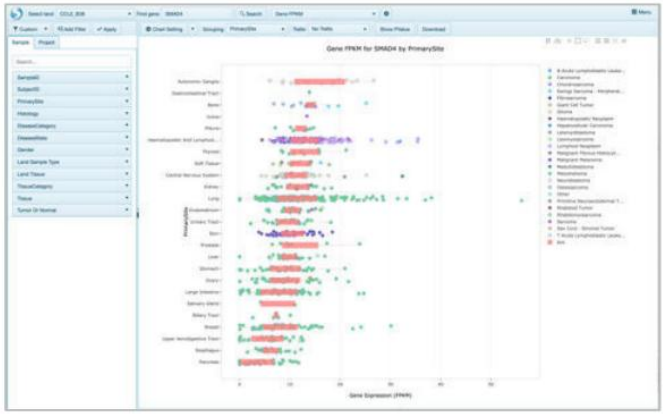
IPA with OmicSoft Land Explorer

Expression in Rat, Mouse, and Human Disease

Mutation frequency

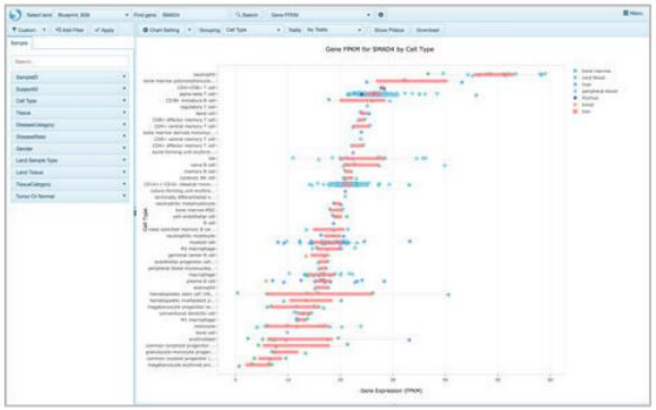


Survival plots



Cell line expression

Tumor expression



Hematopoietic expression (BluePrint)

IPA Interpret Result

QIAGEN IPA Interpret | Analysis

Help Gene Chen

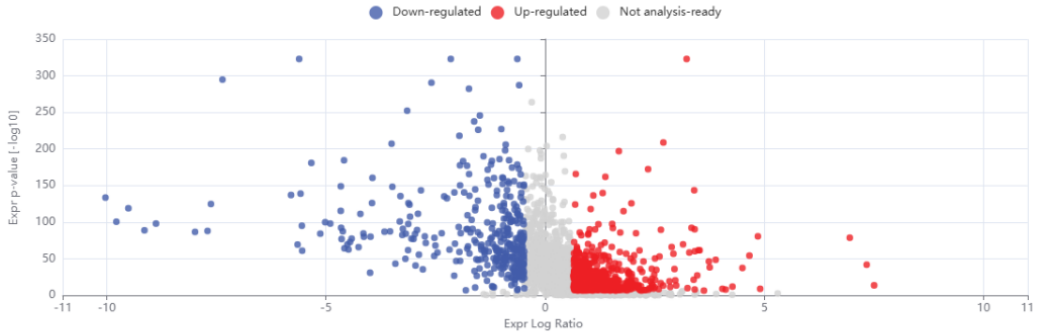
View Details →

Dataset

992 genes passed cutoffs (356 down and 636 up)

Cutoffs: Expr Other >1.0

X Axis: Choose an option Y Axis: Choose an option

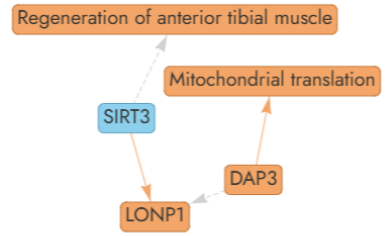


Dataset molecules

Name	Entrez Gene	Identifier	Expr p-value	Expr Log Ratio	Molecule Type
Filter	Filter	Filter	Filter ≤	Filter abs. ≥	Select or type to filter
A2M	alpha-2-macroglobulin	ENSG00000175899.14	1.32e-26	0.59	other
A2M-AS1	A2M antisense RNA 1	ENSG00000245105.4	0.20	0.69	other
AAK1	AP2 associated kinase 1	ENSG00000115977.19	2.15e-34	0.37	kinase
ABCA1	ATP binding cassette subfamily A member 1	ENSG00000165029.16	6.37e-4	0.49	transporter
ABI3	ABI family member 3	ENSG00000108798.9	1.28e-33	-0.67	other
ABL2	ABL proto-oncogene 2, non-receptor tyrosine kinase	ENSG00000143322.21	4.13e-6	-1.20	kinase

View Details →

Graphical Summary



AI suggestion

Mitochondrial Proteostasis and Muscle Regeneration: A DAP3–SIRT3–LONP1 Axis

AI-Suggested

Mitochondrial Translation Control via DAP3

The network directly links increased DAP3 activity to increased mitochondrial translation, indicating that DAP3 acts as a positive regulator of protein synthesis within mitochondria. This is consistent with DAP3's known role as a component of the mitochondrial ribosome, where it influences assembly and function of the translation machinery. The directional edge from DAP3 to mitochondrial translation suggests that changes in DAP3 levels upstream can modulate the rate or efficiency of mitochondrial protein production, thereby shaping respiratory chain biogenesis and overall mitochondrial function.

Mitochondrial Proteostasis Regulation through LONP1

Both increased DAP3 and decreased SIRT3 converge on increased LONP1 activity, highlighting LONP1 as a central node in mitochondrial proteostasis. LONP1 is a key ATP-dependent protease that degrades misfolded or damaged mitochondrial proteins. The DAP3 → LONP1 connection suggests that enhanced mitochondrial translation may necessitate higher protease activity to maintain protein quality control. The SIRT3 → LONP1 relationship indicates a separate regulatory route whereby loss of the deacetylase SIRT3 relieves repression or alters post-translational modification of LONP1,

IPA Interpret Result

Canonical pathway

View Details →

Canonical Pathways

Signaling and metabolic pathways that are potentially activated or inhibited in the dataset

Pathway	P-value	Activation z-score	Percentage overlap
Filter	Filter ≤	Filter abs. ≥	Filter ≥
Antimicrobial peptides	1.25e-6	-2.45	16.22%
Keratinization	2.25e-5	-2.65	7.87%
Role of IL-17A in Psoriasis	1.75e-4	--	25.00%
Arachidonate metabolism	6.71e-4	-2.00	9.52%
Atorvastatin ADME	8.85e-4	--	40.00%
Tyrosine Degradation I	8.85e-4	--	40.00%
Atherosclerosis Signaling	9.36e-4	-2.45	5.08%

Upstream Regulators

View Details →

Upstream Regulators

Potentially activated or inhibited upstream molecules driving differential changes in the dataset

Regulator	P-value	Activation z-score	Percentage overlap
Filter	Filter ≤	Filter abs. ≥	Filter ≥
estradiol-17beta-benzoate	8.46e-10	-0.57	7.69%
IL17A	2.77e-6	-2.28	3.91%
IL22	2.67e-5	-1.92	7.87%
IL17C	3.80e-5	-1.97	20.00%
Ca2	5.78e-5	-1.16	4.18%
diethylstilbestrol	9.79e-5	-0.79	3.94%
EFNA5	1.26e-4	-1.34	10.00%

Disease and Function

View Details →

Diseases and Functions

Diseases and biological functions that ar

Disease or Function	P-value	Activation z-score	Percentage overlap
Filter	Filter ≤	Filter abs. ≥	Filter ≥
Hereditary palmoplantar keratoderma	2.71e-7	--	20.69%
Familial cornification disorder	2.30e-6	--	8.89%
Focal or diffuse nonepidermolytic palmoplantar keratoderma	2.49e-6	--	36.36%
Cornification disorder	2.62e-6	--	5.67%
Congenital erythroderma with palmoplantar keratoderma, hypotrichosis, and hyper-IgE	3.37e-6	--	75.00%
Focal palmoplantar keratoderma	8.37e-6	--	60.00%
Metabolism of coumarin	8.37e-6	--	60.00%

Tox Function

View Details →

Tox Functions

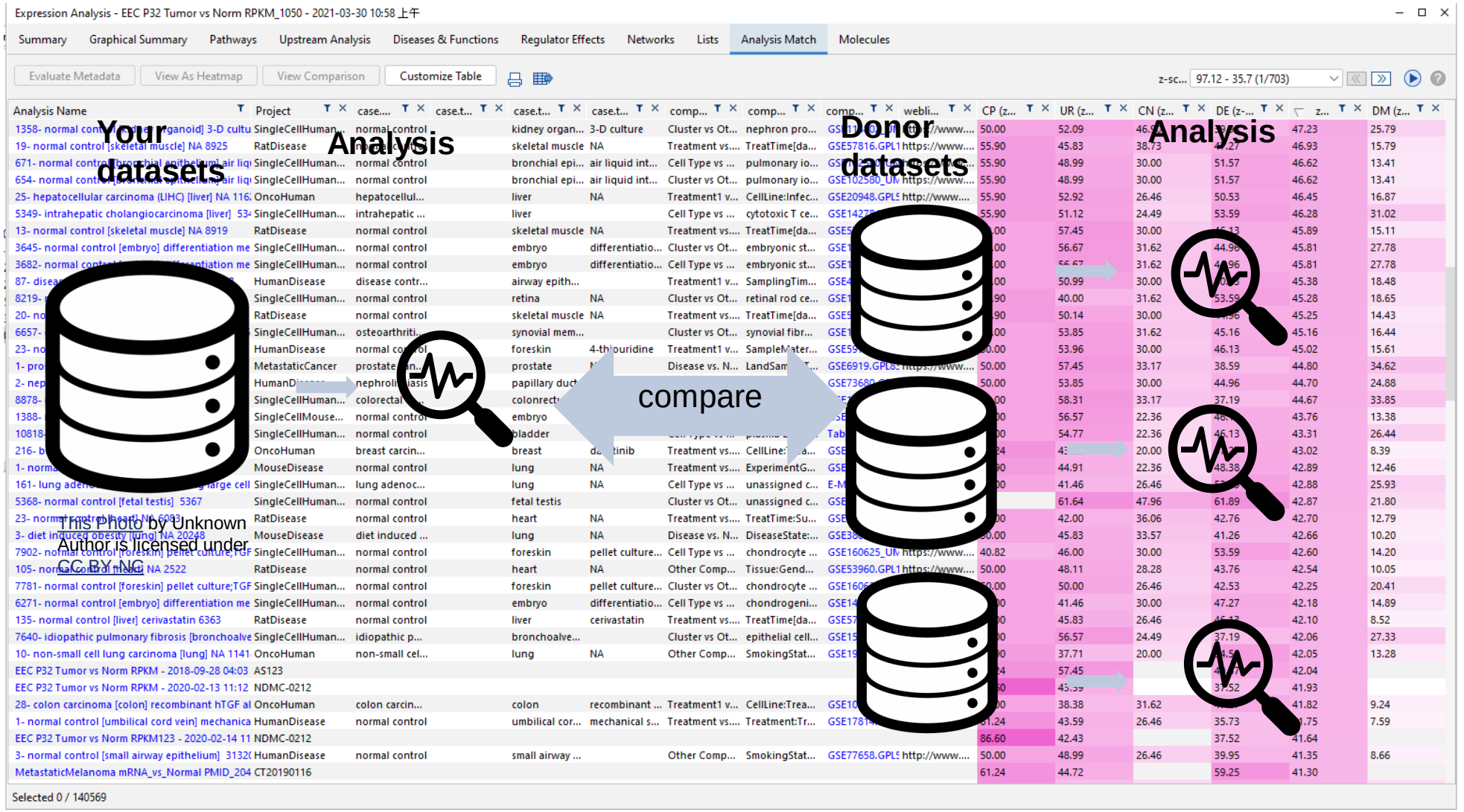
Toxicity endpoints and phenotypes and their causal associations with genes or proteins in the dataset

Tox Function	P-value	Activation z-score	Percentage overlap
Filter	Filter ≤	Filter abs. ≥	Filter ≥
Combined hepatocellular carcinoma and cholangiocarcinoma	2.57e-3	--	5.05%
Calcification of aortic valve	2.58e-3	--	2.75%
Proximal tubular toxicity	4.94e-3	--	5.56%
End-stage chronic kidney disease	5.59e-3	--	16.67%
End-stage renal failure	5.59e-3	--	16.67%
Severe acute renal failure	5.59e-3	--	16.67%
Arrhythmia of heart ventricle	8.45e-3	--	3.26%

View Details →

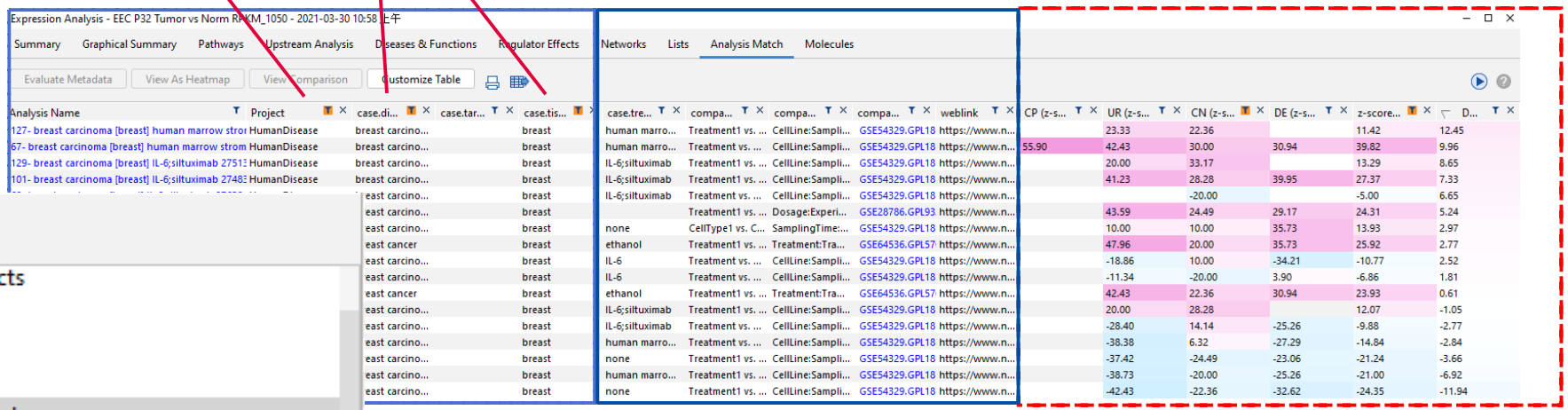
Analysis matching

Automatically discover other IPA Core Analyses with similar (or opposite) biological results as compared to yours, to help confirm your interpretation of the results or to provide unexpected insights into underlying shared biological mechanisms



Mapping Your Results to OmicSoft Datasets by IPA Analysis Match

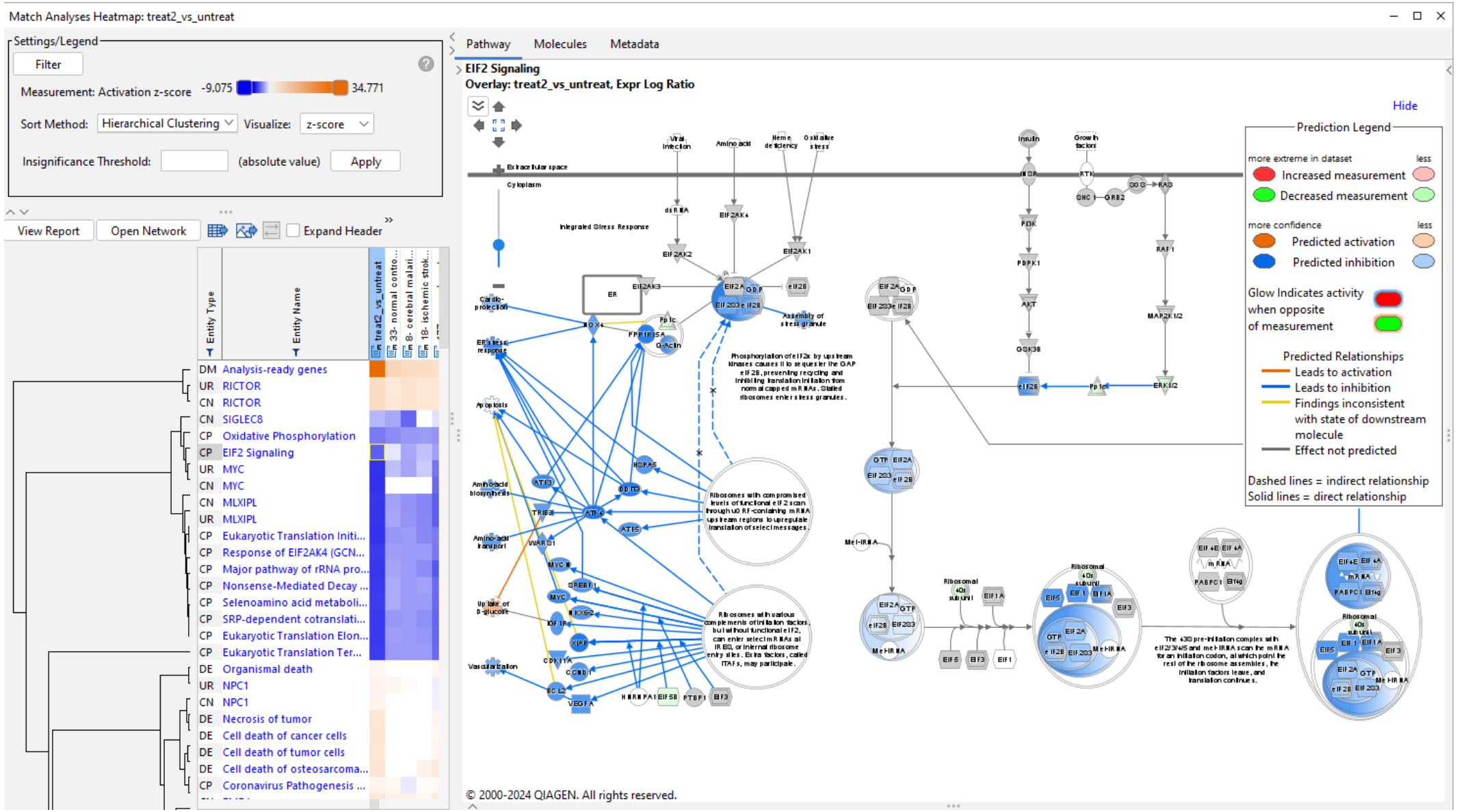
Project **Cell & Tissue** Datasets information **similar** **opposite**



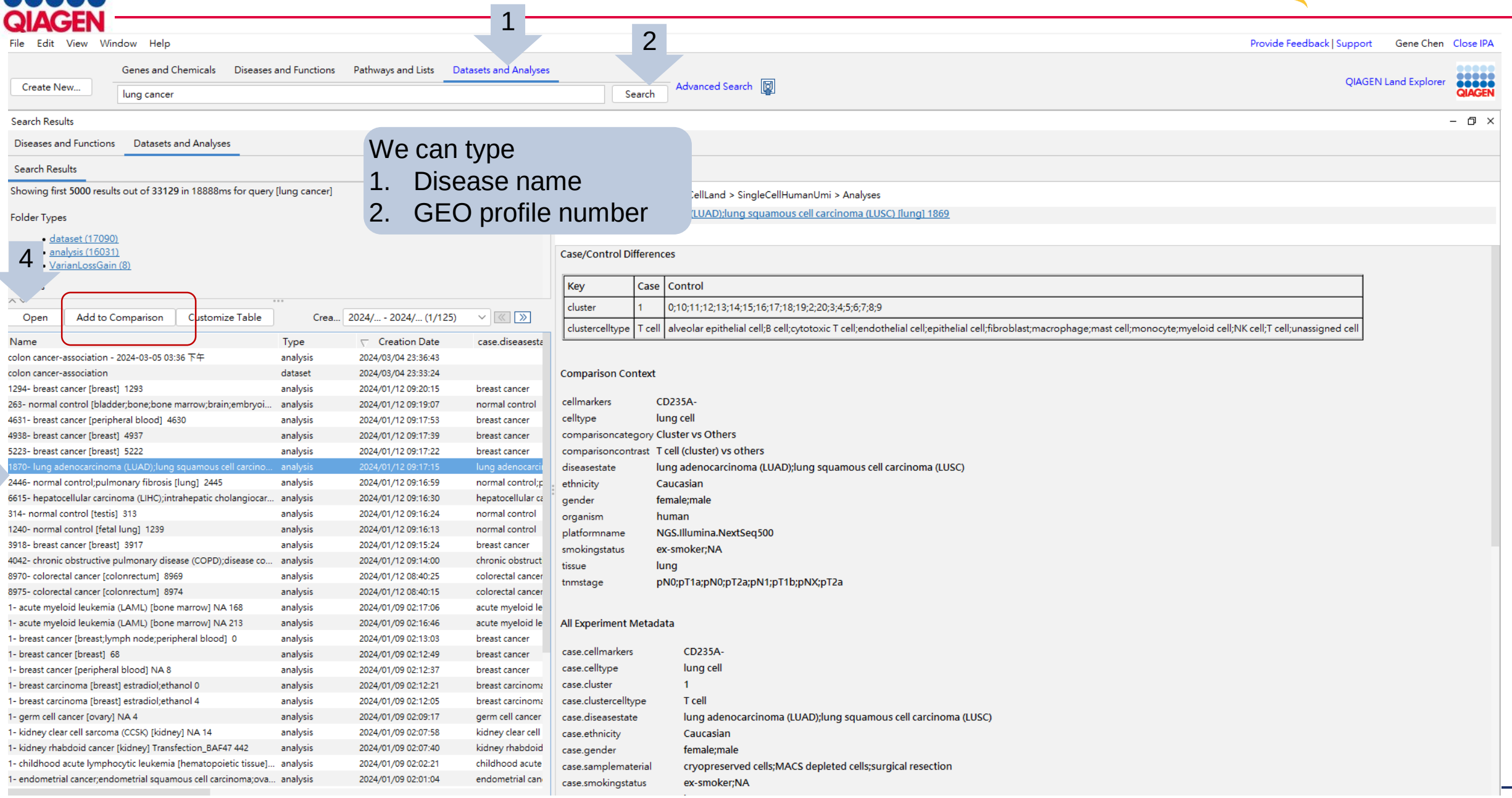
tasets
ta

z-scores

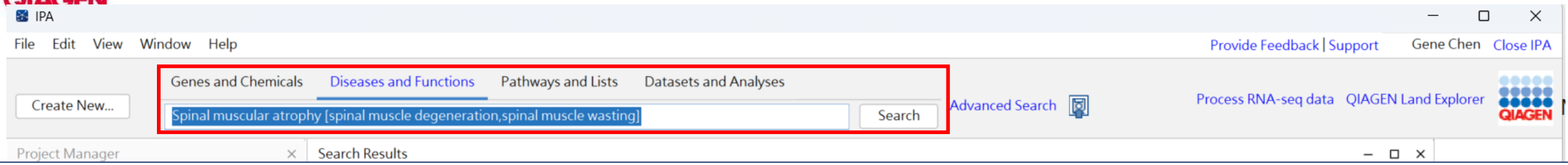
Analysis Match



Dataset and analysis search



Diseases and Function



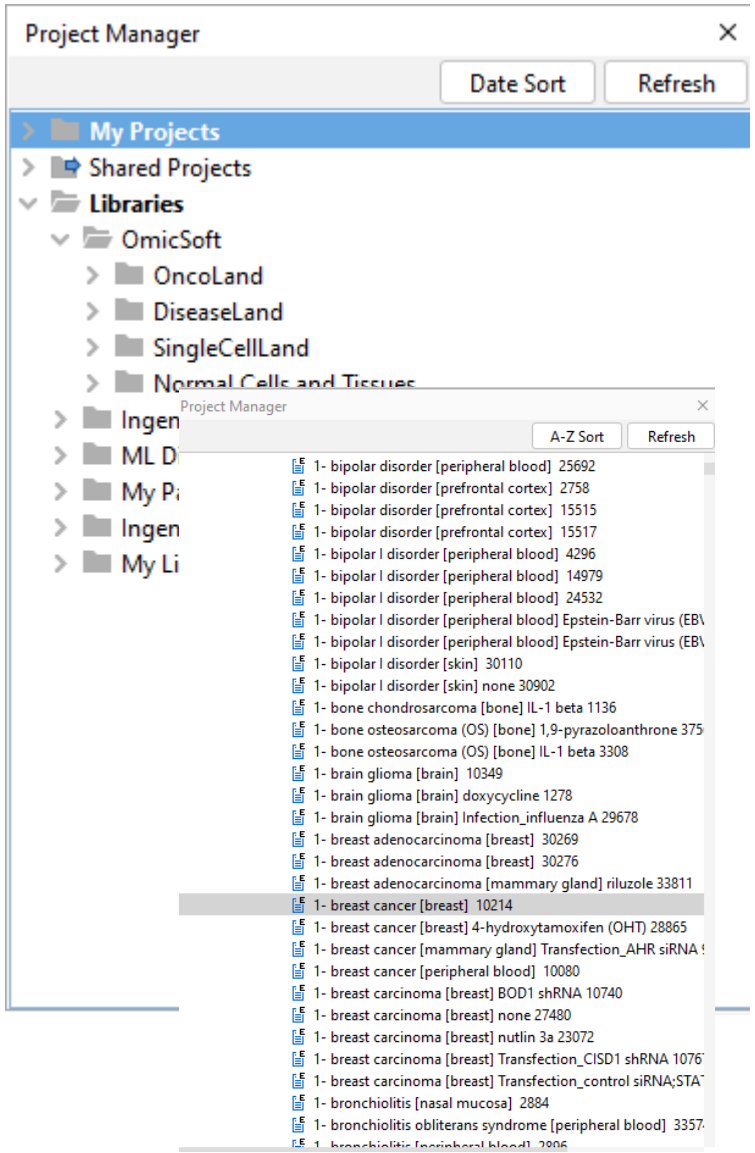
Molecule Annotations

Add To My Pathway | Add To My List | Create Dataset | Customize Table | Symbol: AARS1 - NEFL (1/2)

Symbol	Entrez Gene Name	Location	Type(s)	Biomarker Application(s)	Drug(s)
AARS1	alanyl-tRNA synthetase 1	Cytoplasm	enzyme		
acetaminophen	--	Other	chemical drug		
ALT (family)	--	Other	group	efficacy, safety	
amantadine	--	Other	chemical drug		
apitegromab	--	Other	biologic drug		
AR	androgen receptor	Nucleus	ligand-dependent nuclear receptor	diagnosis, disease progression,	clascoterone, nandrolone phenpro...
ASAH1	N-acylsphingosine amidohydrolase 1	Cytoplasm	enzyme	unspecified application	
ASCC1	activating signal cointegrator 1 complex s...	Nucleus	transcription regulator		
ATP2A1	ATPase sarcoplasmic/endoplasmic reticul...	Cytoplasm	transporter	unspecified application	
ATP7A	ATPase copper transporting alpha	Plasma Membrane	transporter		
BAG3	BAG cochaperone 3	Cytoplasm	other		
BCL2L1	BCL2 like 1	Cytoplasm	other	efficacy, prognosis	LP-118, AZD0466
BICD2	BICD cargo adaptor 2	Cytoplasm	other		
BSCL2	BSCL2 lipid droplet biogenesis associated,...	Cytoplasm	other		
butyric acid	--	Other	chemical - endogenous mammalian		
C1QB	complement C1q B chain	Extracellular Space	other		
CASQ1	calsequestrin 1	Cytoplasm	other	unspecified application	
ceramide	--	Other	chemical - endogenous mammalian		
CHCHD10	coiled-coil-helix-coiled-coil-helix domain c...	Cytoplasm	other		
CHMP1A	charged multivesicular body protein 1A	Extracellular Space	peptidase		
creatine	--	Other	chemical - endogenous mammalian	efficacy, safety	
CREATINE KINASE (family)	--	Other	group	efficacy, safety	

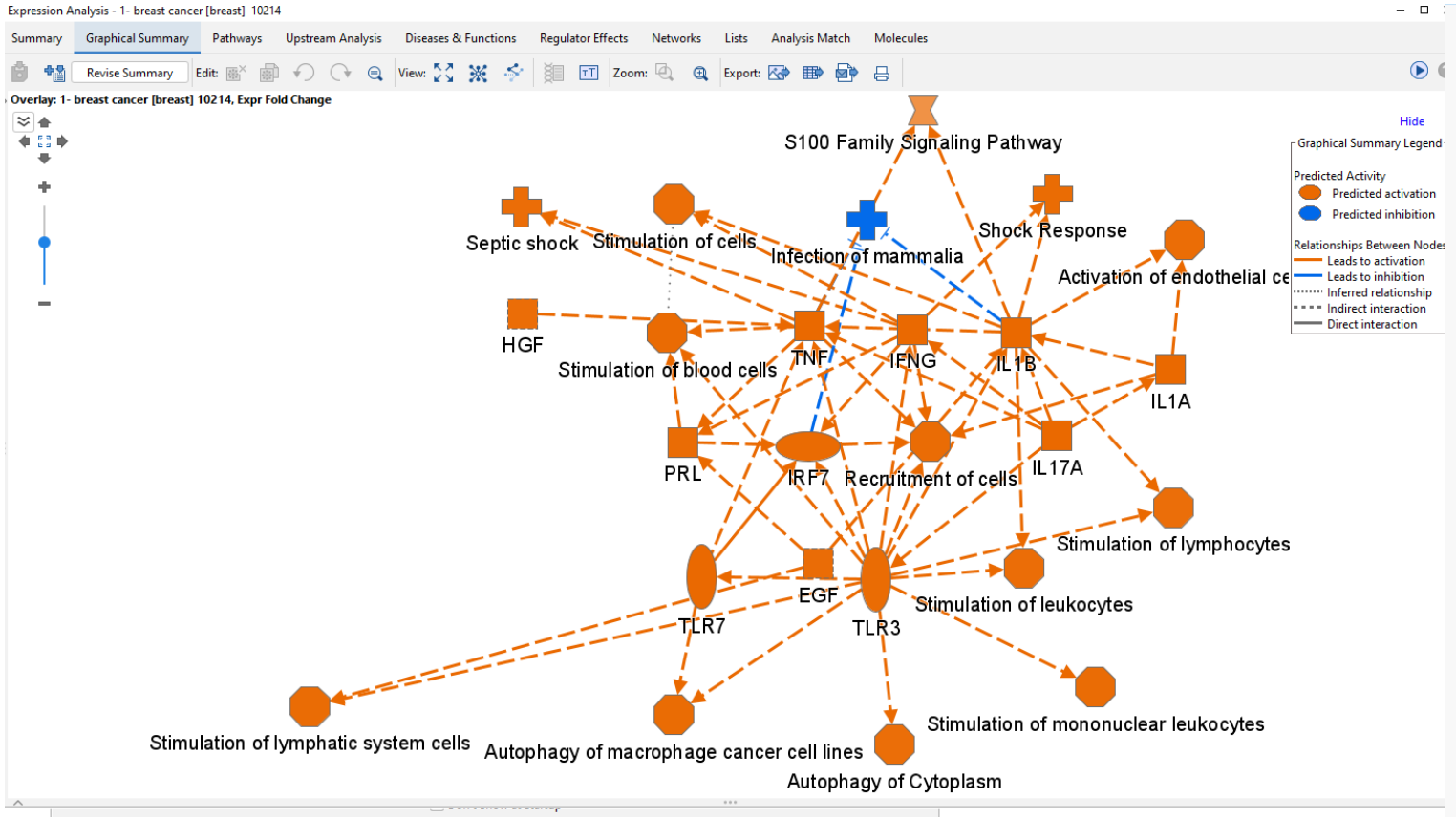
Selected/Total molecules: 0/144

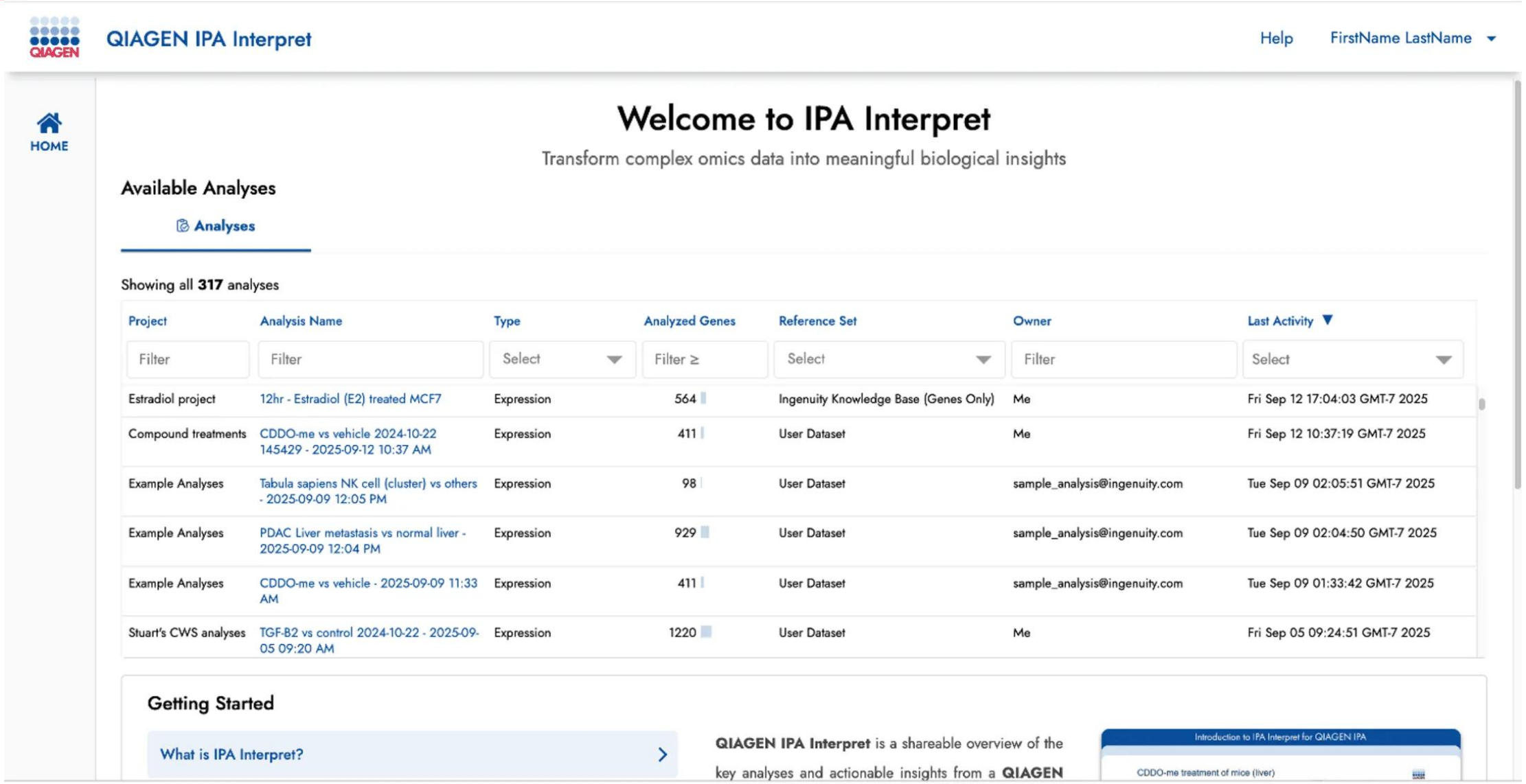
OmicSoft data storage and analysis in IPA



You can also use the repository without your own analysis, just by searching for available analyses of interest.

Graphical summary




QIAGEN IPA Interpret
Help
FirstName LastName
HOME
Welcome to IPA Interpret
Transform complex omics data into meaningful biological insights
Available Analyses
Analyses
Showing all 317 analyses
Project
Analysis Name
Type
Analyzed Genes
Reference Set
Owner
Last Activity
Filter
Filter
Select
Filter ≥
Select
Filter
Select
Estradiol project
12hr - Estradiol (E2) treated MCF7
Expression
564
Ingenuity Knowledge Base (Genes Only)
Me
Fri Sep 12 17:04:03 GMT-7 2025
Compound treatments
CDDO-me vs vehicle 2024-10-22 145429 - 2025-09-12 10:37 AM
Expression
411
User Dataset
Me
Fri Sep 12 10:37:19 GMT-7 2025
Example Analyses
Tabula sapiens NK cell (cluster) vs others - 2025-09-09 12:05 PM
Expression
98
User Dataset
sample_analysis@ingenuity.com
Tue Sep 09 02:05:51 GMT-7 2025
Example Analyses
PDAC Liver metastasis vs normal liver - 2025-09-09 12:04 PM
Expression
929
User Dataset
sample_analysis@ingenuity.com
Tue Sep 09 02:04:50 GMT-7 2025
Example Analyses
CDDO-me vs vehicle - 2025-09-09 11:33 AM
Expression
411
User Dataset
sample_analysis@ingenuity.com
Tue Sep 09 01:33:42 GMT-7 2025
Stuart's CWS analyses
TGF-B2 vs control 2024-10-22 - 2025-09-05 09:20 AM
Expression
1220
User Dataset
Me
Fri Sep 05 09:24:51 GMT-7 2025
Getting Started
What is IPA Interpret?
QIAGEN IPA Interpret is a shareable overview of the key analyses and actionable insights from a QIAGEN
Introduction to IPA Interpret for QIAGEN IPA
CDDO-me treatment of mice (liver)
Powered by QIAGEN Digital Insights
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M-B / Canonical Pathways / Bubble Chart

Canonical Pathways

Signaling and metabolic pathways that are potentially activated or inhibited in the dataset

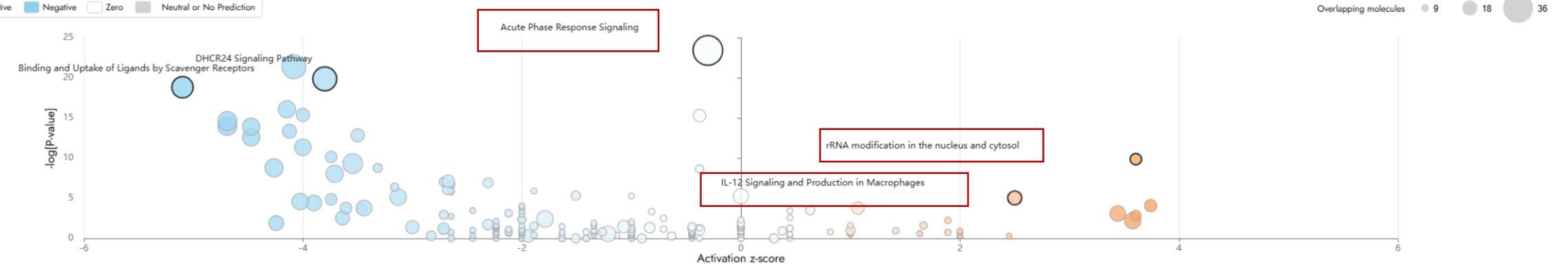
Table | Bar Chart | **Bubble Chart**

Chart Type: Bubble volcano chart | X-axis: Activation z-score | Y-axis: -log[P-value] | Bubble size: Overlapping molecules | Bubble color: Activation z-score | Data display: Select Range... | More filters | Clear Selection

Figure Legend ON

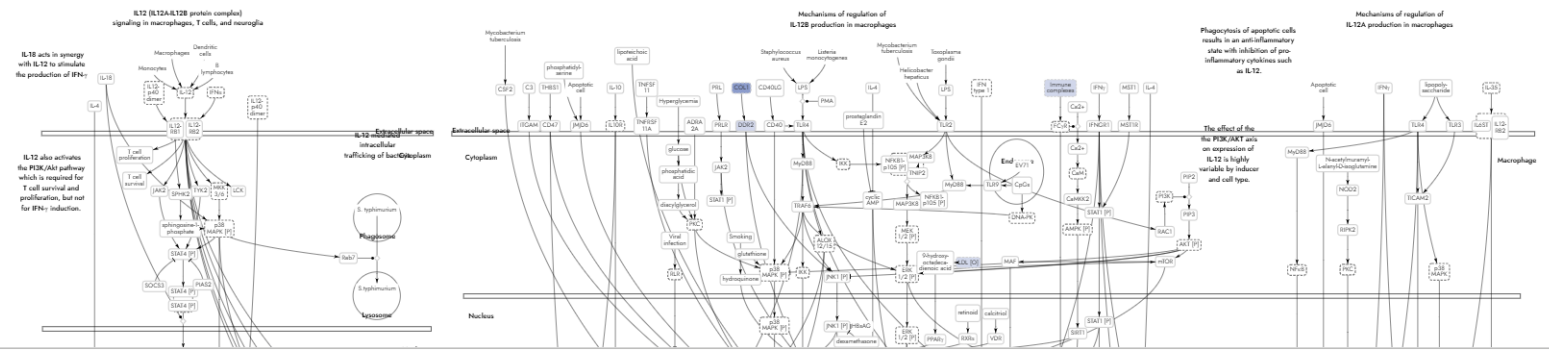
Z-Score: Positive | Negative | Zero | Neutral or No Prediction

Overlapping molecules: 9 | 18 | 36



Pathway representation

IL-12 Signaling and Production in Macrophages Figure Legend OFF

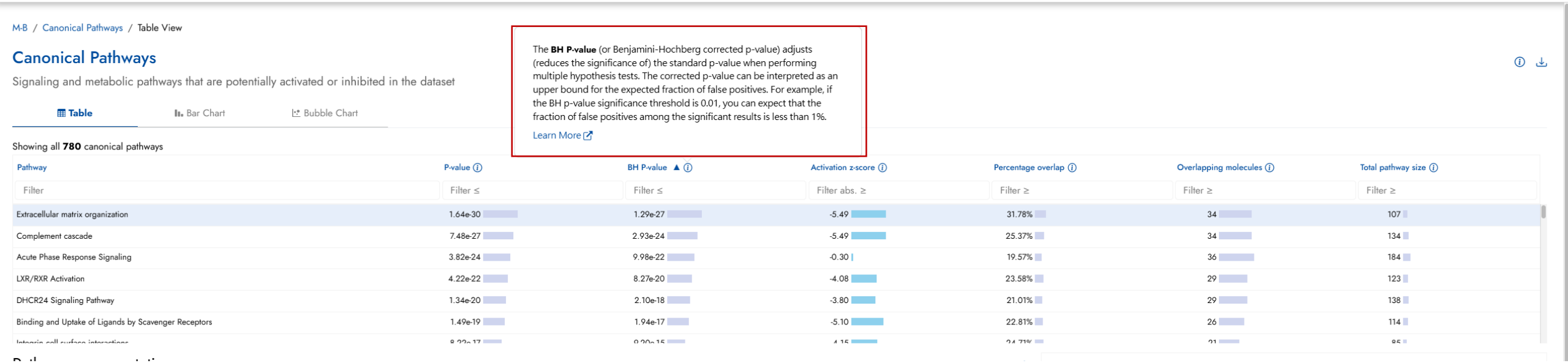


IL-12 Signaling and Production in Macrophages

Interleukin 12 (IL-12p70 or IL-12) is a heterodimeric pro-inflammatory cytokine produced by macrophages that are activated by pathogens or T lymphocytes. IL-12p70 is part of a family of dimeric cytokines, and is comprised of subunits p40 and p35. The IL-12p40 monomer can homodimerize to producing IL-12p80. Or it can heterodimerize with another monomer p19 to give rise to the IL-12 related cytokine IL-23. In addition to producing IL-12, macrophages also respond to it; thus IL-12 demonstrates an autocrine effect in macrophages and other cell types like dendritic cells. The signaling by IL-12 is effected through heterodimeric IL-12 receptors (IL-12R). The IL-12R protein composed of β1 and β2 chains is found on resting macrophages, and expression of these chains is upregulated during cell activation.

One of the major effects of IL-12 signaling on macrophages is the induction of interferon gamma (IFN γ), which favors the differentiation of T helper 1 cells (TH1) cells, affecting the development of adaptive immunity. IL-12-induced production of interferon gamma (IFN γ) by macrophages is dependent on signal transducers and activators of transcription 4 (STAT4). The cytokine IL-18 secreted by several cell types including macrophages, synergizes with IL-12 by activating nuclear translocation of STAT4. In addition, this synergy also increases the production of nitric oxide, which in turn promotes intracellular bacterial death. Complex reciprocal influences take place between IL-12 and IFN γ , both of which are involved in the initiation of cell-mediated immunity. IFN γ can enhance the expression of IL-12Rβ1 thereby increasing the number of IL-12 binding sites expressed on macrophages. Autocrine production

Reduced learning curve with accessible definitions for statistics in IPA Interpret



ID not on the left

Multi observation

	A	B	C	D	E	F	G	H	I
1	Metabolite	HMDB	KEGG	Log2FC_M-B	Log2FC_M-D	Log2FC_B-D	Pval_M-B	Pval_M-D	Pval_B-D
2	Uracil	HMDB00	C00106	0.063778306	0.054996167	NA	0	0.0057048	NA
3	Fumaric acid	HMDB00	C00122	-0.015374258	NA	NA	0	NA	NA
4	p-Cresol sulfate	HMDB00	-	-0.110212803	NA	NA	0	NA	NA
5	2-Methylhippuric acid	HMDB00	C01586	0.079419552	NA	NA	0	NA	NA
6	(黃)-Anisoxide	HMDB00	-	-0.020309069	-0.074907841	NA	0	0.01090889	NA
7	Indoxyl sulfate	HMDB00	-	-0.082471626	-0.005070156	NA	0	0.01866236	NA
8	Varenicline	HMDB00	-	0.061591798	NA	NA	0	NA	NA
9	1-Isopropyl citrate	HMDB00	-	-0.266587082	NA	0.20588052	0	NA	0.045405
10	Asparaginyl-Hydroxyproline	HMDB00	-	0.035167221	NA	NA	0	NA	NA
11	Prenyl glucoside	HMDB00	C09808	-0.001194566	NA	NA	0	NA	NA
12	2'-Deoxyadenosine	HMDB00	C00559	0.052776526	0.127315183	0.07453866	0	0.00295749	0.046854
13	modafinil acid	-	-	0.143163905	NA	NA	0	NA	NA
14	Aspartylphenylalanine	HMDB00	-	-0.024029247	NA	NA	0	NA	NA
15	N1-Methyladenosine	HMDB00	C02494	-0.012577063	NA	NA	0	NA	NA
16	Fosthiazate	-	-	0.18631347	NA	NA	0	NA	NA
17	Estradiol-17beta 3-sulfate	HMDB00	C08357	-0.087844827	NA	NA	0	NA	NA
18	N-({[4-(AMINOSULFONYL)PHENYL]AMINO}CARBONYL)-4-METHYLBENZENESULFONAMIDE	-	-	0.098155449	0.097618308	NA	0	0.02067507	NA
19	Rivoglitazone	-	-	-0.086180769	NA	NA	0	NA	NA
20	Flecainide	HMDB00	C07001	0.217340677	0.19207361	NA	0	0.00433429	NA
21	(2-hydroxy-5-[3-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)prop-2-enoyl]phenyl}oxidanesulfonic acid	-	-	-0.00309481	-0.070693348	NA	0	0.01031109	NA

AI can help pares and map automatically

Raw Data (487) | Dataset Summary (274) | Metadata

Edit Observation Names | Infer Observations

ID/Observation Name	Ignore	ID	ID	Ignore	Ignore	Ignore	Ignore
Measurement/Annotation		Human Met...	KEGG				
49	1-Methylhypoxanthi...	HMDB0013141	-	151.0614_1.6	8.852885000000000...	1.59866E-3	M-D
50	1,5-Dihydroxy-3-me...	HMDB0030605	-	325.1073_6.2	0.16434707800000001	1.703099999999999...	M-D
51	12-Oxo-2,3-dinor-1...	HMDB0032090	-	263.1648_8.7	-0.18209656499999...	5.067939999999999...	M-D
52	17-hydroxy-11,15-di...	-	-	353.067_3.9	-0.26151849799999...	1.94006E-3	M-D
53	2-(4-Hydroxyphenyl)...	-	-	289.0497_8.8	0.20510102499999999	3.726257999999999...	M-D
54	2-(Methylthiomethyl...	-	-	193.0677_1.5	0.23968714799999999	4.495472999999999...	M-D
55	2-{[hydroxy(1-oxo-1...	-	-	246.0415_9.7	-0.16949968900000...	7.225800000000000...	M-D
56	2-{[hydroxy(5-hydrox...	-	-	233.0564_5.1	-0.77596192100000...	3.961799999999999...	M-D
57	2-Decylfuran	HMDB0032215	-	209.1896_9.7	-4.75624190000000...	2.428599999999999...	M-D
58	2-Deoxy-2-Amino Gl...	HMDB0001504	C06605	260.0533_3.1	-0.193207566	5.902499999999999...	M-D
59	2-Methoxyxanthone	HMDB0032998	-	225.055_7.9	0.29050186300000003	3.906299999999999...	M-D
60	2-oxo-3-(3,4,5-trihy...	-	-	211.0247_8.9	-0.12797825800000...	3.038522000000000...	M-D
61	2-Pyrrolidinone	HMDB0002039	C11118	86.06_1.8	-0.13496873100000...	1.376500000000000...	M-D
62	2,4-Diamino-6-[N-(2...	-	-	340.177_6.6	-0.19252112499999...	2.596532999999999...	M-D
63	2,4,6-Triethyl-1,3,5-...	-	-	207.0877_1.2	-0.13045403799999...	3.546219999999999...	M-D

Comparison Analysis

Trend Analysis Summary of this Comparison AI-Suggested

Robust Activation of Pro-inflammatory Pathways

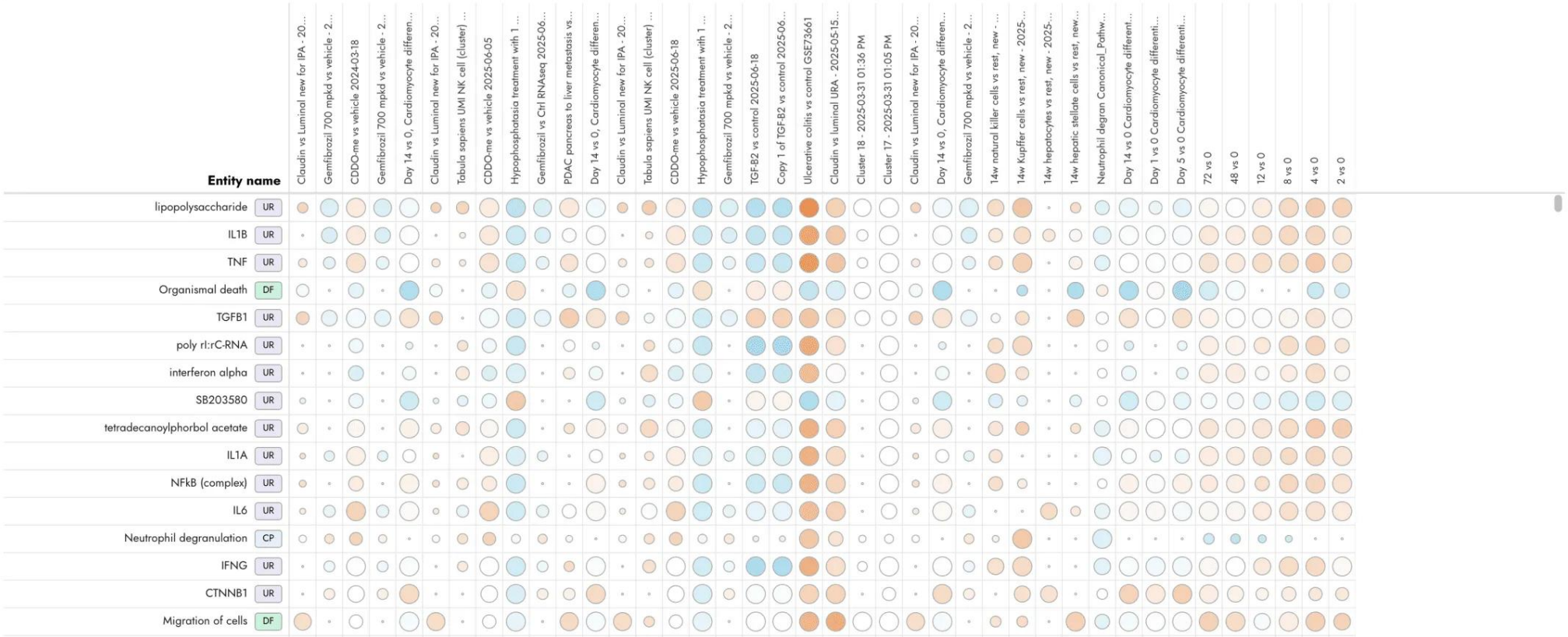
IL1B (Upstream Regulator), **lipopolysaccharide**, and **TNF** show high positive z-scores (8.686, 11.318, 9.719, respectively), indicating cross-analysis activation. Coupled with elevated -log10(BH p)-values, this pattern reflects dominant innate immune signaling and suggests a pronounced inflammatory response across the datasets....

View Full AI Summary

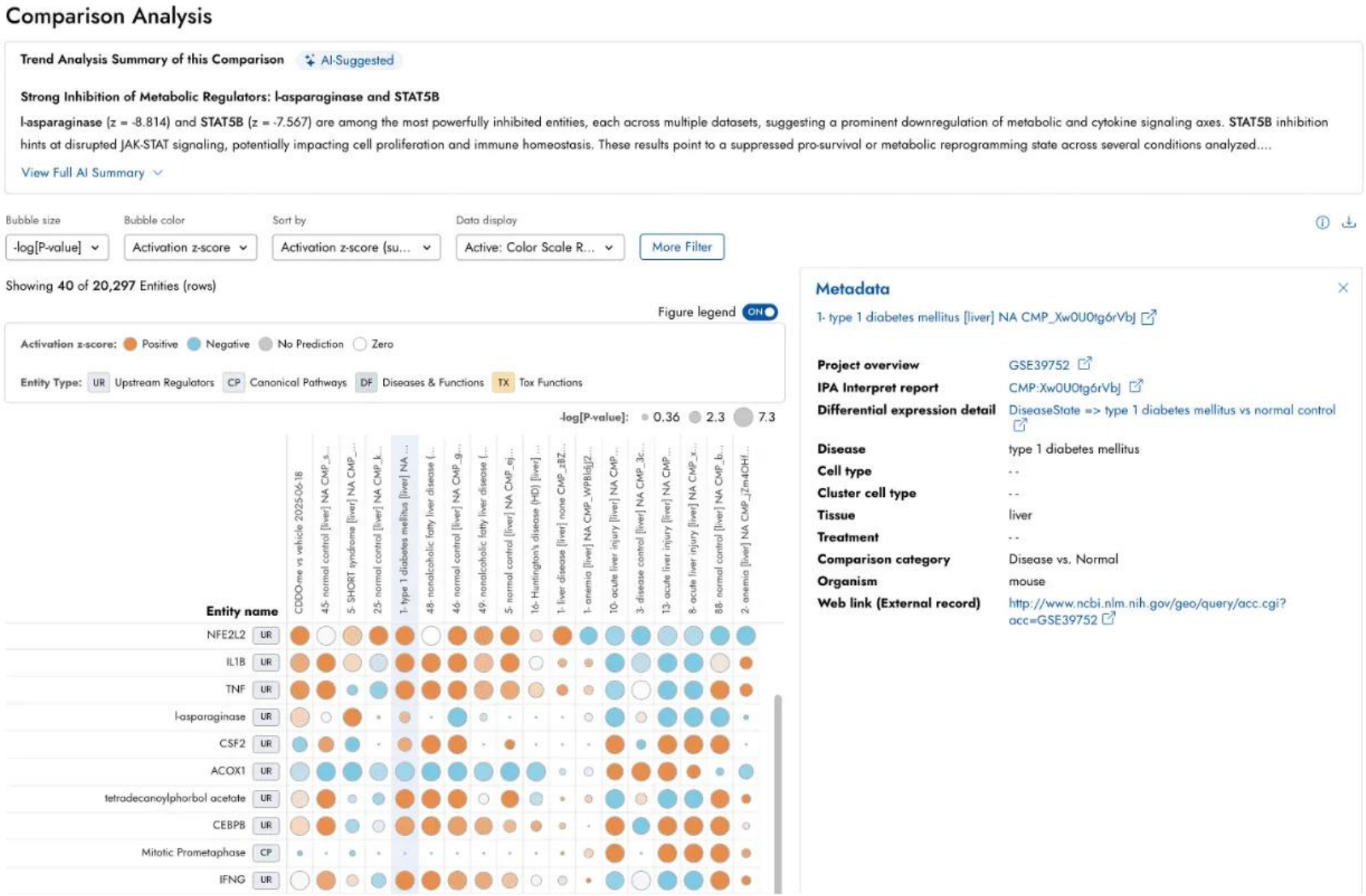
Bubble size: -log[P-value] | Bubble color: Activation z-score | Sort by: Activation z-score (sum of absolute scores across the row) | Data display: Active Filters: BH P-value, Z-score, Entity types | Expand labels

Figure legend: ON

Activation z-score: Positive, Negative, Zero, Neutral / No Prediction — Entity Type: UR Upstream Regulators, CP Canonical Pathways, DF Diseases & Functions — -log[P-value]: 0.37, 2.3, 7.6



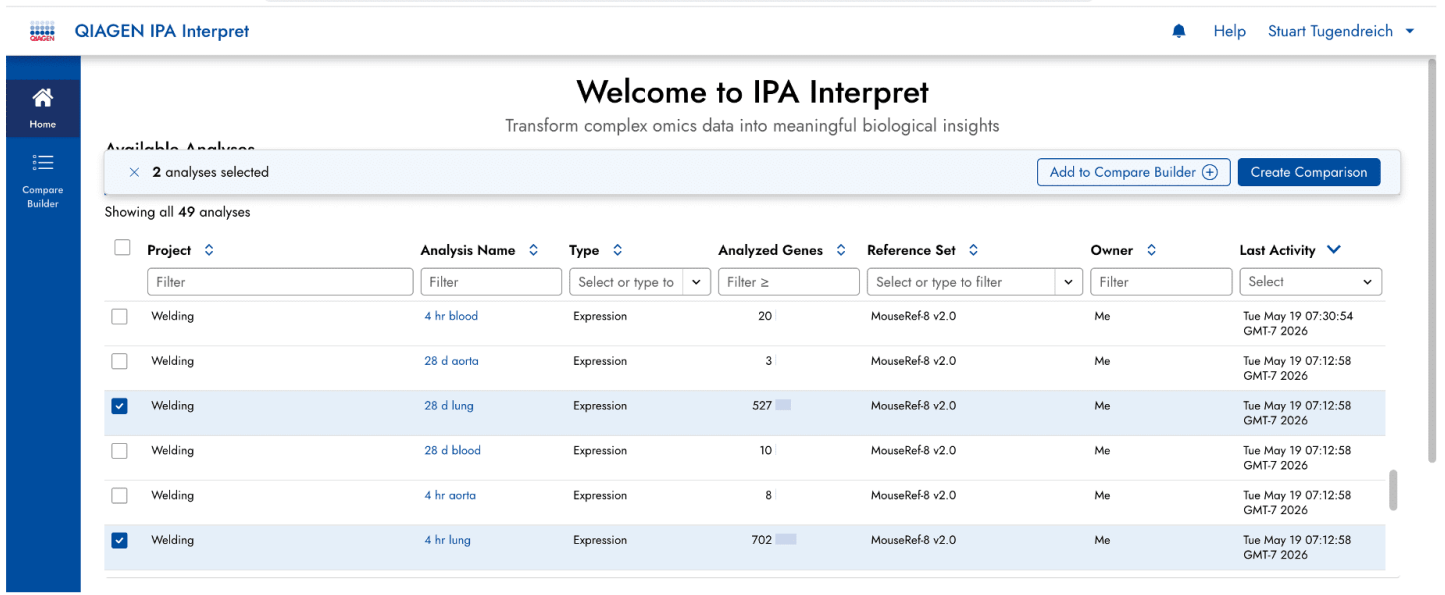
Make discoveries by including OmicSoft analyses in a Comparison Analysis



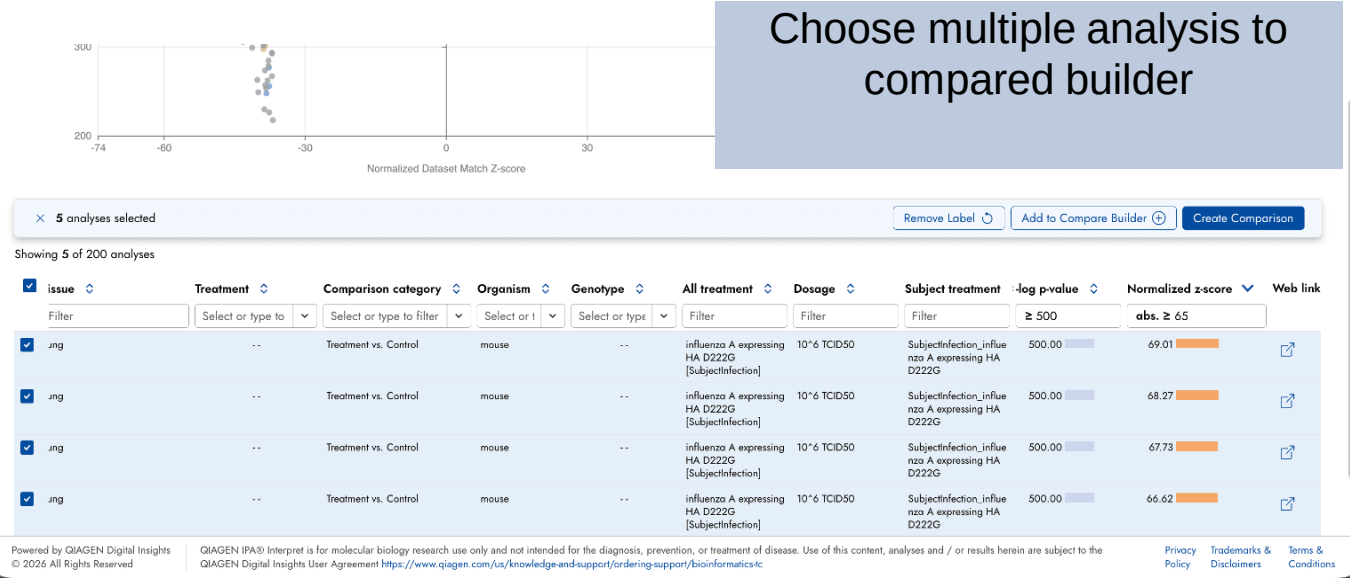
How to build your comparison

Choose which you want to compared and add to Compare Builder

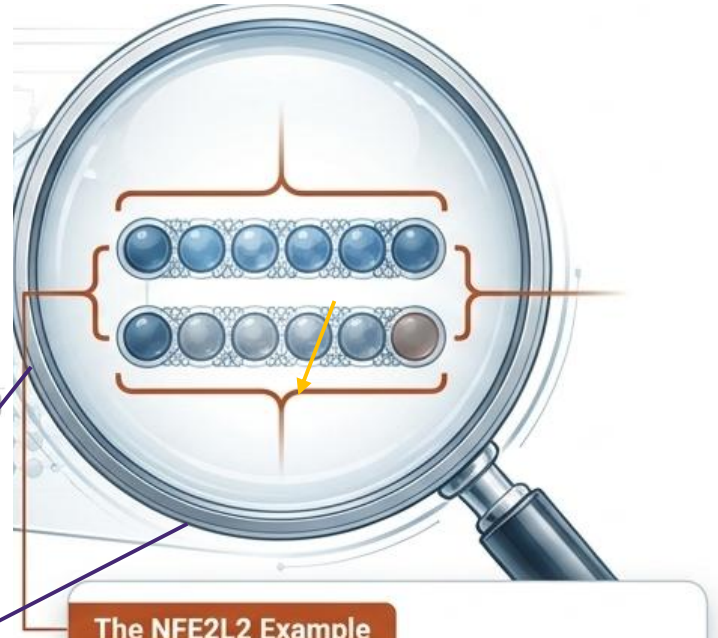
From omicsoft similar analysis, choose and add to Compare Builder



Choose multiple analysis to compared builder



Discover biological patterns by hierarchically clustering the rows and/or columns

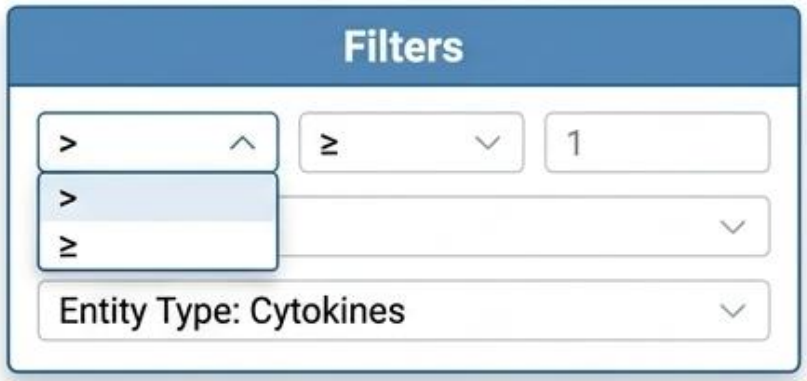


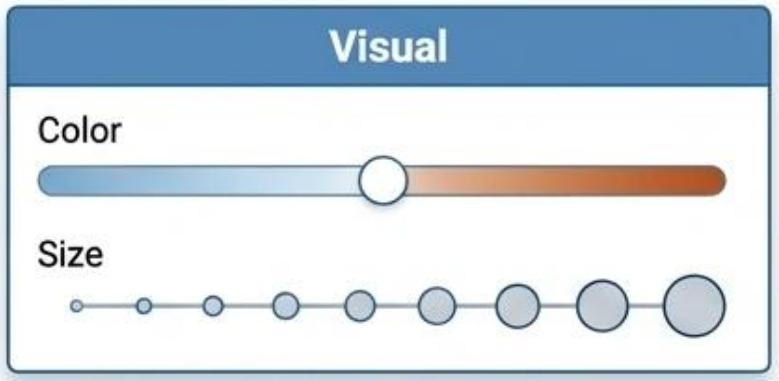
The NFE2L2 Example

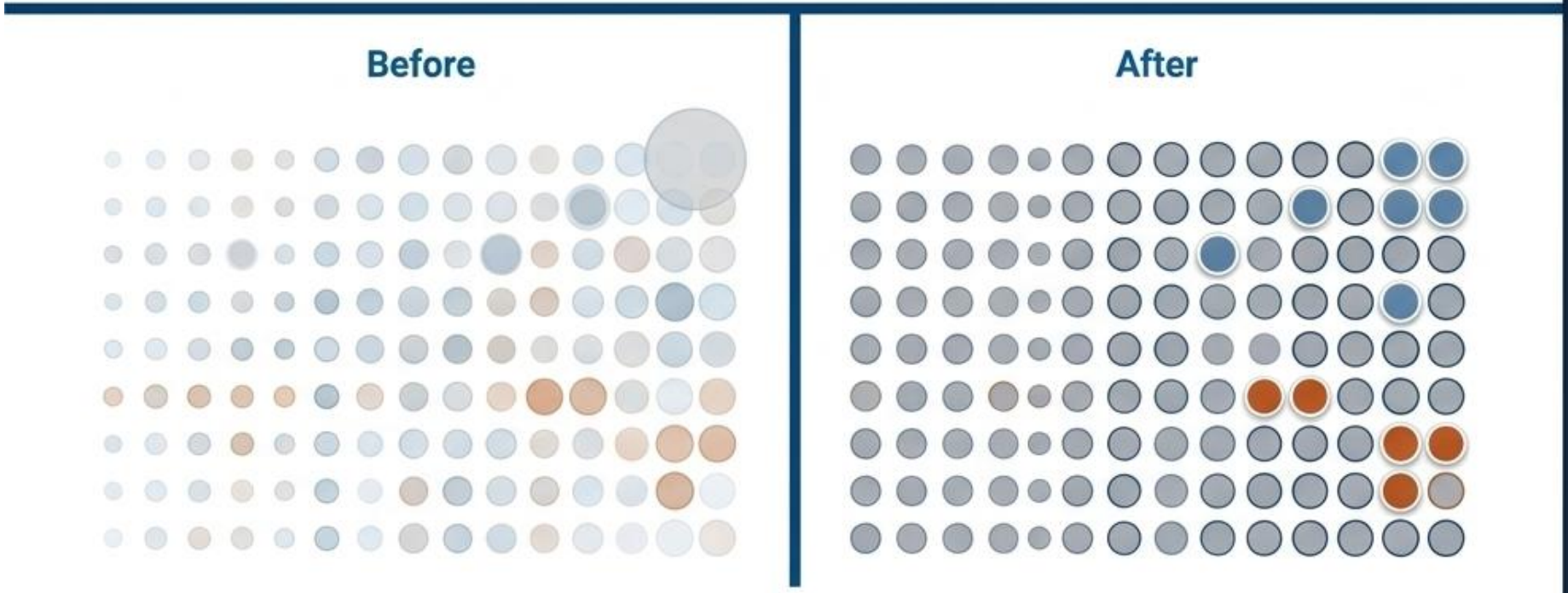
- **The Pattern:** The chemical 1,2-dithiole-3-thione clusters tightly with the upstream regulator NFE2L2.
- **The Biology:** They do not just share genes; they share the same predicted activity pattern across analyses, driving similar downstream expression impacts.
- **The Outcome:** Immediate identification of shared activation mechanisms and novel pattern discovery.

Cluster up to 7,000 entities to discover hidden similarities across subsets of pathways and regulators.

Precision Control & Data Display

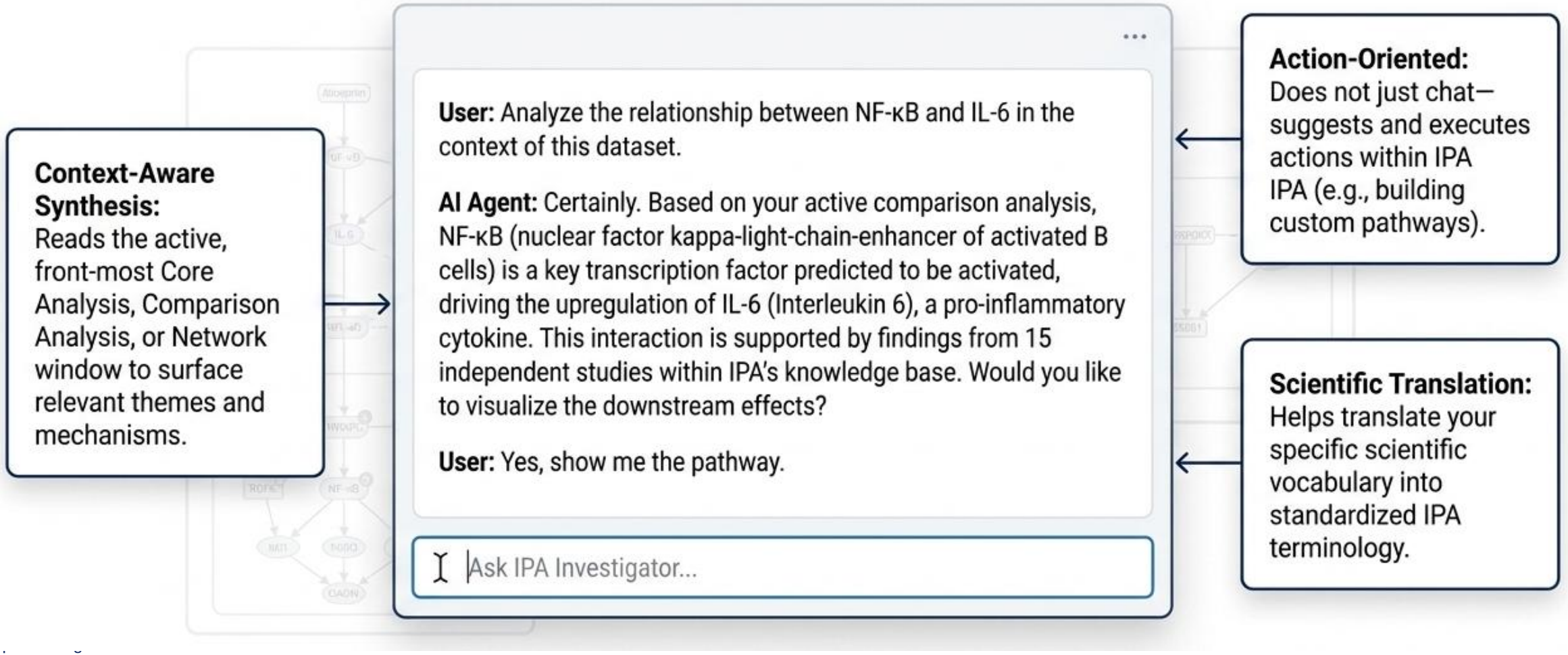




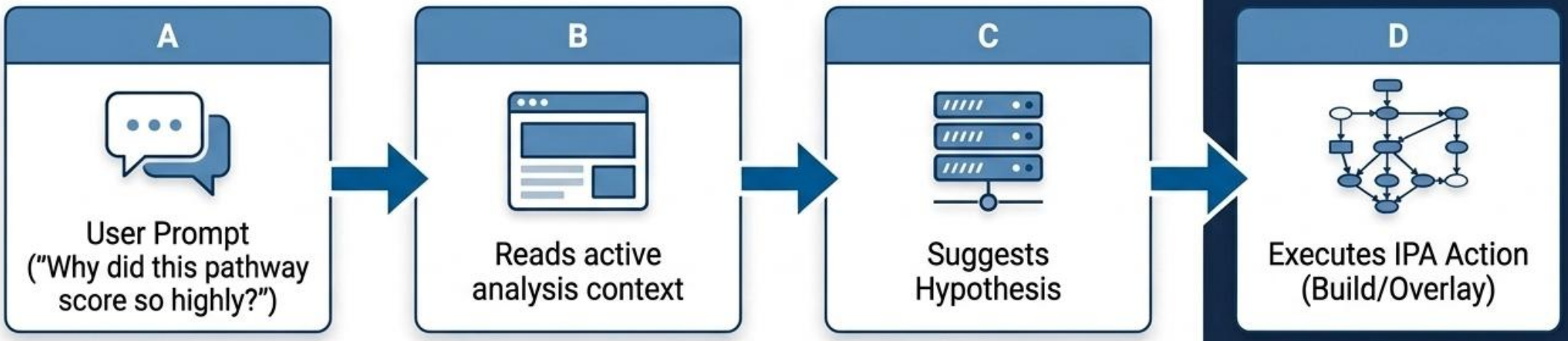


- **Exact Cutoffs:** New operator precision (>, ≥) and entity type filtering (e.g., isolate only Cytokines).
- **Visual Sliders:** Manually adjust bubble size and color intensity to correct for large value outliers washing out the map.
- **Signal vs. Noise:** Set an insignificance threshold (e.g., z-score < 2) to gray out statistically insignificant bubbles.
- **Publication Ready:** Fully customize fonts, colors, and aspect ratios for direct export to journals.

Introducing of IPA Investigator [Beta]



AI Action Architecture



How AI works with IPA deterministic tools

1. **AI Suggests**: The Investigator provides hypotheses based on your data context.

2. **IPA Computes**: Actions (like creating an 'AnalysisTheme' or executing a 'GrowToBioFunctions' causal analysis) are powered purely by IPA's built-in tools.

3. **No Hallucinated Networks**: All generated visual networks use relationship information sourced strictly from the QIAGEN Knowledge Base.

Enterprise AI Security & Compliance

Security Dimension	Public Generative AI	IPA Investigator [Enterprise]
AI Model	Standard Public Models	**Enterprise GPT 5.1** hosted securely via Microsoft Azure.
Data Training	✗	✓ Prompts and interactions are **NEVER** retained or used to train general or specific AI models.
Access Protocol	Always On / Public	✓ **Opt-in** strictly required. Feature is turned **OFF** by default globally.
Data Input Policy	Unrestricted	✓ Strictly Research Use Only (RUO). **NO** patient-identifiable data, PHI, or biometric data allowed.
Oversight	Automated Output	✓ Outputs remain subject to human review and independent verification.

QIAGEN IPA – a dual approach to data analysis

With dataset	Without dataset
• Find connections in your data	• Search and explore the QIAGEN Knowledge Base
• Identify novel biomarkers	• Test hypothesis in silico
• Uncover key targets and regulators	• Identify degree of novelty in a hypothesis
• Discover novel disease mechanisms	
• Compare across experiments	

Formatting ‘omics data before uploading to IPA

Observation 1

Observation 2

	A	B	C	D	E
1	**geneid**	**UCvsNormal.Log2FoldChange**	**UCvsNormal.pval**	**52wksVedolizumabvsBaseline.Log2FoldChange**	**52wksVedolizumabvsBaseline.pval**
2	DDX11L1	-0.1067	0.2878	0.1183	0.1624
3	WASH7P	-0.1883	0.0097	0.3063	0.0006
4	FAM138F	-0.0761	0.4699	0.2466	0.0191
5	OR4F5	0.1474	0.5311	0.1713	0.2913
6	LOC729737	0.4789	0.0017	0.029	0.8331
7	LOC100133331	0.4789	0.0017	0.029	0.8331
8	LOC100132062	0.4789	0.0017	0.029	0.8331
9	OR4F29	0.2495	0.2389	0.2181	0.1887
10	JA429831	0.1215	0.3338	0.2556	0.0004

Analyte identifier REQUIRED to explore enrichment

RNA examples: Gene symbols, array identifiers from Affymetrix, Ensembl, etc.

Protein examples: UniProt, GenPept, Gene symbols, Ensembl. etc.

Metabolite examples: KEGG, CAS registry number, etc. **add multiple columns of ids to ensure best mapping*

Change values needed to calculate activity predictions

Change value examples: fold changes, ratios, etc.

Significance values: P-values **optional but recommended to enable filtering for significance*

Accepted file formats:

- ✓ .txt (tab-delimited text files)
- ✓ .xls, .xlsx, .csv (Excel tables
- ✓ .diff (Cuffdiff output

Multiple comparisons or observations may be uploaded in one file

Formatting proteomics data before uploading to IPA

IDs (required)

	A	B	C	D
1	**Proteins**	**Fold change**	**P_value**	**P_value_adjust**
2	P00738	0.592740341	0.000671209	0.016736513
3	P01008	0.25826353	0.000155027	0.006454004
4	P01011	0.47378079	0.000628734	0.016577608
5	P04003	0.312321917	2.2507E-05	0.001618456
6	P06681	0.272046102	0.001374078	0.027869114
7	P05155	0.429462469	4.19294E-05	0.002551241
8	P02748	0.580232999	0.002252137	0.038734209
9	P02763	0.555940063	0.00014192	0.006236575
10	Q14520	0.368464274	9.75518E-05	0.004786156
11	Q08380	0.536007179	0.000258392	0.009290371
12	Q9BXR6	0.332814513	0.00075662	0.01813594
13	P03951	0.306633696	0.000594476	0.016236342
14	P08185	0.304349939	1.12204E-05	0.000914984
15	P05090	0.302847519	0.000817844	0.018730825

Ratio, fold change, etc. (recommended)

Significance (optional)

Common protein IDs

- Ensembl
- Gene symbols (Entrez or HUGO)
- GenPept and GenBank
- International Protein Index
- UniProt and SwissProt

UniProt ID conversion tool:

- https://www.uniprot.org/mapping/

Formatting proteomics data before uploading to IPA

IDs (required)

	A	B	C	D	E
1	ID	Symbol	Phospho Fold Change	Phospho p-value	Phospho Site
2	IPI00137139	1700003H04Rik	-1.271	0.221	_M(ox)ET(ph)LGEK_
3	IPI00224491	2900026A02Rik	-1.244	0.25	_RQS(ph)LYENQA_
4	IPI00224491	2900026A02Rik	-1.404	0.156	_SEECS(ph)PQWLK_
5	IPI00652957	4930594M22Rik	-5.729	5.47E-09	_MFKSS(ph)PR_
6	IPI00137111	4933402E13Rik	2.196	0.000423	_AWALNDS(ph)ANT(ph)SPNAWFVER_
7	IPI00137111	4933402E13Rik	2.196	0.000423	_AWALNDS(ph)ANT(ph)SPNAWFVER_
8	IPI00137111	4933402E13Rik	2.196	0.000423	_AWALNDS(ph)ANT(ph)SPNAWFVER_
9	IPI00654190	4933431E20Rik	-1.184	0.304	_VGGLS(ph)PR_
10	IPI00654176	4933439C10Rik	-1.097	0.431	_SPHLSGS(ph)LPR_
11	IPI00225598	A430057M04Rik	1.079	0.299	_ALPT(ph)EPR_
12	IPI00227449	A730008H23Rik	-1.448	0.133	_GM(ox)TLQWLIS(ph)PVK_
13	IPI00311509	AAAS	-1.085	0.37	_ITHIPLYFVNAQFPRFS(ph)PVLGR_
14	IPI00458612	AAK1	1.07	0.311	_VGSLT(ph)PPSS(ph)PKTQR_
15	IPI00458612	AAK1	1.07	0.311	_VGSLT(ph)PPSS(ph)PKTQR_
16	IPI00458612	AAK1	1.057	0.332	AGQTQPNPGILPIQPALT(ph)PR

Observation 1

Ratio, fold change, etc. (recommended)

Significance (optional)

Common protein IDs

- Ensembl
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- GenPept and GenBank
- International Protein Index
- UniProt and SwissProt

UniProt ID conversion tool:

- https://www.uniprot.org/mapping/

Formatting metabolomics data before uploading to IPA

Multiple ID columns

Ratio, fold change, etc. (recommended)

(optional)

Significance (optional)

	A	B	C	D	E	F	G	H
1	**Pubchem**	**Kegg**	**HMDB**	**CAS**	**Metabolites**	**Fold change**	**P_value**	**P_value_adjust**
2					(2 or 3)-decenoate (10:1n7 or n8)	1.212936133	4.44028E-05	0.000585189
3	6443013	C14762	HMDB0004667	29623-28-7	13-HODE + 9-HODE	0.584109411	0.003698077	0.016919182
4	10111	C02294	HMDB01522	471-29-4	1-methylguanidine	1.219937764	0.015399637	0.049446834
5	5462190	C15606	HMDB0012134	746507-19-7	2,3-dihydroxy-5-methylthio-4-pentenoate (DMTPA)*	1.566518315	0.002802172	0.013670263
6	80283	C02356	HMDB00452	1492-24-6	2-aminobutyrate	0.633800292	0.011016709	0.038805594
7	10796774		HMDB00317	488-15-3	2-hydroxy-3-methylvalerate	0.997343835	0.006172648	0.024774766
8	11427		HMDB37115	120-91-2	2-hydroxy-4-(methylthio)butanoic acid	1.294720456	0.000305912	0.002622524

Observation 1

Common metabolite IDs

- CAS registry number
- Human Metabolome Database
- KEGG
- PubChem CID

Metabolite ID conversion tools:

- https://biodbnet-abcc.ncifcrf.gov/db/db2db.php
- https://cts.fiehnlab.ucdavis.edu/batch
- http://csbg.cnb.csic.es/mbrole2/conversion.php

Formatting metabolomics data before uploading to IPA

Multiple ID columns

Ratio, fold change, etc. (recommended)

(optional)

Significance (optional)

	A	B	C	D	E	F	G	H
1	**Pubchem**	**Kegg**	**HMDB**	**CAS**	**Metabolites**	**Fold change**	**P_value**	**P_value_adjust**
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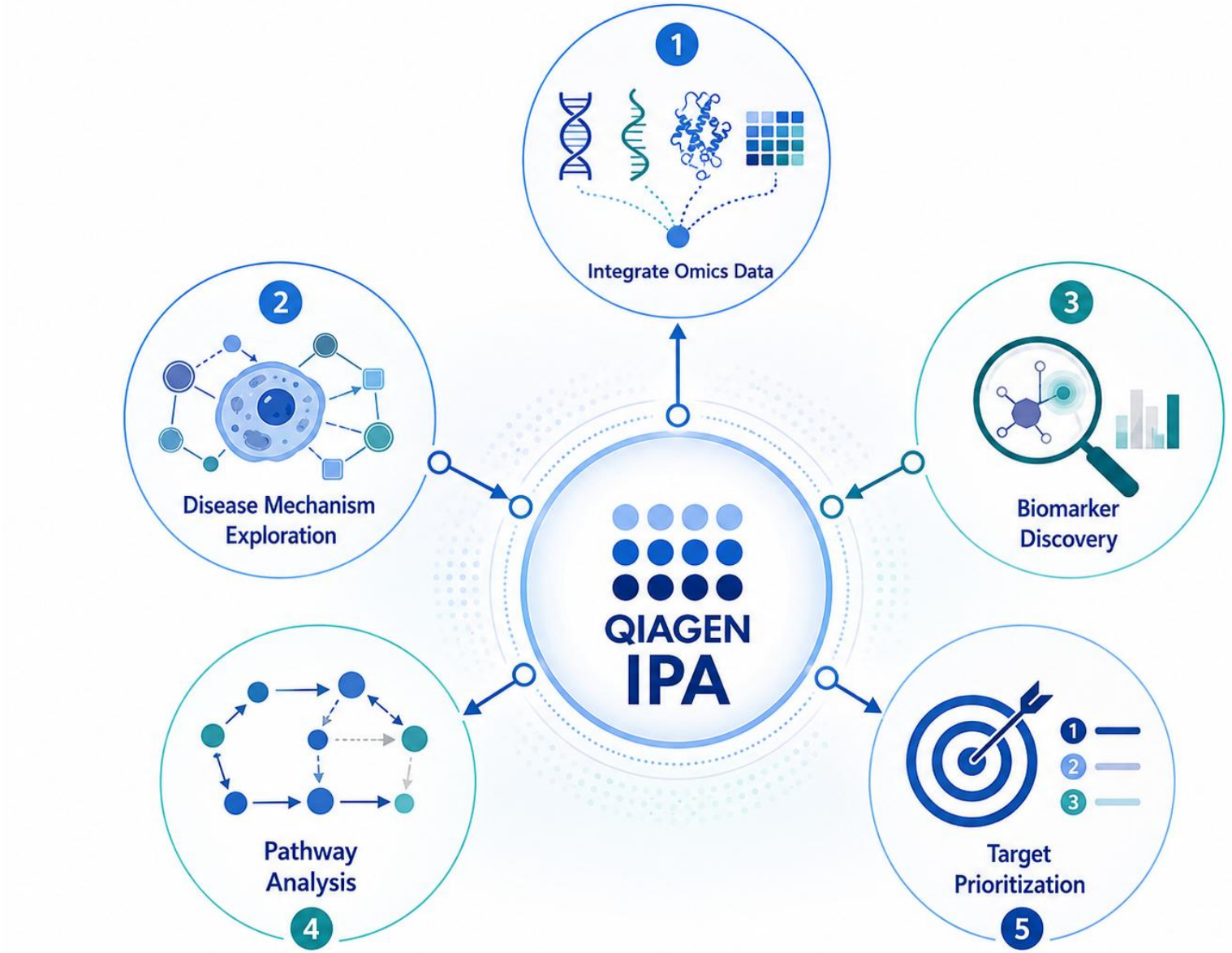
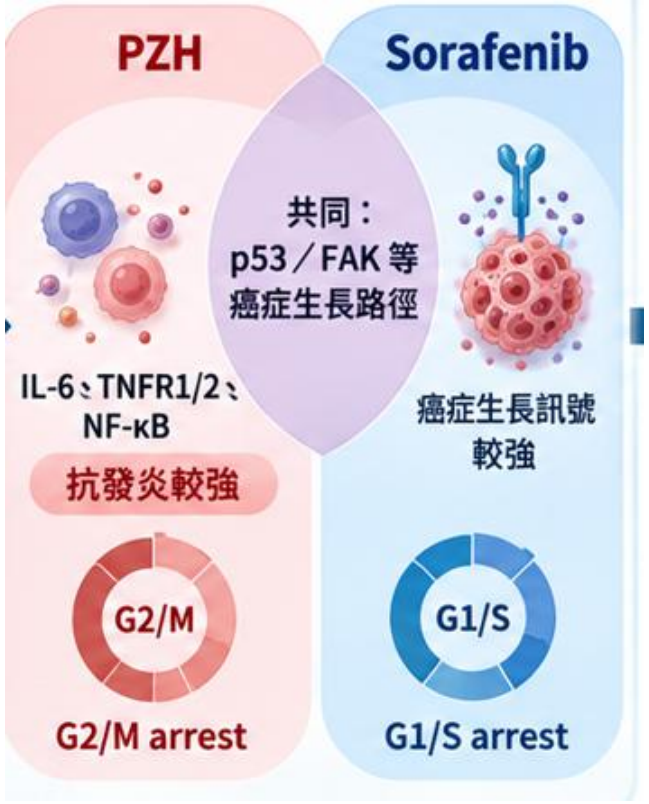
Five Key Applications of QIAGEN IPA in Drug Discovery



Anti-tumor mechanism of PTZ



分子變化 → 生物機轉 → 候選分子 → 實驗驗證

https://doi.org/10.1155/2020/4876251

Research Article

Deciphering Antitumor Mechanism of Pien Tze Huang in Mice of Hepatocellular Carcinoma Based on Proteomics

Dancai Fan,[1,2] **Chang Liu**,[3,4] **Li Li**,[2] **Cheng Lu**,[2] **Ning Zhao**,[2] **Jun Shu**,[5] **Xiaojuan He**,[2] **and Aiping Lu**[3,6]

[1]*The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou 510006, China*
[2]*Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China*
[3]*Law Sau Fai Institute for Advancing Translational Medicine in Bone and Joint Diseases, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong, SAR, China*
[4]*Sino-America Chinmedomics Technology Collaboration Center, National TCM Key Laboratory of Serum Pharmacochemistry, Laboratory of Metabolomics, Department of Pharmaceutical Analysis, Heilongjiang University of Chinese Medicine, Harbin 150040, China*
[5]*Institute of Clinical Medical Science, China-Japan Friendship Hospital, Beijing 100029, China*
[6]*Academy of Integrative Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China*

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Academic Editor: Pedro A. Reche

The Chinese formula Pien Tze Huang (PZH) has been used to treat hepatocellular carcinoma (HCC) and showed positive clinical effects. However, the antitumor mechanism of PZH in HCC remains unclear. In this study, HCC xenograft Balb/c mice were treated with PZH; then, proteomics detection and Ingenuity Pathway Analysis (IPA) were used to analyze the differentiated phosphorylated proteins in tumor tissues. The results indicated that PZH could inhibit tumor weight by 50.76%. Eighty-four upregulated and 11 downregulated phosphorylated proteins were identified in PZH-treated mice. Twenty signaling pathways were associated with inflammation (including the IL-6 and TNFR1/2 pathways), cancer growth (including the p53 and FAK pathways), and the cell cycle (including the G2/M and G1/S checkpoint regulation pathways). Moreover, TNF-α, IL-6, and several typical differentially expressed phosphorylated proteins (such as p-CCNB1, p-FOXO3, and p-STAT3) in tumor tissues, tumor cell viability, and cell cycle arrest assay *in vitro* further verify the results of IPA. These results revealed that PZH achieved antitumor activity in HCC; the underlying mechanisms of which were mainly through regulating the inflammation-associated cytokine secretion, cancer growth pathways, and induction of G2/M arrest. These data provided the potential molecular basis for PZH to act as a therapeutic drug or a supplement to chemotherapy drugs for human HCC in the future.

1. Introduction

Liver cancer, the fourth leading cause of cancer death worldwide, is one of the most common cancers in China [1, 2]. It is estimated to be responsible for more than 700,000 deaths in one year; the age-standardized 5-year relative survival rate of liver cancer is only 10.1% [3]. The most predominant type of liver cancer is hepatocellular carcinoma (HCC) [4]. Although there are various risk factors for inducing HCC, including viral infections, alcohol abuse, autoimmune hepatitis, diabetes mellitus, and obesity, these factors, especially hepatitis, point to induce chronic inflammation or even injury in the liver [1]. The mechanism of HCC has been shown to involve several pathways mainly related to cancer growth in HCC progression. In this context, previous studies have reported that inactivation of the tumor suppressor p53 pathway and alterations in the cell cycle are major defects in HCC [4–6]. Recently, increasing research has focused on inflammation, especially chronic inflammation and cytokines, in HCC. In the etiology and pathogenesis of HCC, persistent inflammation has been proven to exacerbate HCC, and most HCC cases arise in the context

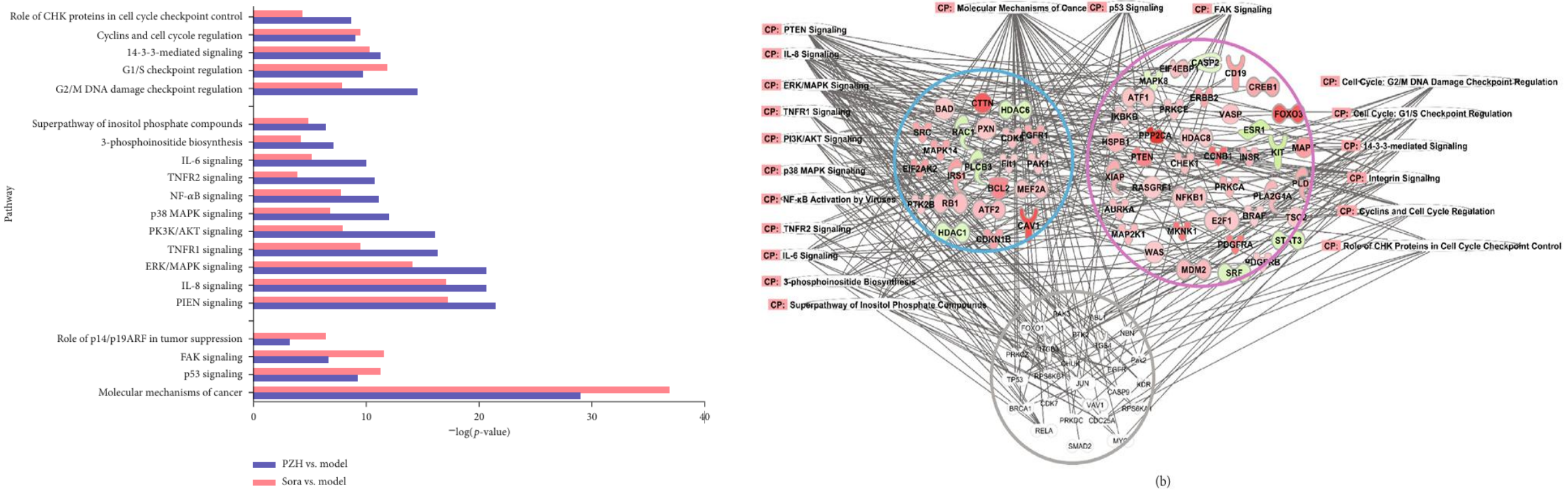
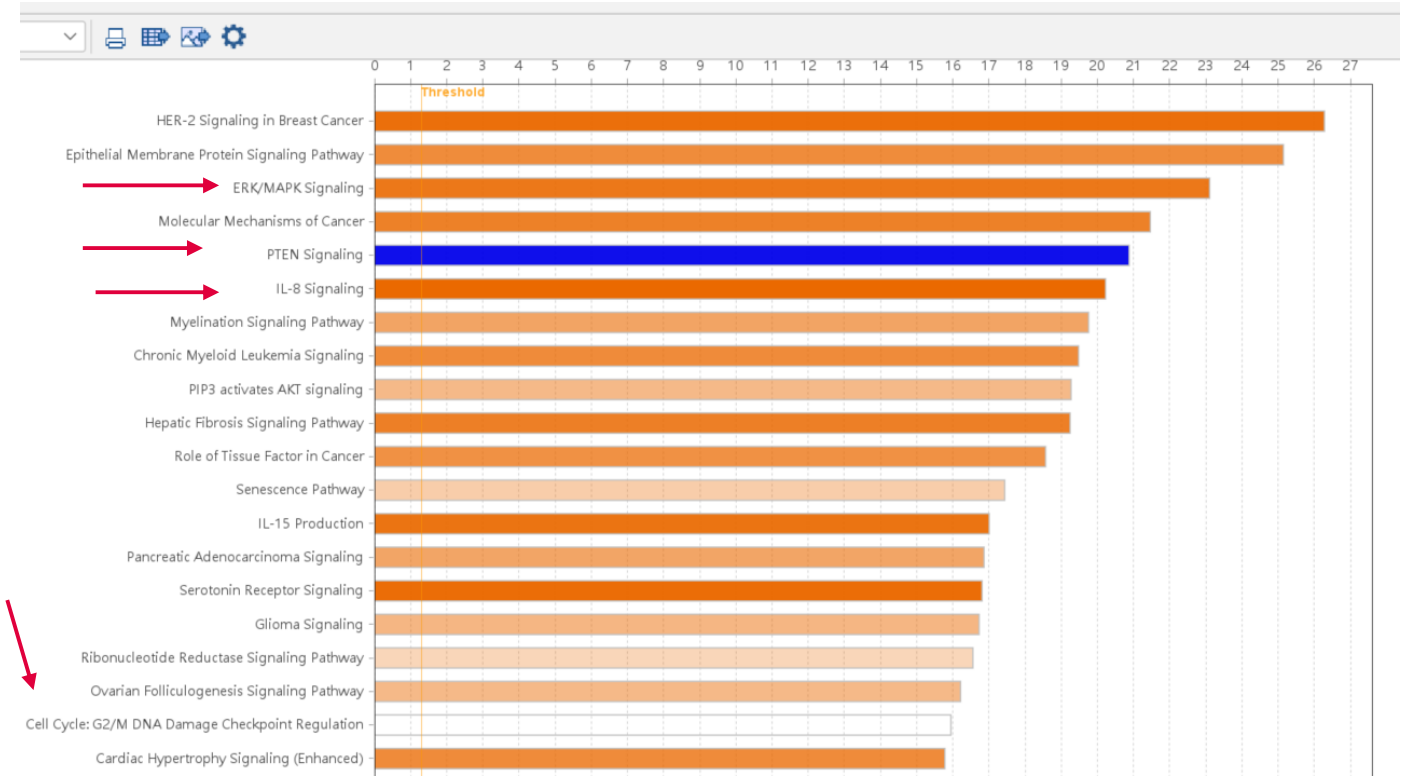
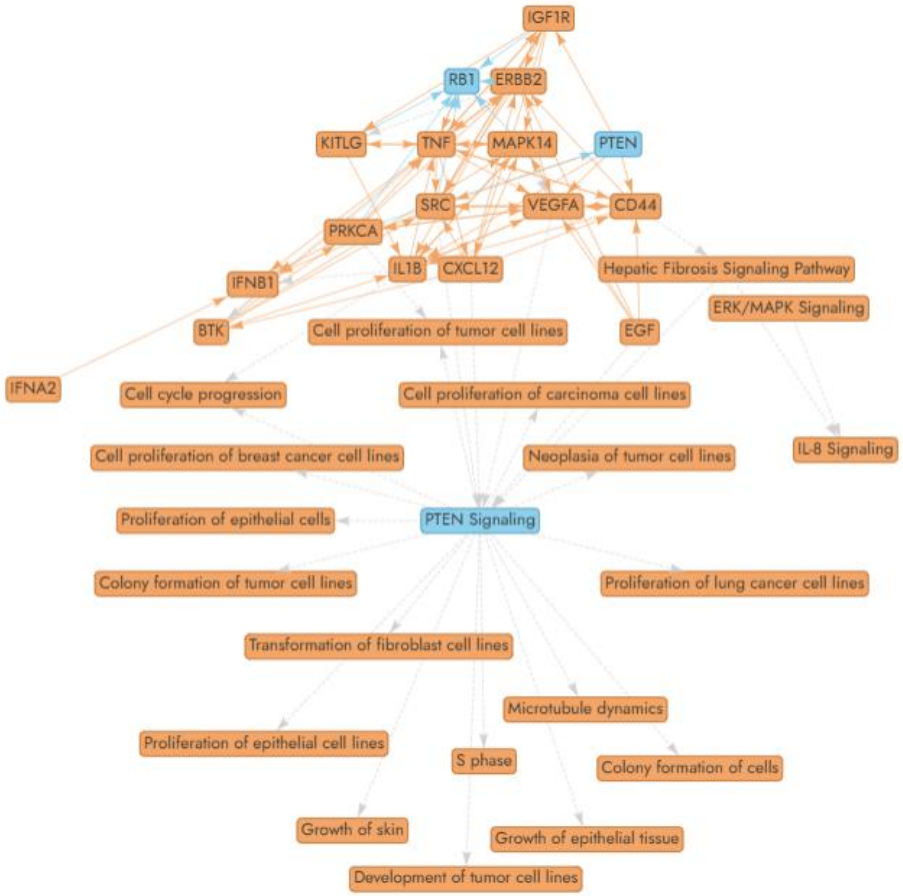
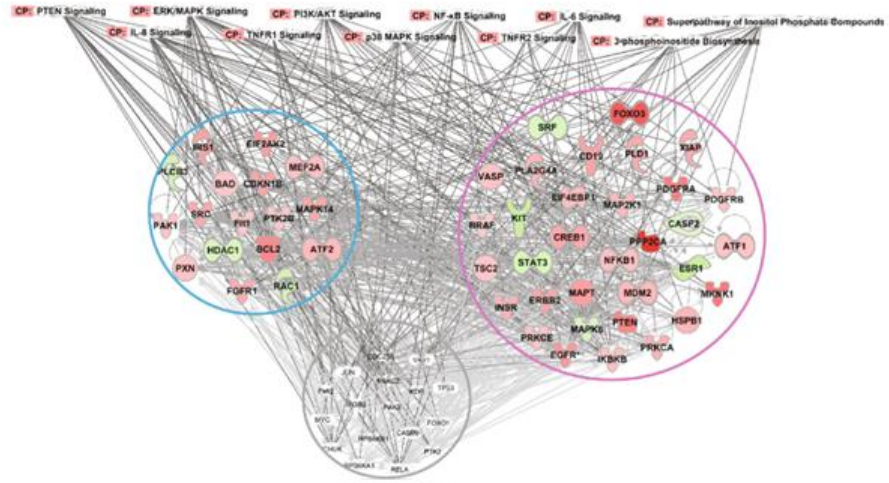


Figure 3: Comparison of involved pathways between PZH and Sora treatment. (a) The-log (p value) value of involved pathways in PZH and Sora groups. (b) The molecular network involved in those pathways regulated by PZH and Sora treatment.

PZH remodels tumor-associated phospho-signaling networks






CP: PTEN Signaling
CP: ERK/MAPK Signaling
CP: PI3K/AKT Signaling
CP: NF-κB Signaling
CP: IL-6 Signaling
CP: IL-8 Signaling
CP: TNFR1 Signaling
CP: p38 MAPK Signaling
CP: TNFR2 Signaling
CP: Superpathway of Inositol Phosphate Compounds
CP: 3-phosphoinositide Biosynthesis
IRS1
EIF2AK2
MEF2A
PLCB3
BAD
CDKN1B
SRC
MAPK14
PAK1
FYN
PTK2B
HDAC1
BCL2
ATF2
PXN
FGFR1
RAC1
FOXO3
SRF
CD13
PLD1
XIAP
VASP
PLA2G4A
EIF4EBP1
MAP2K1
PDGFRA
PDGFRB
BRAF
KIT
CASP2
CREB1
PPP2CA
ATF1
TSC2
STAT3
NFKB1
ESR1
INSR
ERBB2
MAPT
MDM2
MKNK1
PRKCE
MAPK8
PTEN
HSPB1
EGFR
IKBKB
PRKCA
(a)
CP: Cell Cycle: G2/M DNA Damage Checkpoint Regulation
CP: 14-3-3-mediated Signaling
CP: Role of CHK Proteins in Cell Cycle Checkpoint Co
CP: Cell Cycle: G1/S Checkpoint Regulation
CP: Cyclins and Cell Cycle Regulation
RAC1
CAV1
IRS1
PLCB3
CTTN
HDAC1
HDAC6
CDKN1B
SRC
FGFR1*
PXN
RB1
PAK1
BAD
E2F1
CCNB1
AURKA
MAPK8
MDM2
CHEK1
HDAC8
WAS
BRAF
MAP2K1
VASP
PPP2CA
PTEN
JUN
NBN
ITGB4
PRKDC
FOXO1
PRKCZ
Pak2
BRCA1
TP53
CDC25A
PAK3
ABL1
RPS6KA1
PTK2
CDK7
ITGB5
MYC
(b)
CP: Molecular Mechanisms of Cancer
CP: FAK Signaling
CP: p53 Signaling
CP: Role of p14/p19ARF in Tumor Suppre
BCL2
BAD
MAPK14
CDKN1B
FGFR1
IRS1
HDAC1
CDK5
RAC1
PLCB3
SRC
PAK1
RB1
PXN
AURKA
BRAF
E2F1
WAS
XIAP
CHEK1
MAP2K1
MAPK8
RASGRF1
NFKB1
MDM2
PTEN
PRKCA
PRKCE
TP53*
CDC25A
MYC
SMAD2
CASP9
CDK7
ABL1
RELA
EGFR
PTK2
PAK3
BRCA1
PRKDC
NBN
FOXO1
Pak2
JUN
PRKCZ
(c)
CP: IL-6 Signaling
CP: TNFR2 Signaling
CP: NF-κB Signaling
CP: TNFR1 Signaling
IRS1
EIF2AK2
FGFR1*
MAPK14
HDAC1
SRF
HSPB1
IKBKB
MAPK8
INSR
STAT3
BRAF
NFKB1
CASP2
XIAP
PDGFRB
PDGFRA
MAP2K1
(d)
CP: Cell Cycle: G1/S Checkpoint Regulation
CP: Cell Cycle: G2/M DNA Damage Checkpoint Regulation
CDKN1B
RB1
HDAC6
HDAC1
CHEK1
MDM2
E2F1
HDAC8
AURKA
CCNB1
(e)
CP: p53 Signaling
CP: FAK Signaling
HDAC1
IRS1
PAK1
SRC
RAC1
PXN
MAPK14
BCL2
RB1
FGFR1
MAP2K1
PTEN
WAS
MDM2
MAPK8
E2F1
CHEK1
Complex
Cytokine/growth factor
Chemical/toxicant
Enzyme
Group/complex
Growth factor
Kinase
Peptidase
Transcription regulator
Transmembrane receptor
Other
Function
Relationship
(f)

PTZ target protein

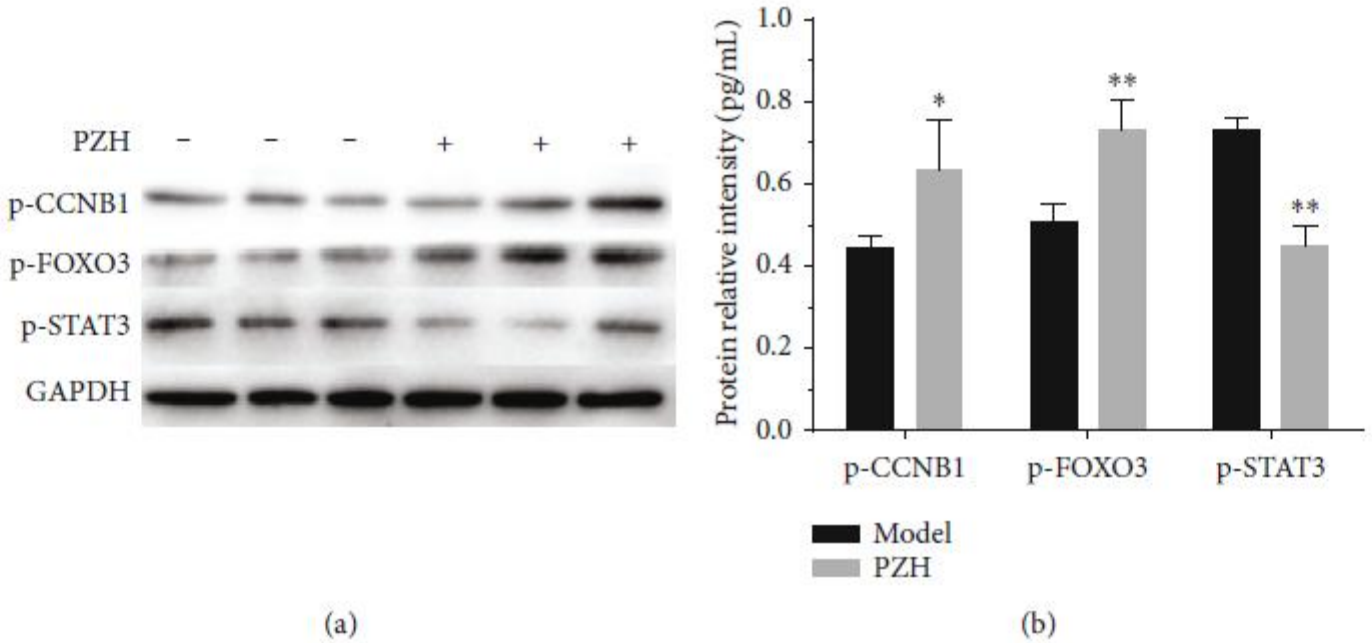


FIGURE 7: PZH upregulates the expression of p-CCNB1 and p-FOXO3 and downregulates the expression of p-STAT3 in tumor tissue of HCC mice. (a) Representative Western blot bands of p-CCNB1, p-FOXO3, and p-STAT3. (b) Analysis of relative protein levels. $^{*}p < 0.05$, $^{**}p < 0.01$ vs. model group.

Case study | Pien Tze Huang (PZH) in Hepatocellular Carcinoma

Proteomics + Ingenuity Pathway Analysis (IPA)

Fan et al. | Journal of Immunology Research | 2020
Deciphering Antitumor Mechanism of Pien Tze Huang in Mice of Hepatocellular Carcinoma Based on Proteomics

1. **PZH treatment** (traditional Chinese medicine / herbal formula)
2. **HCC xenograft mouse model**
3. **Tumor tissue phosphoproteomics profiling**
4. **IPA analysis**
5. **Biological mechanism interpretation**

KEY FINDINGS

- Tumor weight reduced by **50.76%**
- **95** differential phosphoproteins identified
- **84** upregulated | **11** downregulated
- **20** signaling pathways involved

MAJOR PATHWAY THEMES

- **Inflammation:** IL-6, TNF-alpha, TNFR1/2 signaling
- **Cancer growth:** p53 and FAK-related pathways
- **Cell cycle:** G2/M arrest and G1/S checkpoint regulation

TAKE-HOME MESSAGE

PZH shows antitumor activity in HCC by modulating inflammation-associated cytokine signaling, suppressing tumor-growth pathways, and promoting cell-cycle arrest.

Source: Fan D. et al., J Immunol Res. 2020; Article ID 4376251.

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Module 5 | Translational Applications: Drug Effect Prediction and Biomarker Discovery

- Case Study: BOLD-100 in Colorectal Cancer

BOLD-100 links a metal-based drug to ROS-driven cancer stress

KEY MESSAGE FROM THE PAPER

BOLD-100 is a pre-formed Ru(III) coordination drug. The study demonstrates that a metal-based drug can induce ROS-linked stress in cancer cells.

BRAF V600E → AhR / CYP1A1 → ROS
↓
replication stress → ATR / CHK1
↓
apoptosis / cell death

VACO432: IC_{50} 30.69 µM | VT1: IC_{50} 119.67 µM

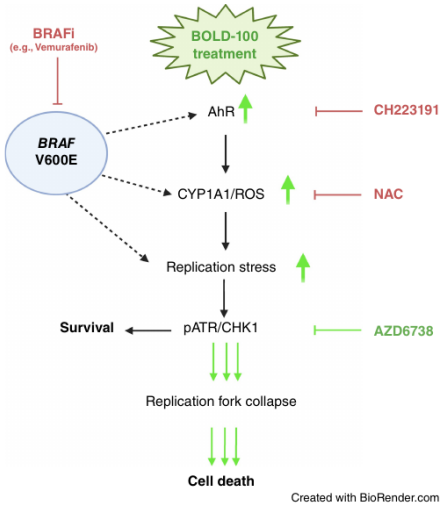
24 h exploratory DEG: VACO432 423↑ / 231↓; VT1 50↑ / 13↓

Shivaali Kareila[6], Richard Kennedy[6], Kienan I. Savage[6], Simon McDade[6], Adam Carie[6], Jim Pankovich[6], Mark Bazett[6], and Sandra Van Schaeybroeck[1]

ABSTRACT

Patients with class I ^{V600E}*BRAF*-mutant (MT) colorectal cancer exhibit a poor prognosis, and their response to combined anti-BRAF/EGFR inhibition remains limited. An unmet need exits for further understanding the biology of ^{V600E}*BRAF*MT colorectal cancer. We used differential gene expression of *BRAF*WT and MT colorectal cancer cells to identify pathways underpinning *BRAF*MT colorectal cancer. We tested a panel of molecularly/genetically subtyped colorectal cancer cells for their sensitivity to the unfolded protein response (UPR) activator BOLD-100. To identify novel combination strategies for BOLD-100, we performed RNA sequencing and high-throughput drug screening. Pathway enrichment analysis identified significant enrichment of the UPR and DNA repair pathways in *BRAF*MT colorectal cancer. We found that oncogenic *BRAF* plays a crucial role in mediating the response to BOLD-100. Using a systems biology approach, we identified ^{V600E}*BRAF*MT-dependent activation of the replication stress response kinase ataxia telangiectasia and Rad3-related (ATR) as a key mediator of resistance to BOLD-100. Further analysis identified acute increases in *BRAF*MT-dependent-reactive oxygen species levels following treatment with BOLD-100, which promoted ATR/CHK1 activation and apoptosis. Furthermore, activation of reactive oxygen species/ATR/CHK1 following BOLD-100 was mediated through the AhR transcription factor and CYP1A1. Importantly, pharmacological blockade of this resistance pathway with ATR inhibitors synergistically increased BOLD-100-induced apoptosis and growth inhibition in *BRAF*MT models. These results highlight a possible novel therapeutic opportunity for *BRAF*MT colorectal cancer.

Implications: BOLD-100 induces *BRAF*MT-dependent replication stress, and targeted strategies against replication stress (e.g., by using ATR inhibitors) in combination with BOLD-100 may serve as a potential novel therapeutic strategy for clinically aggressive *BRAF*MT colorectal cancer.



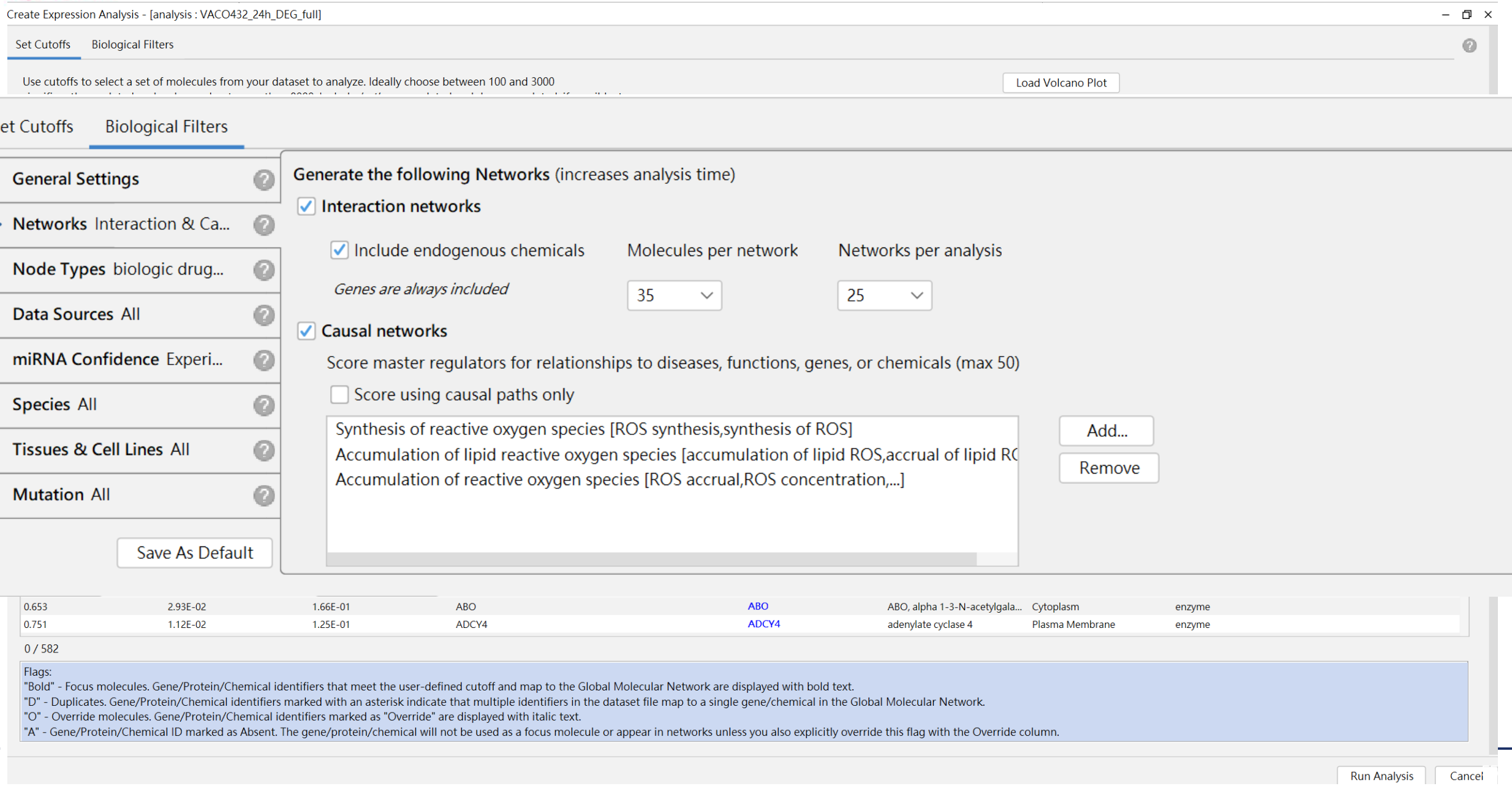
Introduction

BRAF mutations are found in approximately 10% of metastatic colorectal cancer tumors, and around 90% of these tumors harbor a T1799A transversion in exon 15, resulting in a valine amino acid substitution (V600E; ref. 1). The ^{V600E}*BRAF* (class I) mutation identifies a distinct subgroup of colorectal cancer, often associated

[1]Patrick G. Johnston Centre for Cancer Research, School of Medicine, Dentistry, and Biomedical Science, Queen's University Belfast, Belfast, United Kingdom. Queen's University Belfast, 97 Lisburn Road, Belfast BT9 7AE, United Kingdom. E-mail: s.vanschaeybroeck@qub.ac.uk

Source: Griffin et al., Molecular Cancer Research 2024; GSE252858 exploratory analysis

Analysis – Set Cutoff & Biological Filter

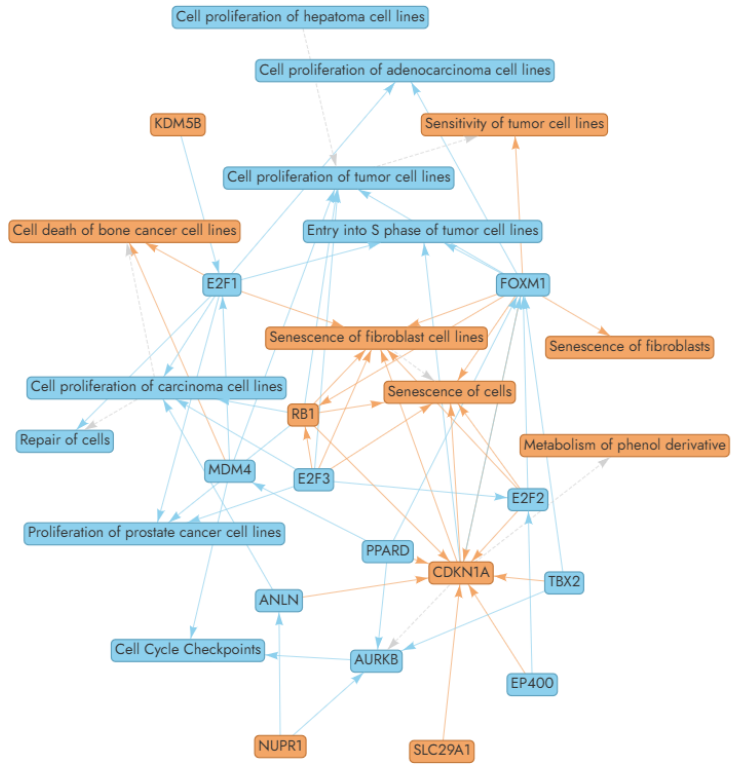


Graphical Summary

VACO432_24h_DEG_full - 2026-08-05 11:01 下午

Created on August 5, 2026, from dataset VACO432_24h_DEG_full

VACO432_24h_DEG_full - 2026-08-05 11:01 下午 Figure Legend OFF



RB–E2F–p21 Axis Orchestrating Cell-Cycle Arrest, Senescence, and Therapy Sensitization in Tumor Cells

AI-Suggested

RB–E2F–FOXM1 Core Cell-Cycle Control Module

The network centers on the classical RB–E2F pathway, extended by FOXM1, as a master regulator of cell-cycle progression in cancer cells. Decreases in E2F1, E2F2, and E2F3 uniformly lead to reduced cell proliferation across carcinoma, adenocarcinoma, and prostate cancer cell lines, as well as reduced entry into S phase and impaired cell repair. FOXM1 is tightly integrated: its decrease mirrors E2F loss, causing reduced tumor cell proliferation and S-phase entry, and increasing RB1. This is consistent with RB1 restraining E2Fs and FOXM1, such that increased RB1 activity decreases cell proliferation (tumor and carcinoma) and prostate cancer cell growth. Upstream regulators such as EP400, PPARD, TBX2, and KDM5B modulate this axis by reducing E2F and FOXM1 activity, thereby reinforcing cell-cycle arrest. Overall, the directionality shows a coherent module where RB1, E2F family members, and FOXM1 coordinate the commitment to cell division in tumor contexts.

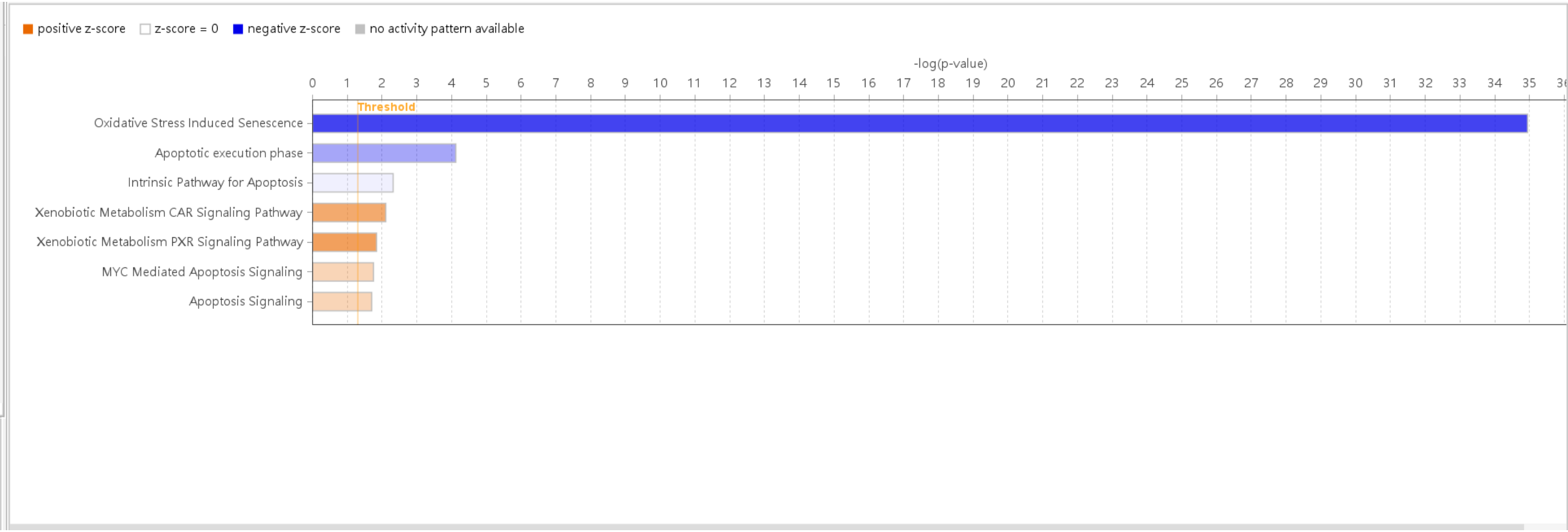
CDKN1A (p21)–Driven Cell-Cycle Arrest and Senescence Program

CDKN1A (p21) emerges as a central effector that converts upstream regulatory changes into durable cell-cycle exit and senescence. Multiple inputs (decrease of ANLN, E2F2, EP400, PPARD, FOXM1, TBX2, and increased RB1, SLC29A1) converge to increase CDKN1A. In turn, elevated CDKN1A decreases AURKB (a mitotic kinase), FOXM1, and tumor cell entry into S phase, directly enforcing cell-cycle arrest. Crucially, increased CDKN1A drives senescence in both general cell populations and fibroblast cell lines, and this fibroblast senescence feeds back to increase overall cellular senescence. The network therefore depicts p21 as the key node linking upstream transcriptional and chromatin regulators to a stable, senescent state rather than transient quiescence, particularly in tumor and fibroblast contexts.

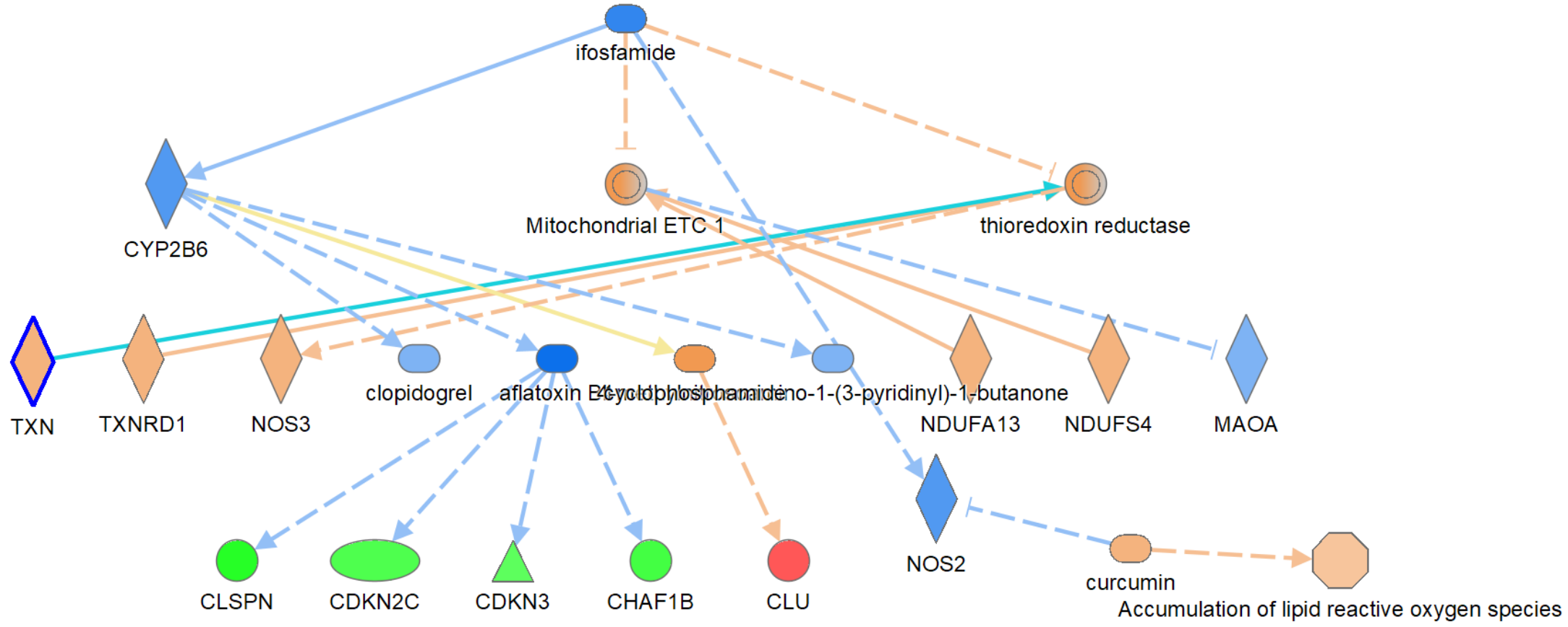
AURKB and MDM4 as Mitotic Checkpoint and Survival Nodes Undermined by p21/RB Signaling

AURKB and MDM4 function as downstream pro-proliferative and pro-survival factors that are suppressed when the RB–p21 axis is engaged. Decreased AURKB leads to reduced cell-cycle checkpoints, highlighting its role in mitotic progression and genomic surveillance; CDKN1A directly inhibits AURKB, and NUPR1 and PPARD also decrease AURKB, reinforcing this checkpoint failure from multiple upstream pressures. MDM4, a key regulator of p53 signaling, is decreased by PPARD, which in turn reduces tumor cell proliferation and cell-cycle checkpoints and promotes cell death in bone cancer cell lines via lowered E2F1. Together, AURKB and MDM4 represent critical nodes where cell-cycle and DNA damage checkpoint signaling intersect; their suppression in this network strengthens the transition from active cycling to arrest and death.

Pathway results



Causal relationship



Agenda

Introduction to pathway analysis

What is QIAGEN Ingenuity Pathway Analysis

- Introduction of Ingenuity Pathway Analysis
- What's new in Ingenuity Pathway Analysis

Module 1 | IPA in Drug Discovery and Translational Medicine

Module 2 | Transcriptomics and Drug Mechanism of Action

- Case Study: BOLD-100 in Colorectal Cancer

Module 3 | miRNA Regulation and Natural Compound Mechanisms

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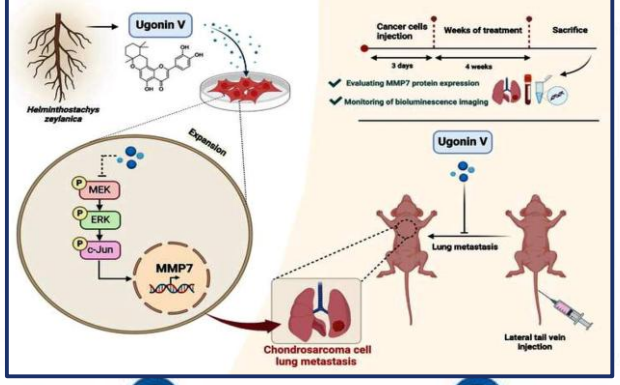
2025 LITERATURE CASE EXAMPLE & IPA RE-ANALYSIS CONCEPT MAP

Using Ugonin V and Chondrosarcoma miRNA Data as an Example



1 2025 PUBLICATION

ARTICLE

Ugonin V inhibits chondrosarcoma progression

2 STUDY MODEL

JJ012 chondrosarcoma cells

Control

Ugonin V treatment

3 miRNA EXPRESSION DATA

GEO / GSE279984

AUGCUAUGC...
UGCCAUAGC...
AUGGCUACU...
UACGUACGC...
AUCUCAGCA...

C1 C2 C3 U1 U2 U3

Low High

4 DIFFERENTIALLY EXPRESSED miRNAs

Identify significantly changed miRNAs

$-\log_{10}$ (p value)

$\log_2$ (Fold Change)

Down (miRNAs)

Up (miRNAs)

5 TARGET GENE PREDICTION

Predict target genes of the differentially expressed miRNAs

miRNA

Example gene list		
CTSV	MMP2	COL10A1
ITGB1	VEGFA	FAK
MET	SNAI1	...

6 QIAGEN IPA ANALYSIS

QIAGEN IPA

Diseases & Functions

Molecular Networks

Canonical Pathways

miRNA / Target Interpretation

7 KEY MECHANISM & VALIDATION

miR-4799-5p

CTSV

migration / invasion / metastasis ↓

Mechanistic validation supports IPA predictions

KEY TAKEAWAYS FROM RE-ANALYSIS

REPRODUCIBLE WITH PUBLIC DATA

Utilizing GEO public data ensures transparency and reproducibility of the analysis pipeline.

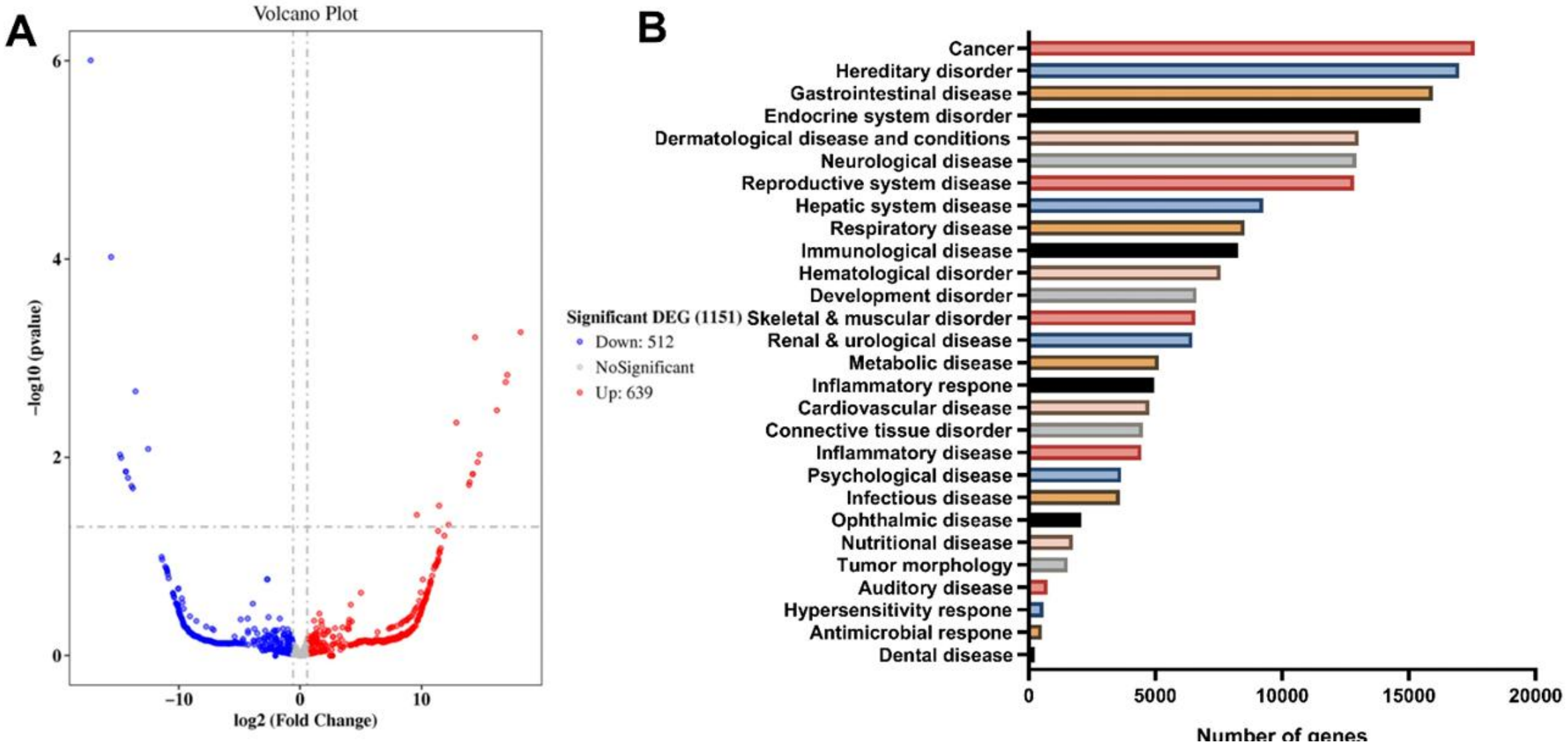
DISEASE & PATHWAY INSIGHTS

Integrating differential miRNA and target genes reveals key disease mechanisms and signaling pathways.

ACTIONABLE FOR FUTURE RESEARCH

Establish a framework for analysis and validation to support future drug discovery and experimental design.

Case Study 2 | Ugonin V inhibits chondrosarcoma metastasis

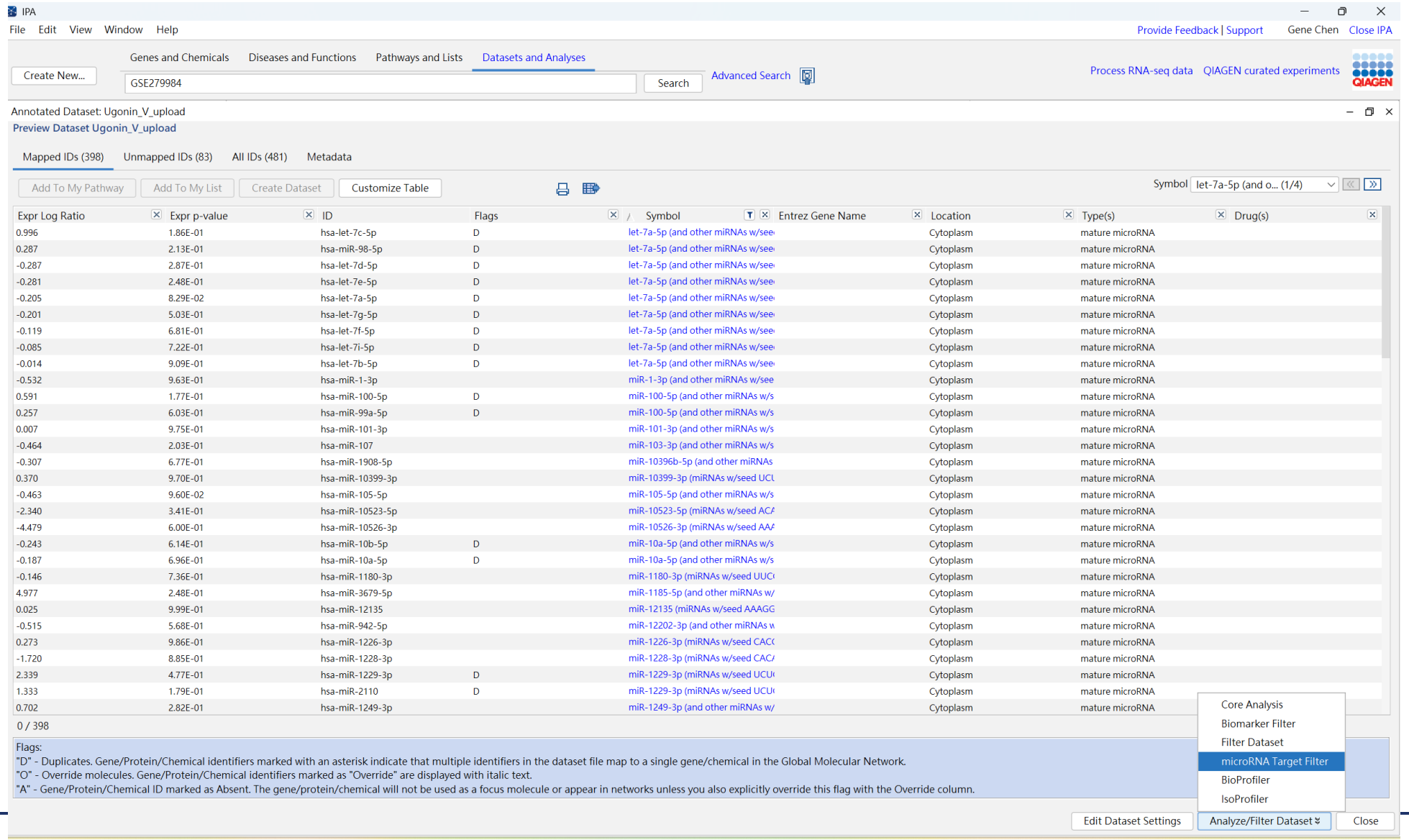


Ugonin V treatment Differential expression

	A	B	C	D	E	F	G	H	I	J	K
1	gene_id	length	Control_mean_TPM	Treatment_mean_TPM	Control_mean_norm_count	Treatment_mean_norm_count	log2FoldChange	pvalue	padj_BH	tested	significance
2	NovelmiRNA-368	21.000	0.000	398.480	0.000	2649.871	12.372	3.35E-04	1.61E-01	☑	Not significant
3	hsa-miR-3912-3p	21.000	2.735	0.000	19.013	0.000	-5.286	1.95E-03	4.70E-01	☑	Not significant
4	NovelmiRNA-12	22.000	0.000	51.040	0.000	337.323	9.400	7.70E-03	7.60E-01	☑	Not significant
5	hsa-miR-548au-3p	22.000	0.000	20.165	0.000	133.536	8.066	6.22E-03	7.60E-01	☑	Not significant
6	NovelmiRNA-155	23.000	0.000	8.105	0.000	53.618	6.758	9.48E-03	7.60E-01	☑	Not significant
7	hsa-miR-222-3p	23.000	12569.520	20970.735	87270.825	139665.775	0.678	8.80E-03	7.60E-01	☑	Not significant
8	NovelmiRNA-554	23.000	869.080	0.000	6053.420	0.000	-13.564	1.24E-02	7.74E-01	☑	Not significant
9	NovelmiRNA-371	24.000	0.000	12.305	0.000	82.657	7.378	1.45E-02	7.74E-01	☑	Not significant
10	hsa-miR-145-5p	23.000	808.955	432.415	5622.889	2883.519	-0.963	1.39E-02	7.74E-01	☑	Not significant
11	hsa-miR-4521	25.000	2796.855	0.000	19511.475	0.000	-15.252	1.75E-02	8.40E-01	☑	Not significant
12	NovelmiRNA-190	22.000	219.440	0.000	1517.937	0.000	-11.568	2.14E-02	8.92E-01	☑	Not significant
13	NovelmiRNA-120	22.000	6.705	0.000	46.471	0.000	-6.554	2.23E-02	8.92E-01	☑	Not significant
14	NovelmiRNA-491	21.000	0.000	13.705	0.000	89.370	7.490	3.00E-02	9.70E-01	☑	Not significant
15	hsa-miR-3661	22.000	0.000	3.365	0.000	22.058	5.496	3.03E-02	9.70E-01	☑	Not significant
16	hsa-miR-324-3p	23.000	151.185	99.540	1050.605	659.282	-0.672	2.75E-02	9.70E-01	☑	Not significant
17	NovelmiRNA-513	18.000	0.000	141.995	0.000	908.639	10.828	4.40E-02	1.00E+00	☑	Not significant
18	NovelmiRNA-230	18.000	108.545	0.000	745.200	0.000	-10.542	8.91E-02	1.00E+00	☑	Not significant
19	NovelmiRNA-736	18.000	0.000	43.235	0.000	312.934	9.292	2.31E-01	1.00E+00	☑	Not significant
20	hsa-miR-4435	22.000	0.055	64.670	0.376	401.966	8.844	1.01E-01	1.00E+00	☑	Not significant

Case Study 2 | Ugonin V inhibits chondrosarcoma metastasis

miRNA target mRNA

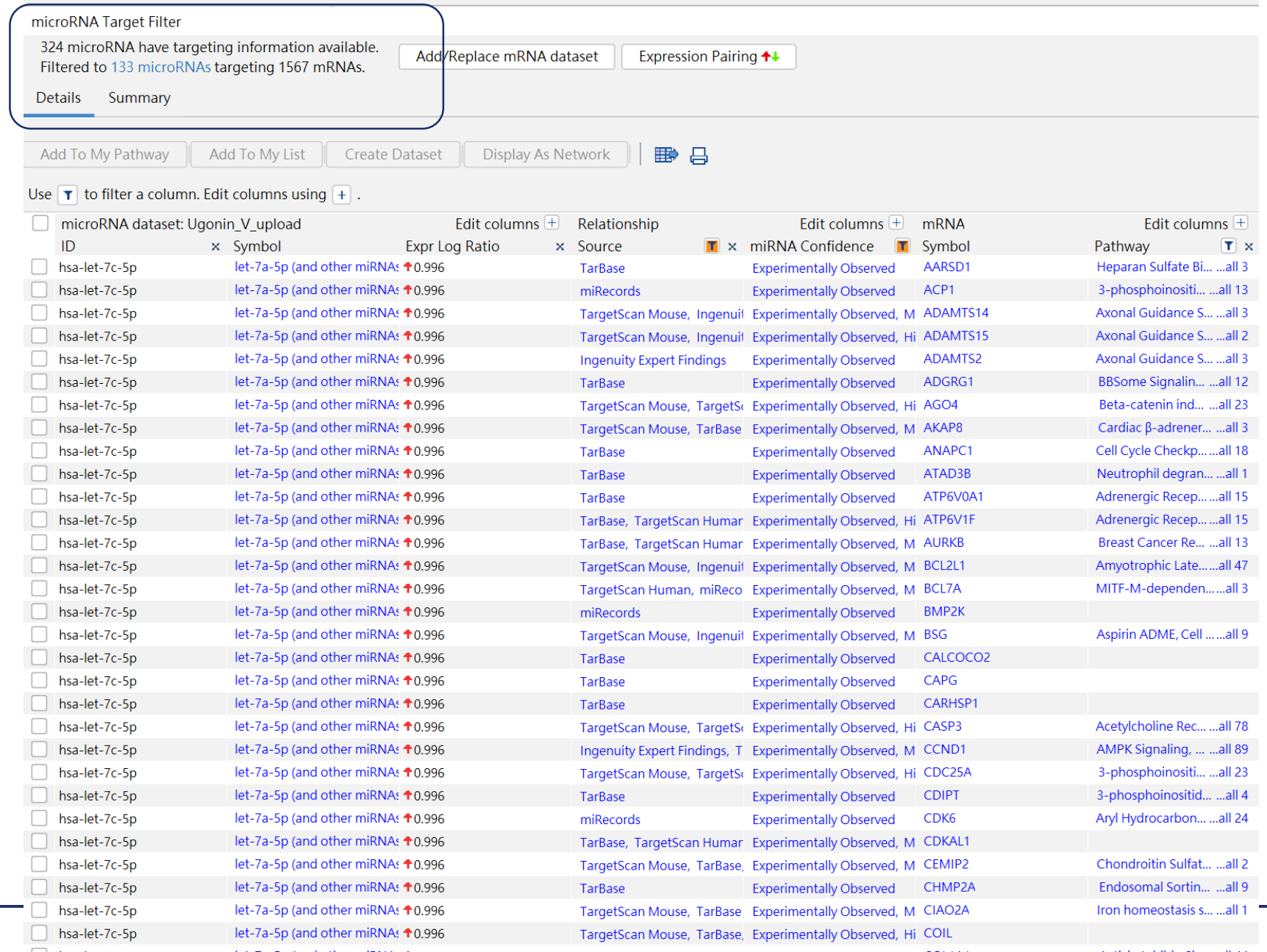


Case Study 1 | Ugonin V inhibits chondrosarcoma metastasis

324 miRNA

↓

1567 mRNA



microRNA Target Filter

324 microRNA have targeting information available.
Filtered to 133 microRNAs targeting 1567 mRNAs.

Add/Replace mRNA dataset | Expression Pairing

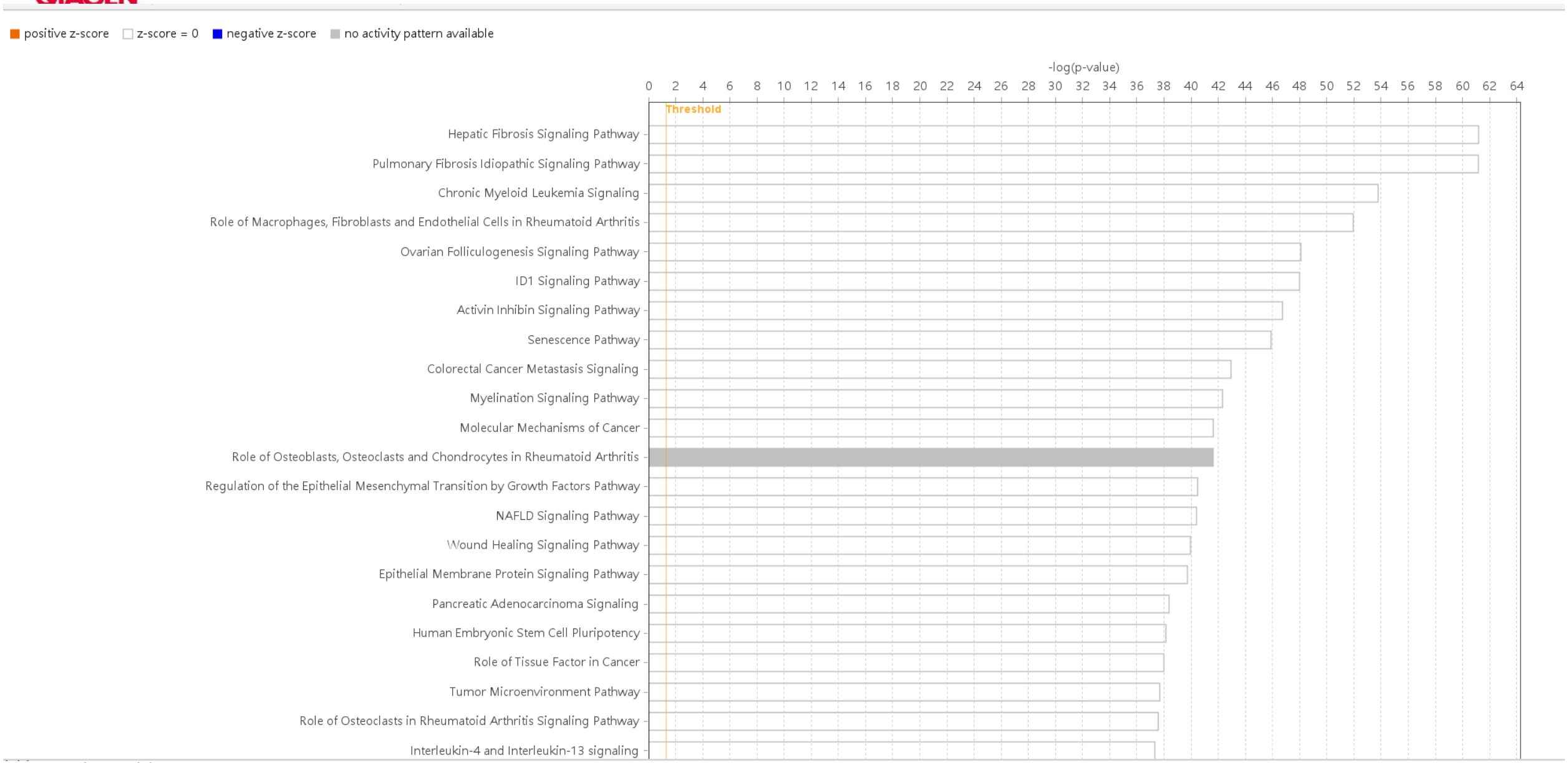
Details | Summary

Add To My Pathway | Add To My List | Create Dataset | Display As Network

Use T to filter a column. Edit columns using + .

microRNA dataset: Ugonin_V_upload			Edit columns	Relationship	Edit columns	mRNA	Edit columns
ID	Symbol	Expr Log Ratio		Source	miRNA Confidence	Symbol	Pathway
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase	Experimentally Observed	AARSD1	Heparan Sulfate Bi... ...all 3
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		miRecords	Experimentally Observed	ACP1	3-phosphoinositi... ...all 13
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TargetScan Mouse, Ingenuit	Experimentally Observed, M	ADAMTS14	Axonal Guidance S... ...all 3
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TargetScan Mouse, Ingenuit	Experimentally Observed, Hi	ADAMTS15	Axonal Guidance S... ...all 2
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		Ingenuity Expert Findings	Experimentally Observed	ADAMTS2	Axonal Guidance S... ...all 3
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase	Experimentally Observed	ADGRG1	BBSome Signalin... ...all 12
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TargetScan Mouse, TargetS	Experimentally Observed, Hi	AGO4	Beta-catenin ind... ...all 23
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TargetScan Mouse, TarBase	Experimentally Observed, M	AKAP8	Cardiac β-adrener... ...all 3
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase	Experimentally Observed	ANAPC1	Cell Cycle Checkp... ...all 18
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase	Experimentally Observed	ATAD3B	Neutrophil degran... ...all 1
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase	Experimentally Observed	ATP6V0A1	Adrenergic Recep... ...all 15
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase, TargetScan Humar	Experimentally Observed, Hi	ATP6V1F	Adrenergic Recep... ...all 15
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase, TargetScan Humar	Experimentally Observed, M	AURKB	Breast Cancer Re... ...all 13
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TargetScan Mouse, Ingenuit	Experimentally Observed, M	BCL2L1	Amyotrophic Late... ...all 47
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TargetScan Human, miReco	Experimentally Observed, M	BCL7A	MITF-M-dependen... ...all 3
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		miRecords	Experimentally Observed	BMP2K	
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TargetScan Mouse, Ingenuit	Experimentally Observed, M	BSG	Aspirin ADME, Cell ... ...all 9
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase	Experimentally Observed	CALCOCO2	
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase	Experimentally Observed	CAPG	
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase	Experimentally Observed	CARHSP1	
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TargetScan Mouse, TargetS	Experimentally Observed, Hi	CASP3	Acetylcholine Rec... ...all 78
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		Ingenuity Expert Findings, T	Experimentally Observed, M	CCND1	AMPK Signaling, ...all 89
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TargetScan Mouse, TargetS	Experimentally Observed, Hi	CDC25A	3-phosphoinositi... ...all 23
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase	Experimentally Observed	CDIPT	3-phosphoinositid... ...all 4
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		miRecords	Experimentally Observed	CDK6	Aryl Hydrocarbon... ...all 24
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase, TargetScan Humar	Experimentally Observed, M	CDKAL1	
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TargetScan Mouse, TarBase,	Experimentally Observed, M	CEMIP2	Chondroitin Sulfat... ...all 2
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TarBase	Experimentally Observed	CHMP2A	Endosomal Sortin... ...all 9
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TargetScan Mouse, TarBase	Experimentally Observed, M	CIAO2A	Iron homeostasis s... ...all 1
hsa-let-7c-5p	let-7a-5p (and other miRNAs	0.996		TargetScan Mouse, TarBase,	Experimentally Observed, Hi	COIL	

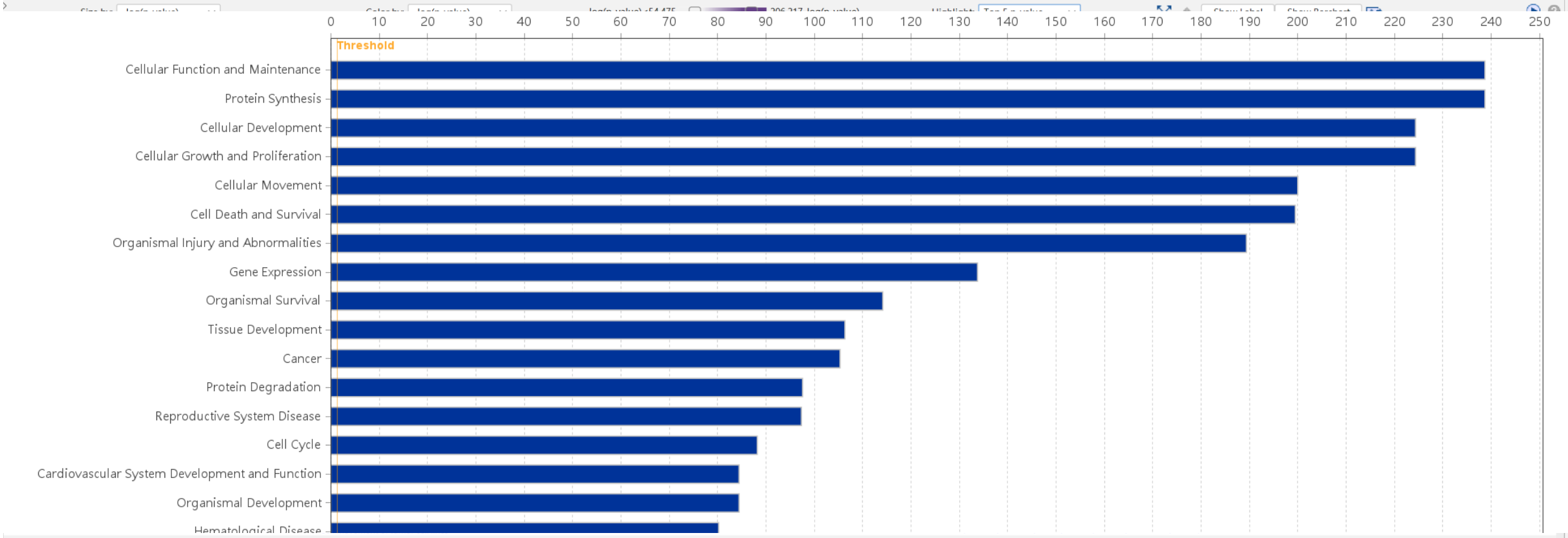
Case Study 1 | Ugonin V inhibits chondrosarcoma metastasis



Disease and function

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

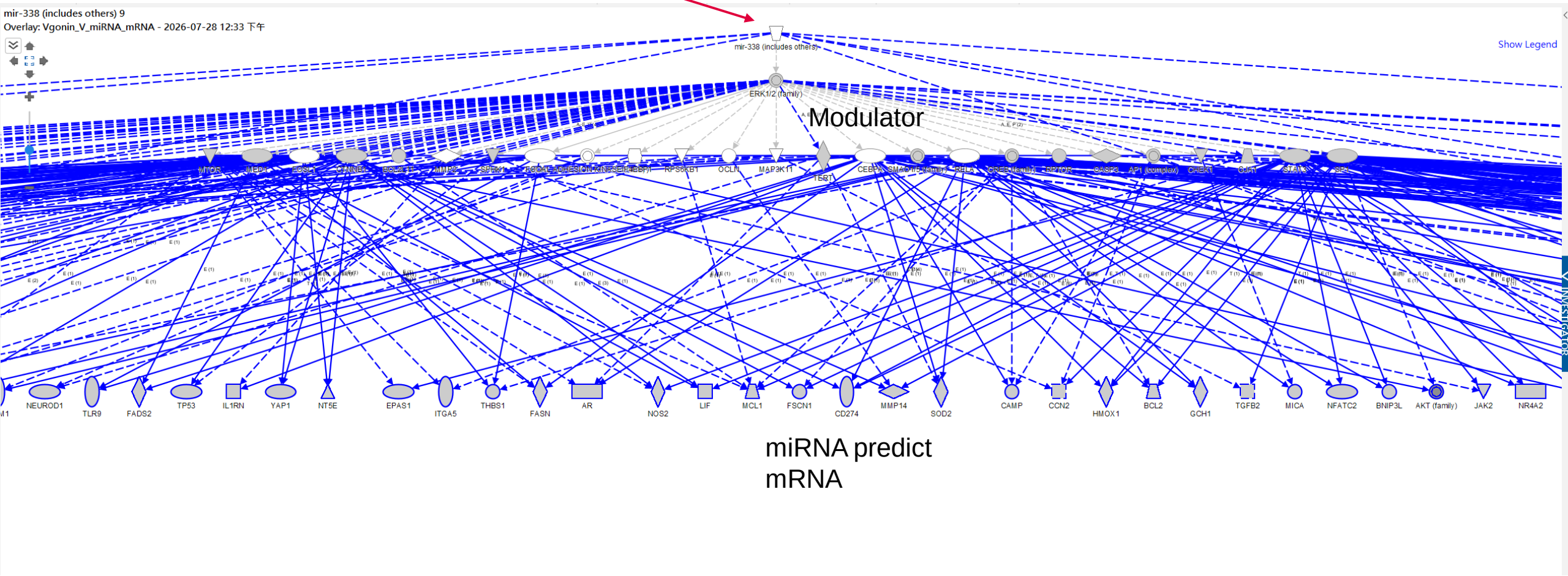
Diseases and Bio Functions | Tox Functions



Cell Death and Survival,Organismal Injury and Abnormalities	Apoptosis of tumor cell lines	4.06E-190	ABCB1, ABCG2, ABL1, ACVR1B, ADIPOR2, ADORA2B, AGO1, AGO2,	...all 645	645
Cellular Movement	Migration of tumor cell lines	3.03E-188	ABCB1, ABCG2, ACOT12, ACTA2, ACVR1, ADAMTS1, ADAR, ADPGK,	...all 705	705
Cell Death and Survival,Organismal Injury and Abnormalities	Cell death of tumor cell lines	1.71E-182	ABCB1, ABCG2, ABL1, ACVR1B, ADAR, ADIPOR2, ADORA2B, AGO1,	...all 703	703
Cell Death and Survival,Organismal Injury and Abnormalities	Necrosis	4.42E-163	ABCB1, ABCG2, ABL1, ACP1, ACVR1B, ADAR, ADIPOR2, ADORA2B,	...all 776	776
Cellular Movement	Invasion of cells	8.11E-157	ABCG2, ABL1, ACOT12, ACTA2, ACVR1, ADAMTS15, ADAR, AGO1,	...all 572	572
Cellular Movement	Invasion of tumor cell lines	3.09E-153	ABCG2, ABL1, ACOT12, ACTA2, ACVR1, ADAMTS15, ADAR, AGO1,	...all 553	553
Gene Expression	Activation of gene	1.75E-134	ACVR1, ACVR1B, ADAMTS1, ADAR, ADORA2B, AGTR1, AKT1, AKT2,	...all 458	458
Cellular Development,Cellular Growth and Proliferation	Cell proliferation of carcinoma cell lines	1.11E-125	ADAMTS1, ADAR, AGO1, AGO2, AGO4, AJUBA, AKT1, AKT2, AMOT,	...all 463	463
Cell Death and Survival	Cell survival	3.05E-118	ABCB1, ABCG2, ABL1, ACVR2A, ADPGK, AGO2, AHNAK, AJUBA, AK...	...all 499	499

Causal network

Causal network



miRNA predict mRNA

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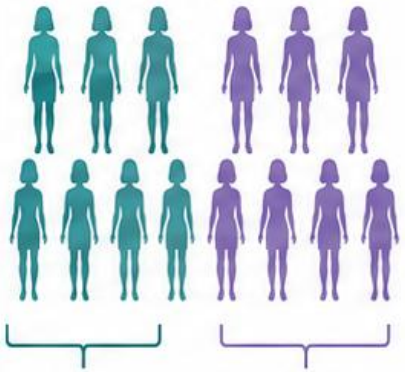
1 Cohort / Clinical Context → 2 Omics Profiling → 3 Differential Expression → 4 IPA Analysis → 5 Key Biological Finding

49 Gynecologic Cancer Patients

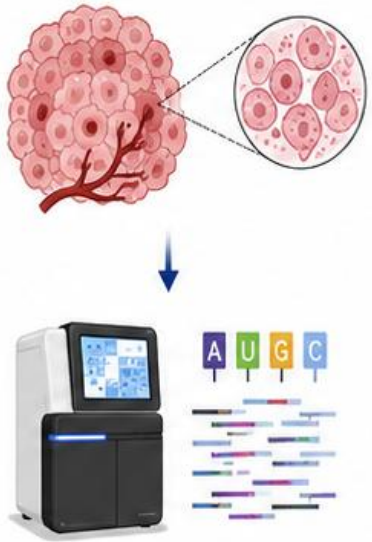
Nivolumab / Pembrolizumab



Responders vs Non-responders

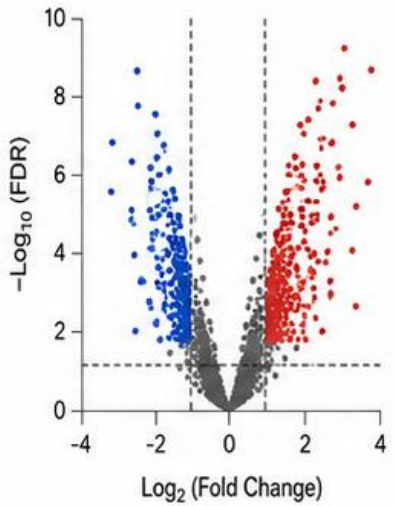
PFS / OS

Tumor RNA-seq / Transcriptome Profiling

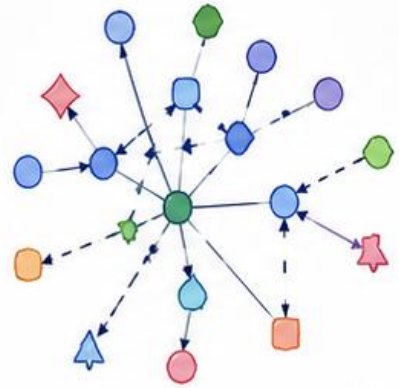


RNA Sequencing

DEG Analysis

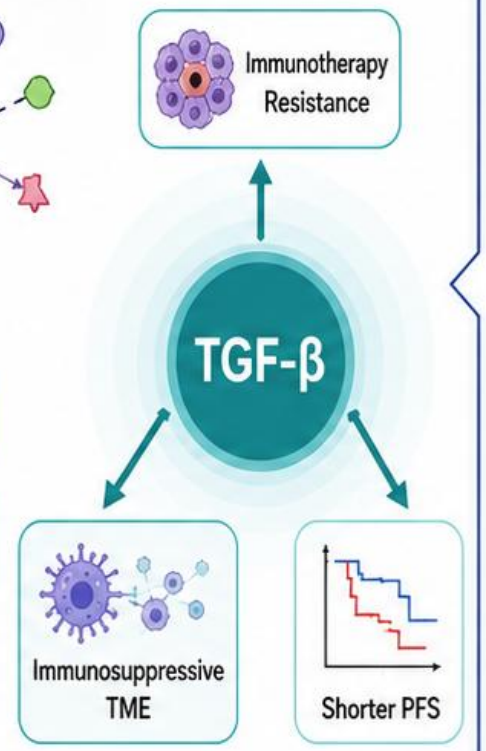


Responder vs Non-responder



- Canonical Pathways
- Upstream Regulators
- Disease Mechanisms

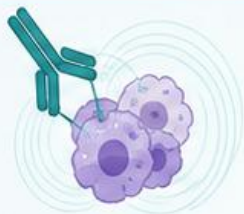
TGF-β Signature



Value of IPA

- Mechanism Discovery
- Biomarker Identification
- Target Prioritization
- Rational Combination Strategy

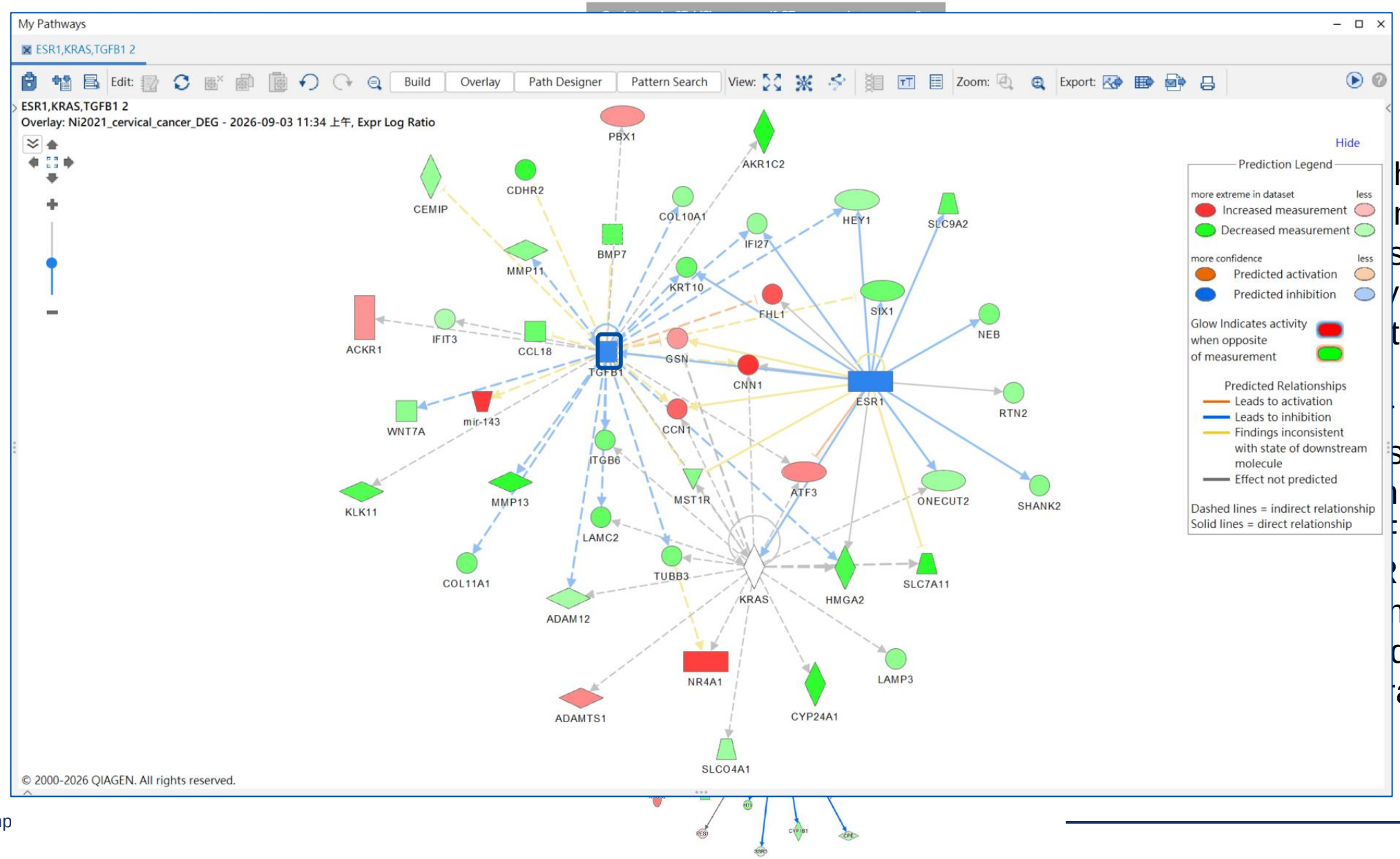
High TGF-β signaling predicts ICI resistance and supports TGF-β-targeted combination approaches.



IPA Enables Target Prioritization from Responder–Non-responder DEGs

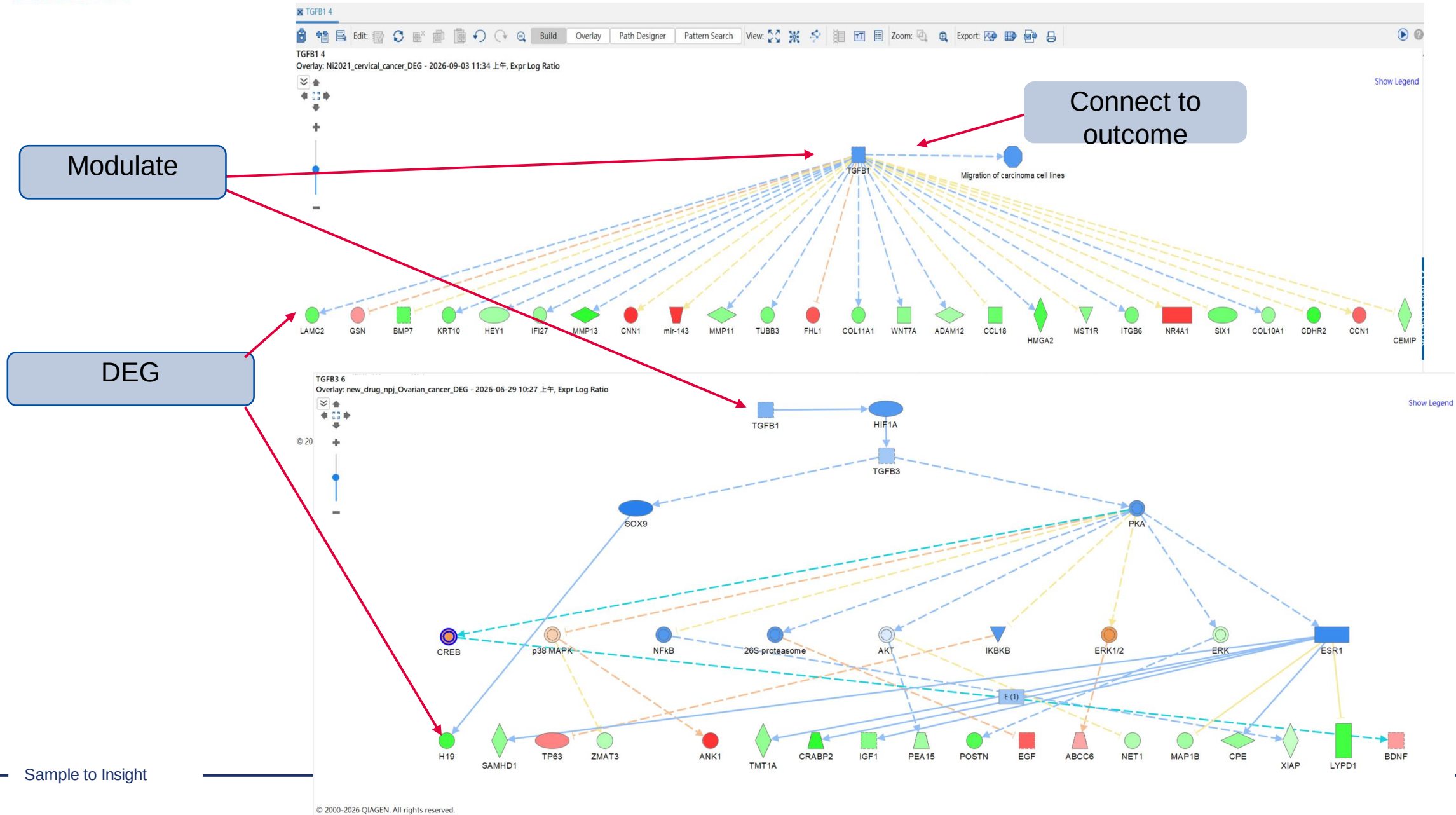
A

B

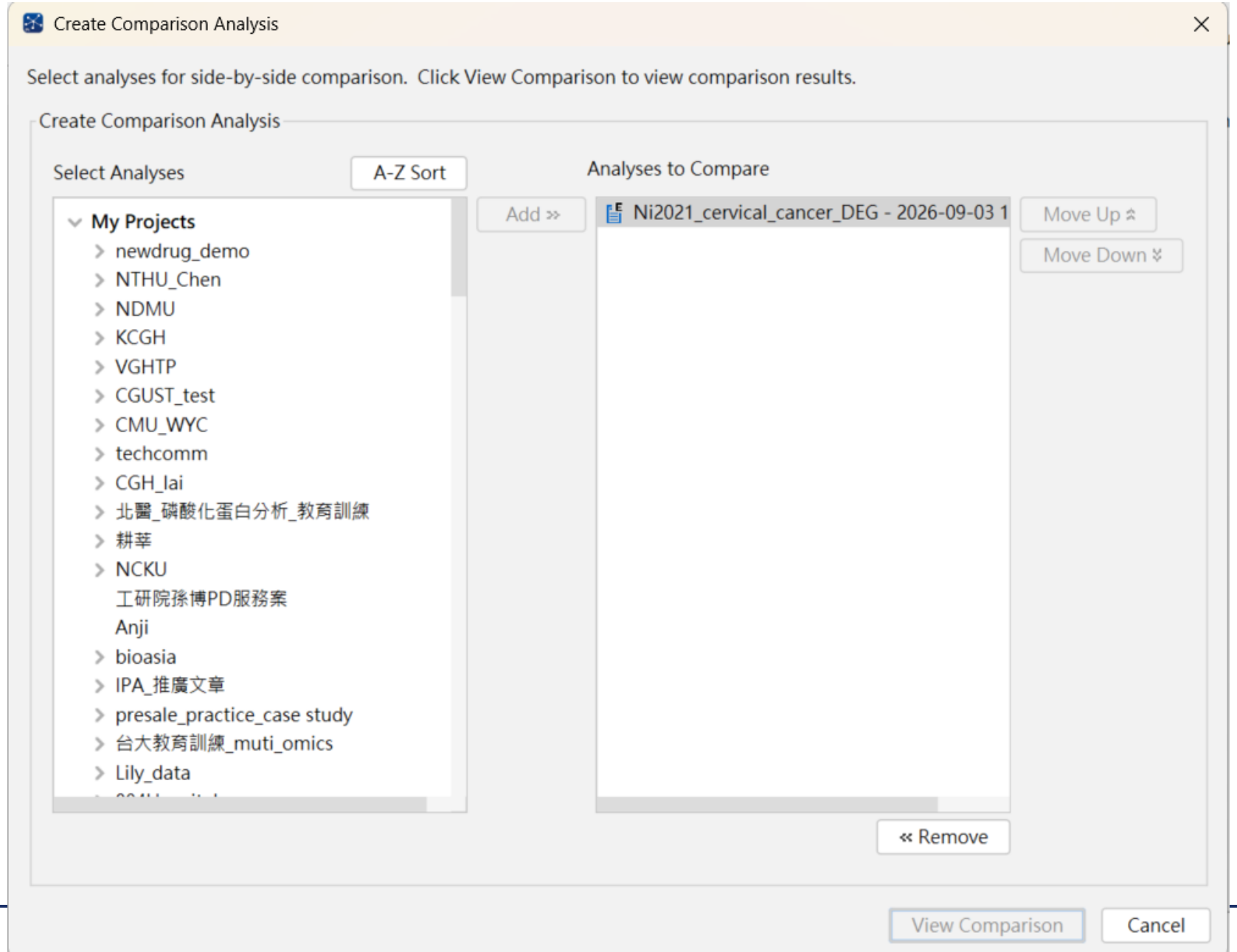


how transcriptomic
munotherapy
sponders can be
potheses using
ting DEGs as
IPA maps them
networks and
s that may drive
is study, shared
FB1, KRAS, IGF1,
RB provided a
echanism
development, and
ategies.

Causal network

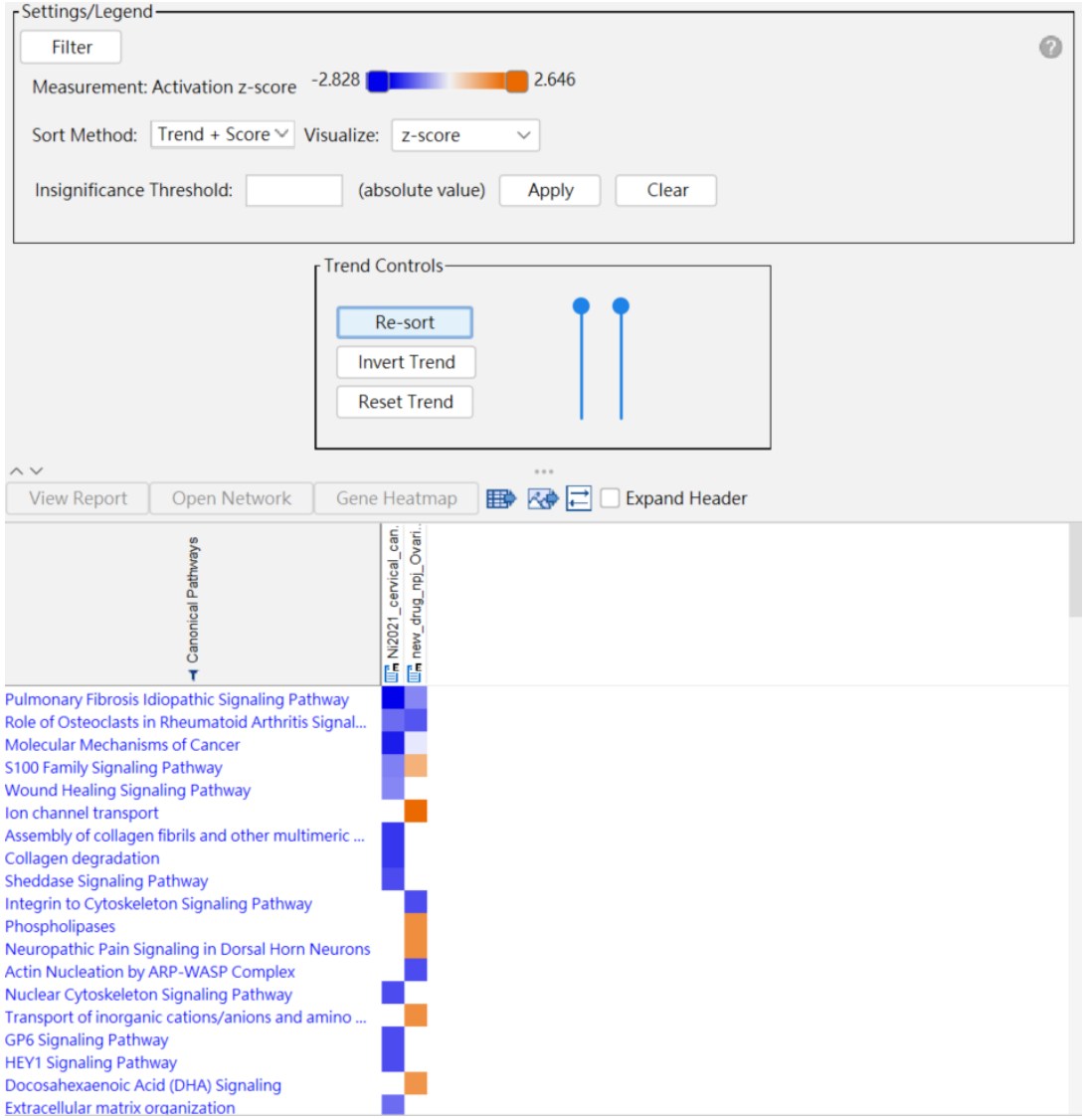


Comparison analysis

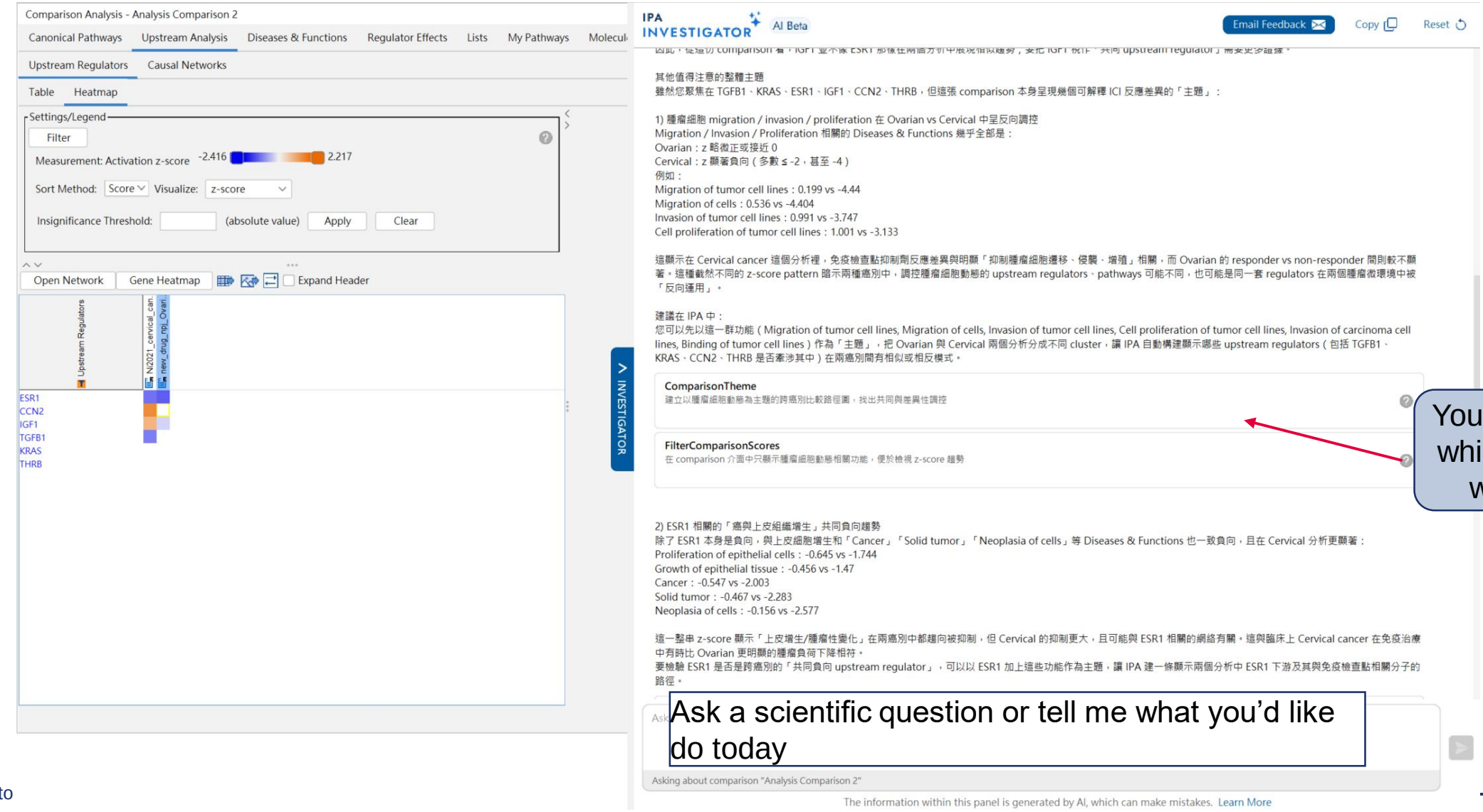


Comparison Analysis

Canonical Pathway

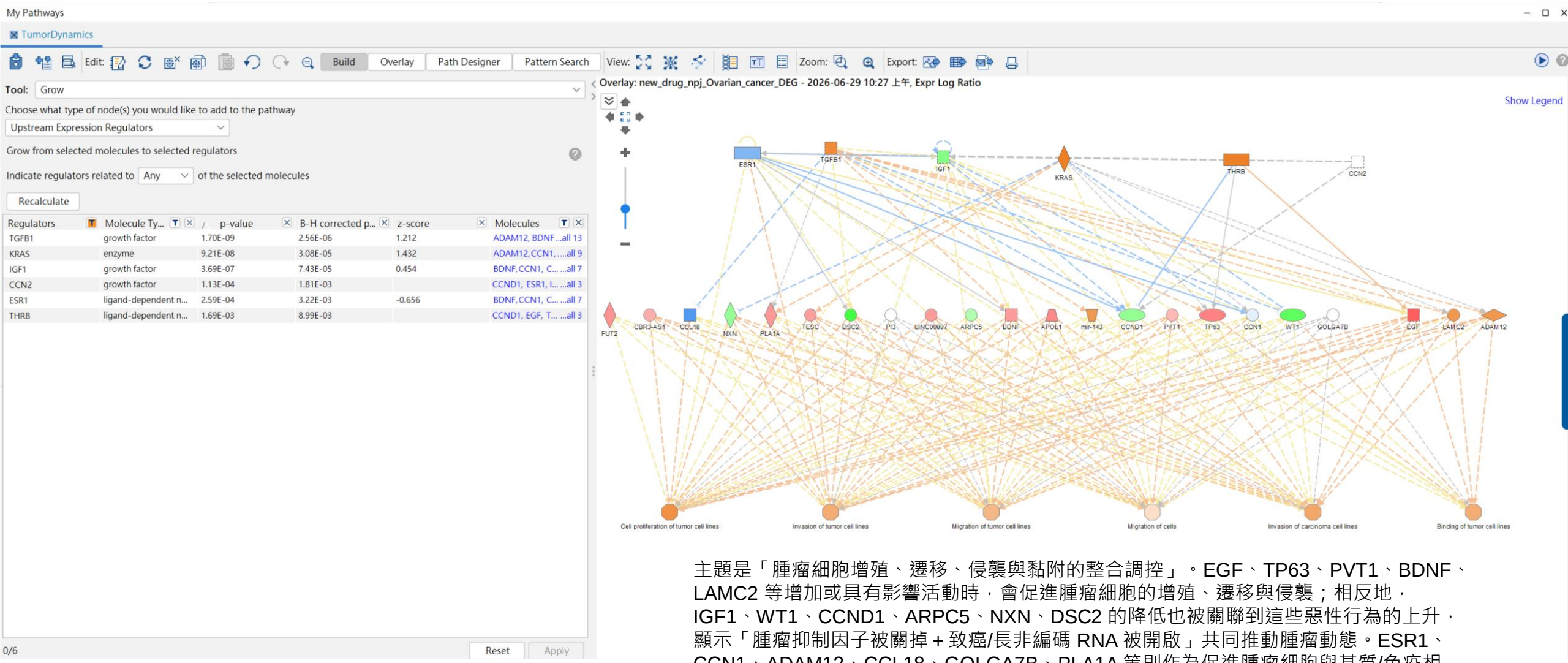


Upstream regulator



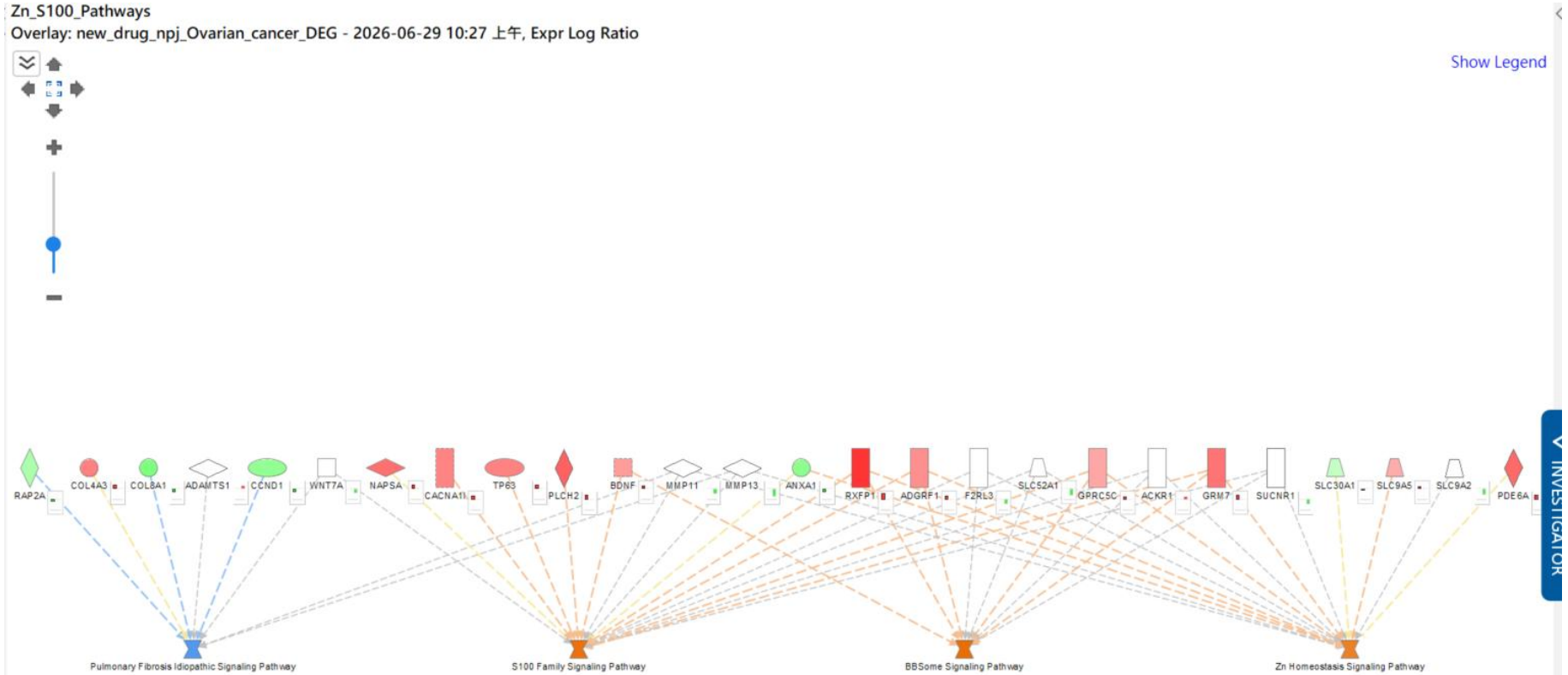
Sample to

Comparison analysis



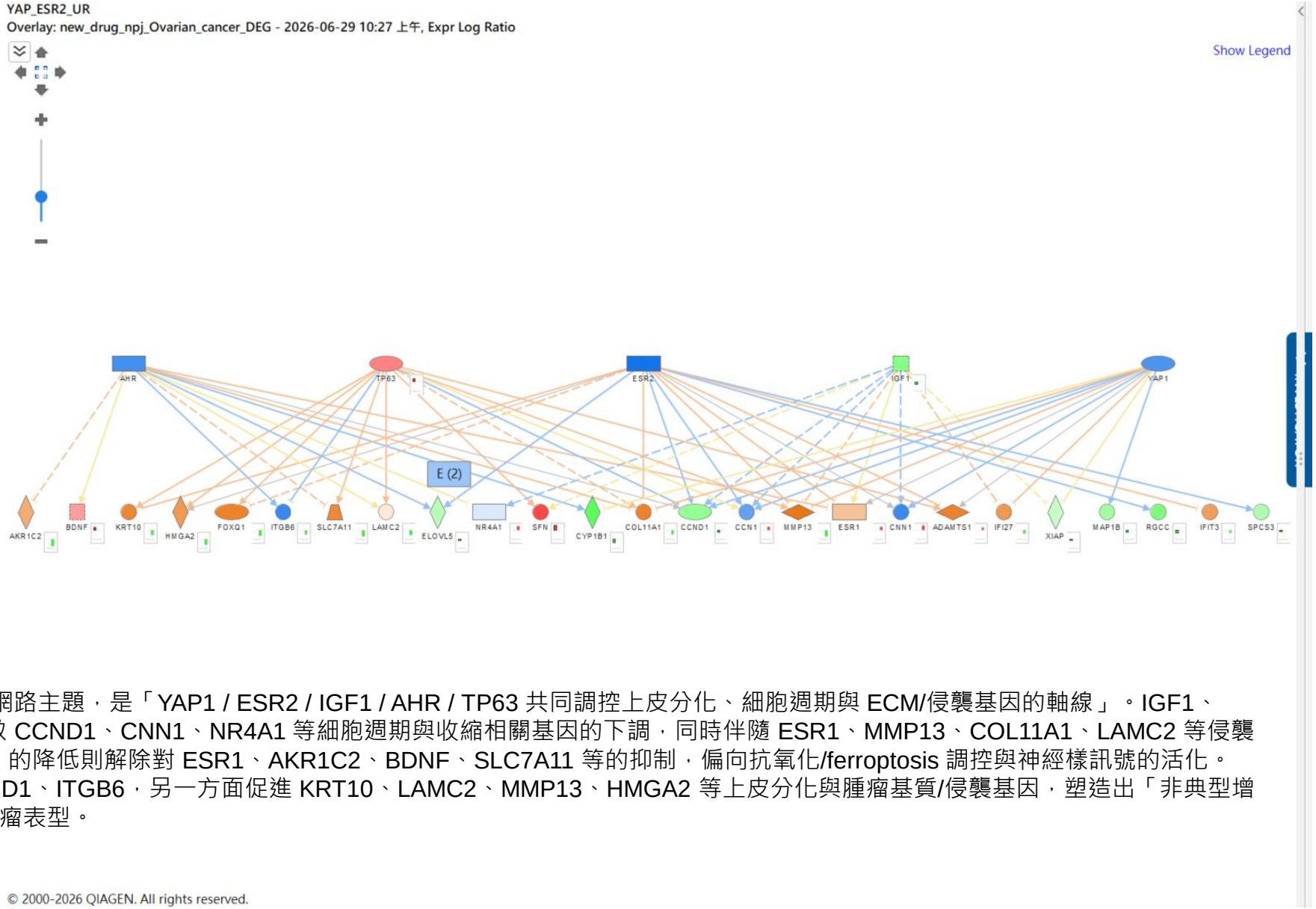
主題是「腫瘤細胞增殖、遷移、侵襲與黏附的整合調控」。EGF、TP63、PVT1、BDNF、LAMC2 等增加或具有影響活動時，會促進腫瘤細胞的增殖、遷移與侵襲；相反地，IGF1、WT1、CCND1、ARPC5、NXN、DSC2 的降低也被關聯到這些惡性行為的上升，顯示「腫瘤抑制因子被關掉 + 致癌/長非編碼 RNA 被開啟」共同推動腫瘤動態。ESR1、CCN1、ADAM12、CCL18、GOLGA7B、PLA1A 等則作為促進腫瘤細胞與基質/免疫相關因子互動的調節節點，加強了黏附與浸潤能力。

Comparison analysis



這條名為 Zn_S100_Pathways 的網路主題是「金屬離子穩態與 S100/纖維化路徑在腫瘤與肺纖維化微環境中的整合調控」。BDNF、TP63、GRM7、RXFP1、GPRC5C、ADGRF1 等的活化共同促進 S100 家族訊號、BBSome 以及 Zn homeostasis 路徑，暗示神經營養因子與 GPCR/離子通道在調控發炎與腫瘤微環境中角色重要；同時，MMP11/MMP13、WNT7A、ADAMTS1 及膠原相關基因（COL4A3、COL8A1）和 cell-cycle 因子 CCND1 的降低與「Idiopathic pulmonary fibrosis pathway 抑制」相關，顯示 ECM 重塑與抗纖維化訊號之間的動態平衡。像 SLC30A1、SLC9A5、PDE6A 等金屬/離子轉運蛋白則直接連結 Zn homeostasis 的調控，可能影響免疫細胞與腫瘤細胞的功能與存活。

Comparison analysis



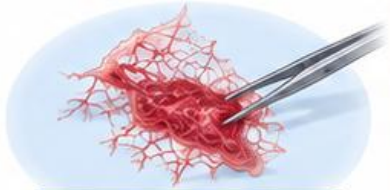
這條名為 YAP_ESR2_UR 的網路主題，是「YAP1 / ESR2 / IGF1 / AHR / TP63 共同調控上皮分化、細胞週期與 ECM/侵襲基因的軸線」。IGF1、YAP1、ESR2 的降低普遍導致 CCND1、CNN1、NR4A1 等細胞週期與收縮相關基因的下調，同時伴隨 ESR1、MMP13、COL11A1、LAMC2 等侵襲與基質重塑基因的上調；AHR 的降低則解除對 ESR1、AKR1C2、BDNF、SLC7A11 等的抑制，偏向抗氧化/ferroptosis 調控與神經樣訊號的活化。TP63 的增加一方面抑制 CCND1、ITGB6，另一方面促進 KRT10、LAMC2、MMP13、HMGA2 等上皮分化與腫瘤基質/侵襲基因，塑造出「非典型增殖 + 高度侵襲與重編程」的腫瘤表型。

McCann et al., STTT 2025: Workflow and Value of IPA

Proliferative diabetic retinopathy subtypes defined by immune defense and endothelial mitochondrial dysfunction

1 Clinical Samples

End-stage PDR

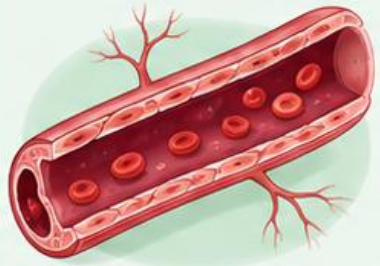


Vitrectomy samples

± Pre-op anti-VEGF

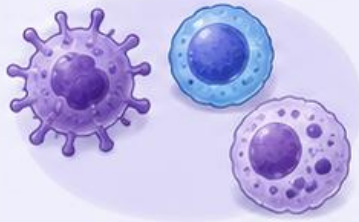
2 Cell-Enriched Profiles

CD31 high



Endothelial-rich

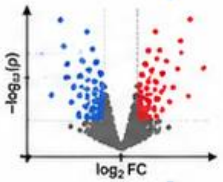
CD31 low



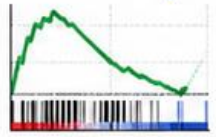
Immune-rich

3 Omics Analysis

RNA-seq



DEGs



GSEA

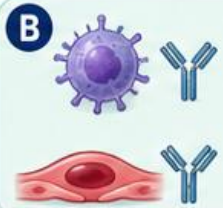
IPA

4 IPA Insights

A Disease Mechanism

- Immune-defense subtype
- Endothelial mitochondrial dysfunction

B Treatment Effect



- Anti-VEGF affects immune cells
- Anti-VEGF affects endothelial cells

C Pathway Changes

↓ Suppressed in immune-rich samples after anti-VEGF

↑↑ Increased in endothelial-related anti-VEGF signatures

5 IPA Value

Define PDR subtypes

Explain anti-VEGF response

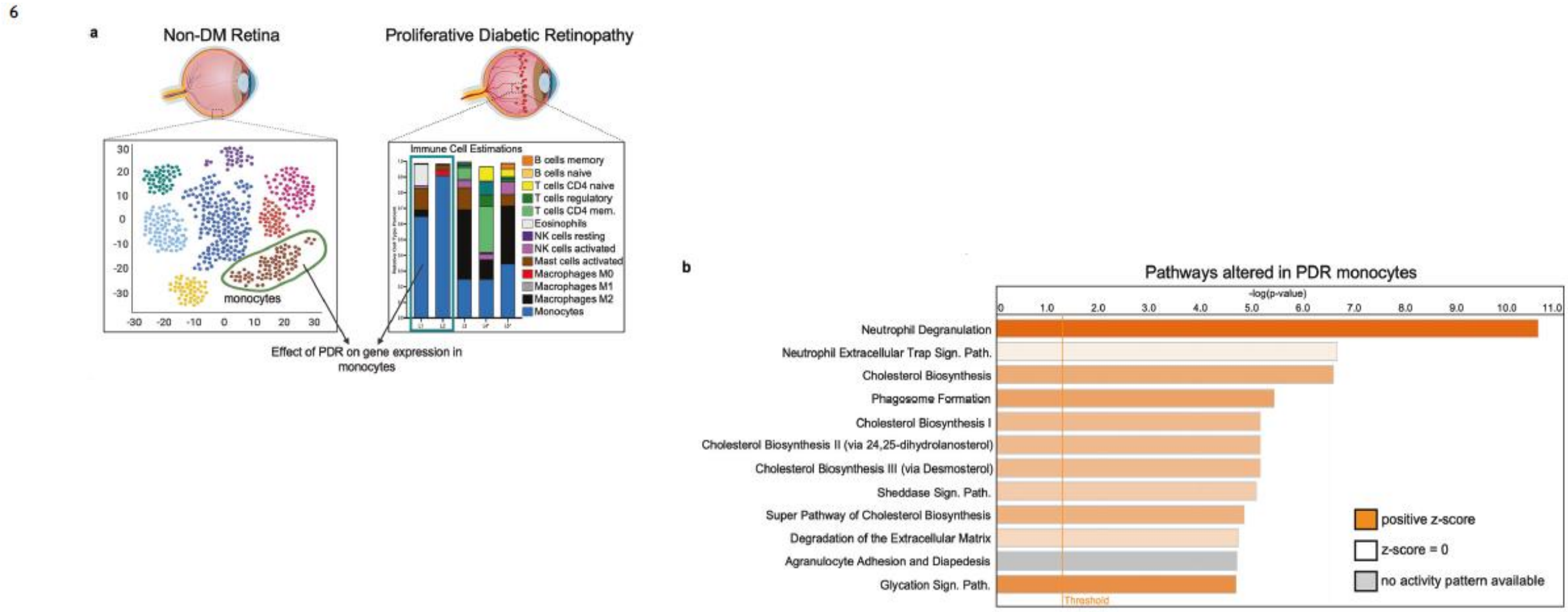
Reveal alternative targets

Guide translational strategy

Key Takeaways

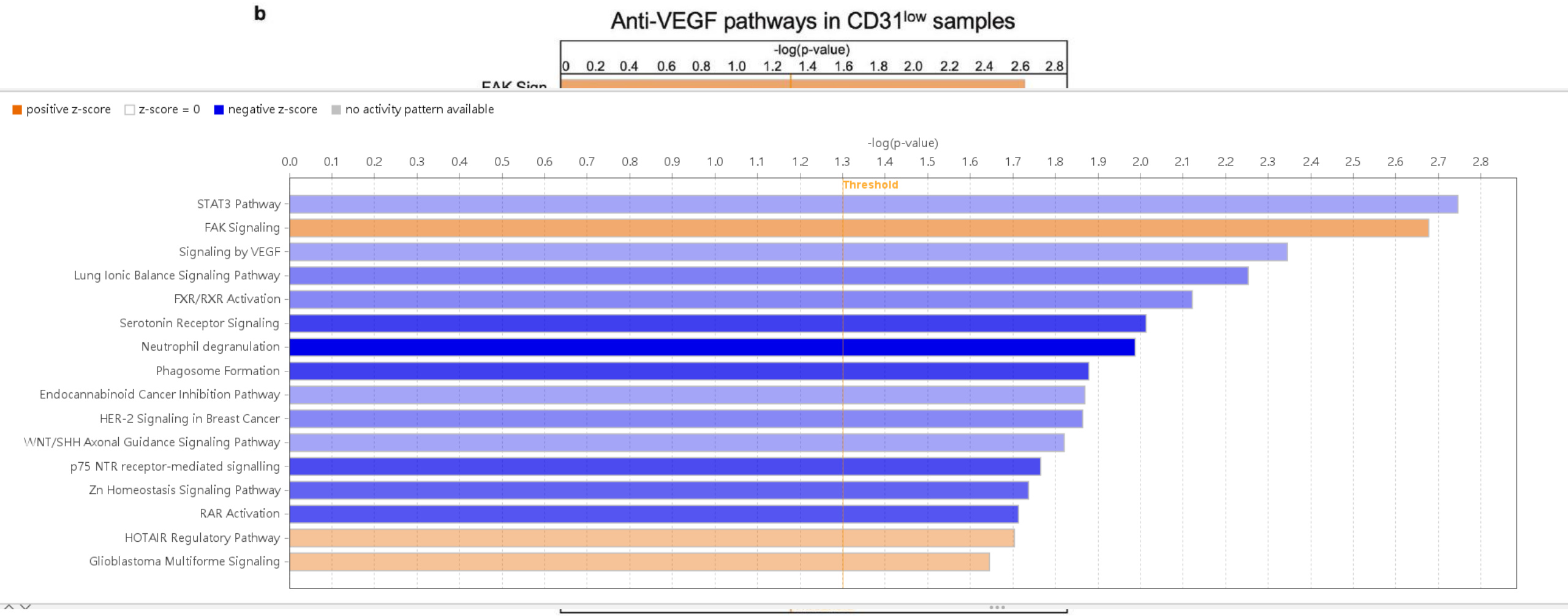
1.  PDR is heterogeneous
2.  Anti-VEGF acts beyond vasculature
3.  IPA converts transcriptomics into actionable biology

PDR Samples Reveal Distinct Endothelial- and Immune-Enriched Profiles



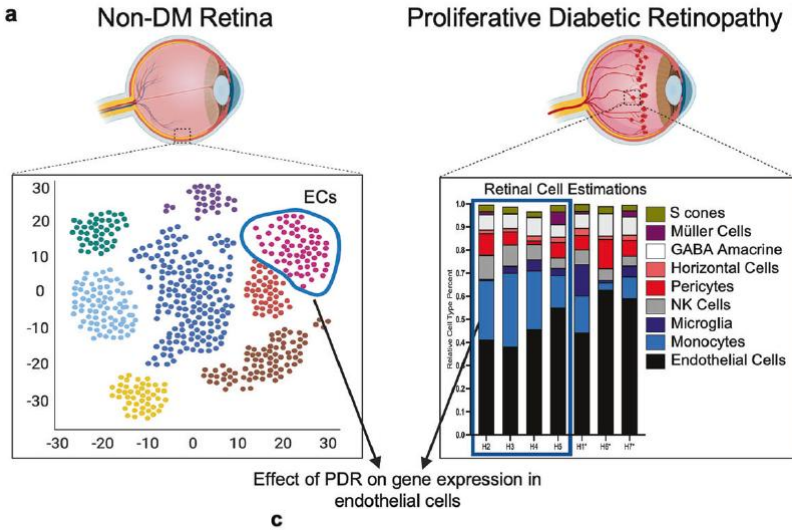
PDR samples were stratified into CD31-high endothelial-rich and CD31-low immune-rich profiles by comparing gene expression signatures with non-diabetic retinal reference cells. This reveals that PDR is not a uniform angiogenic disease, but contains distinct vascular and immune-dominant biological states.

IPA Reveals Endothelial Disease Biology Beyond VEGF Signaling

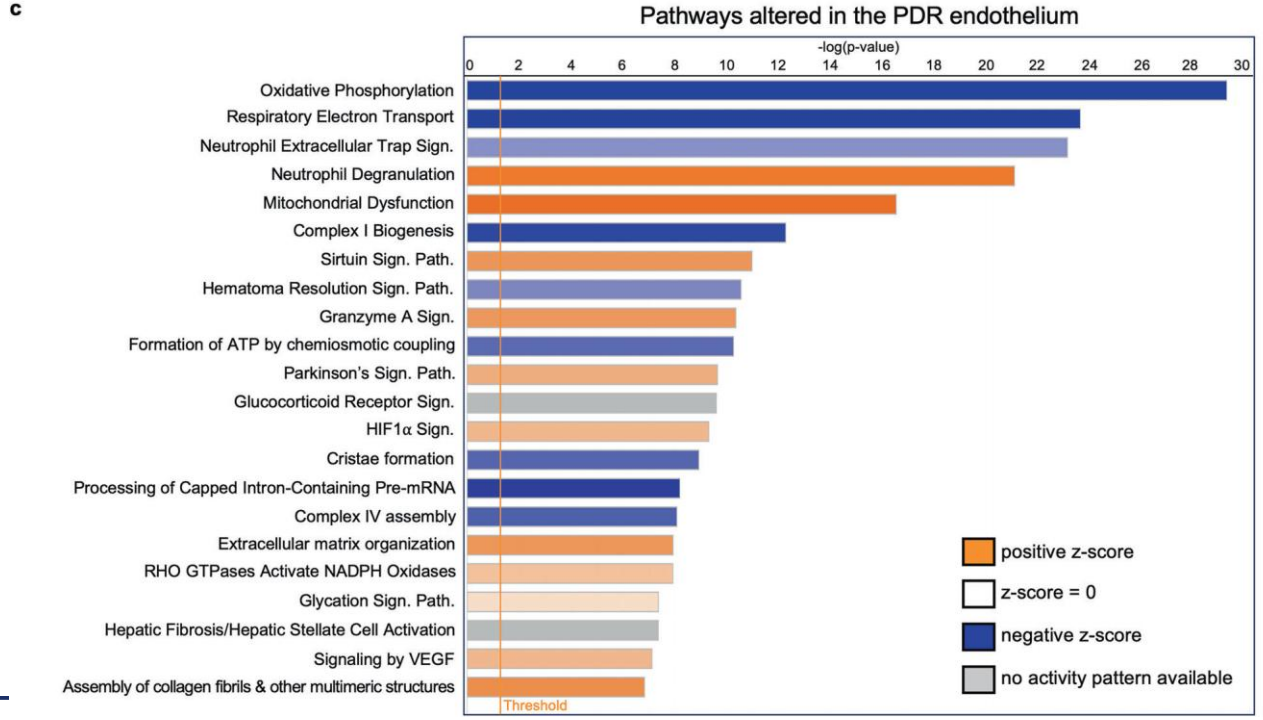


In CD31-low immune-rich PDR samples, IPA showed that anti-VEGF treatment suppressed VEGF signaling together with inflammatory and phagocytic pathways. This indicates that anti-VEGF therapy affects not only vascular biology, but also immune-related disease mechanisms in PDR.

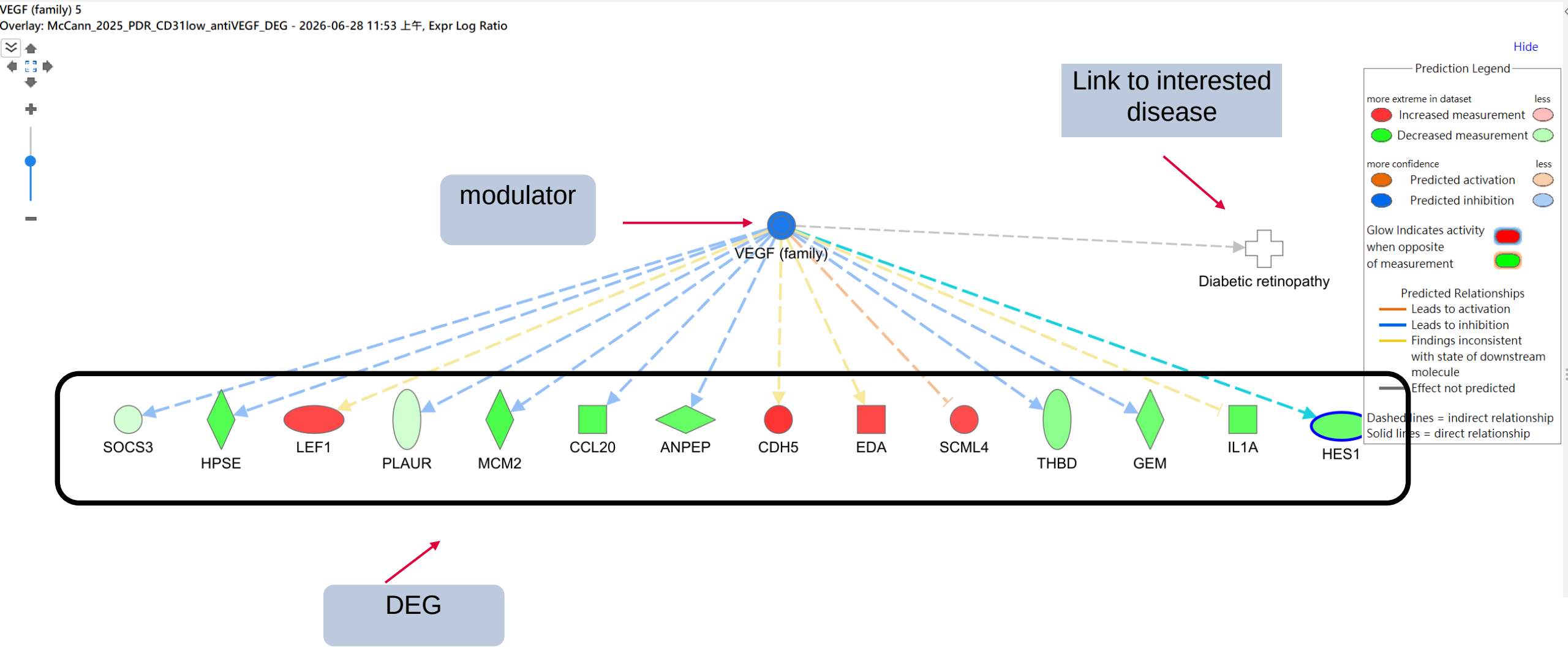
Anti-VEGF Therapy Reshapes Immune-Rich PDR Microenvironment



IPA analysis of CD31-high endothelial-rich PDR samples revealed mitochondrial dysfunction and other disease-associated pathways compared with non-diabetic retinal endothelium. This suggests that PDR endothelium contains VEGF-independent biology, supporting the need to explore complementary therapeutic targets beyond anti-VEGF therapy.



Causal network

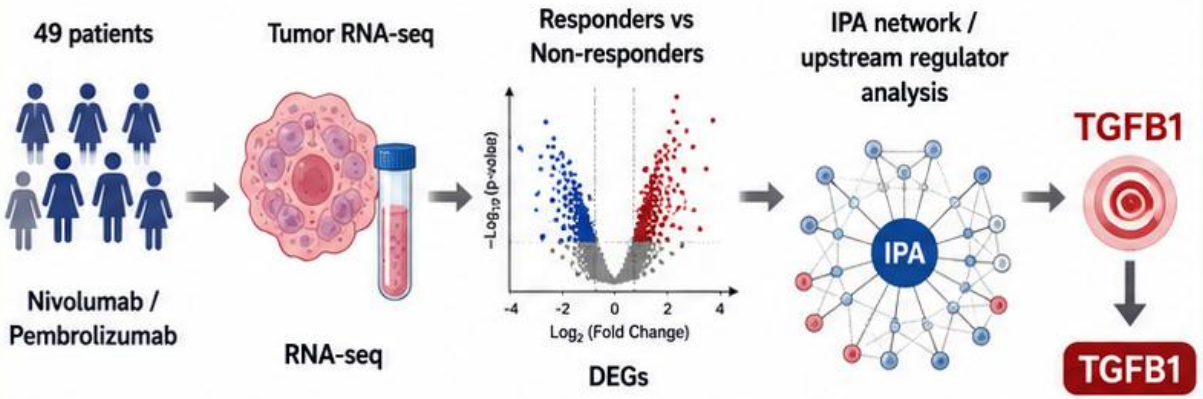


How IPA Supports Drug Development: Two Case Studies

From transcriptomics to mechanism, biomarkers, and target prioritization

Case 1 | Ni et al., npj Precision Oncology (2021)

ICI resistance in gynecologic cancer



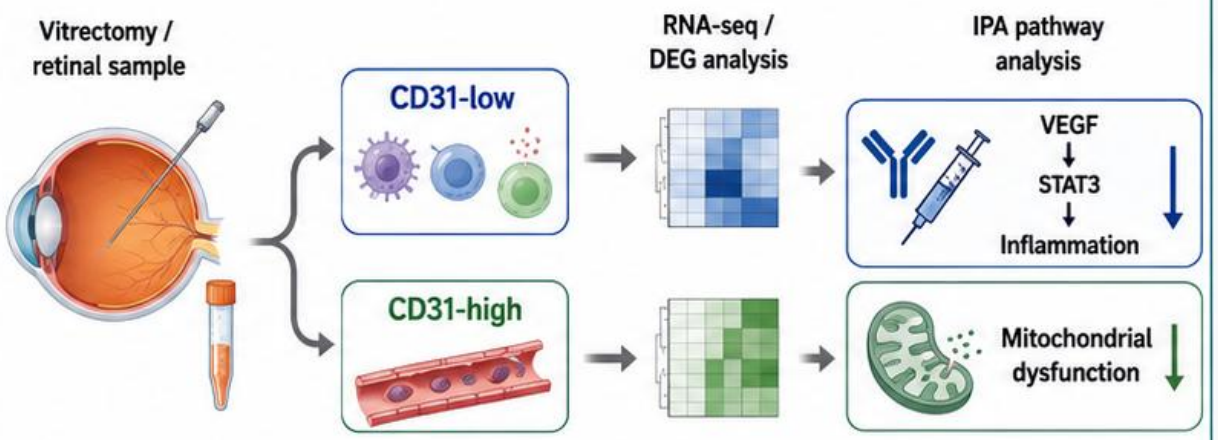
Biomarker: TGF-beta signature

Mechanism: immunotherapy resistance

Strategy: target / combination prioritization

Case 2 | McCann et al., STTT (2025)

PDR heterogeneity and anti-VEGF biology



Mechanism: immune-rich vs endothelial-rich states

MOA: anti-VEGF effects beyond vasculature

Alternative targets beyond VEGF

IPA Contributions to Drug Development

- Integrate Omics Data
- Disease Mechanism
- Biomarker Discovery
- Target Prioritization
- Translational Strategy

IPA converts complex omics data into actionable insights for mechanism discovery, biomarker-guided development, and target selection.

Agenda

Introduction to pathway analysis

What is QIAGEN Ingenuity Pathway Analysis

- Introduction of Ingenuity Pathway Analysis
- What's new in Ingenuity Pathway Analysis

Module 1 | IPA in Drug Discovery and Translational Medicine

Module 2 | Transcriptomics and Drug Mechanism of Action

- Case Study: BOLD-100 in Colorectal Cancer

Module 3 | miRNA Regulation and Natural Compound Mechanisms

- Case Study: Ugonin V in Chondrosarcoma

Module 4 | Comparative Analysis and Candidate Target Discovery

- Case Studies: Immunotherapy Resistance and Single-Cell Heterogeneity

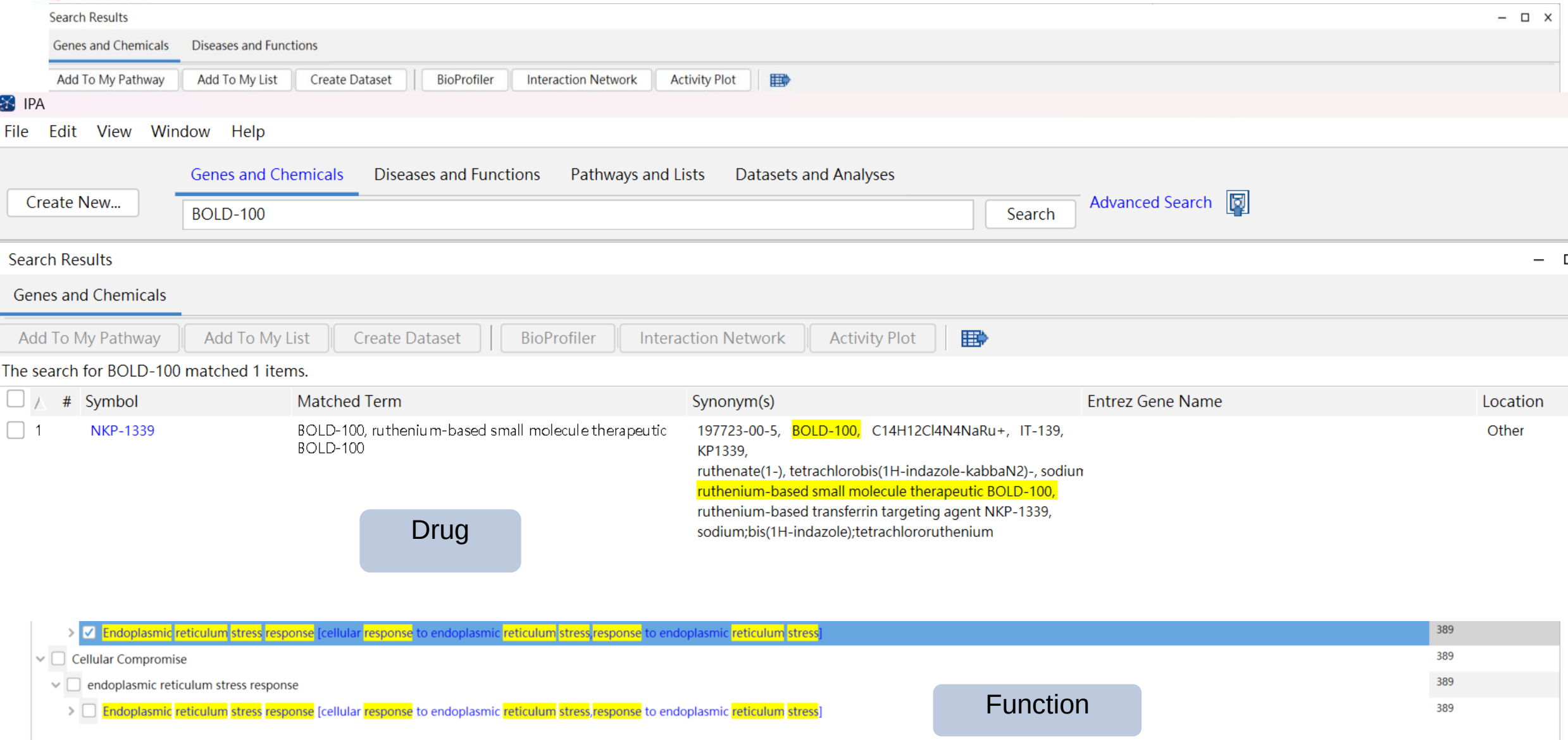
Module 5 | Translational Applications: Drug Effect Prediction and Biomarker Discovery

- Case Study: BOLD-100 in Colorectal Cancer

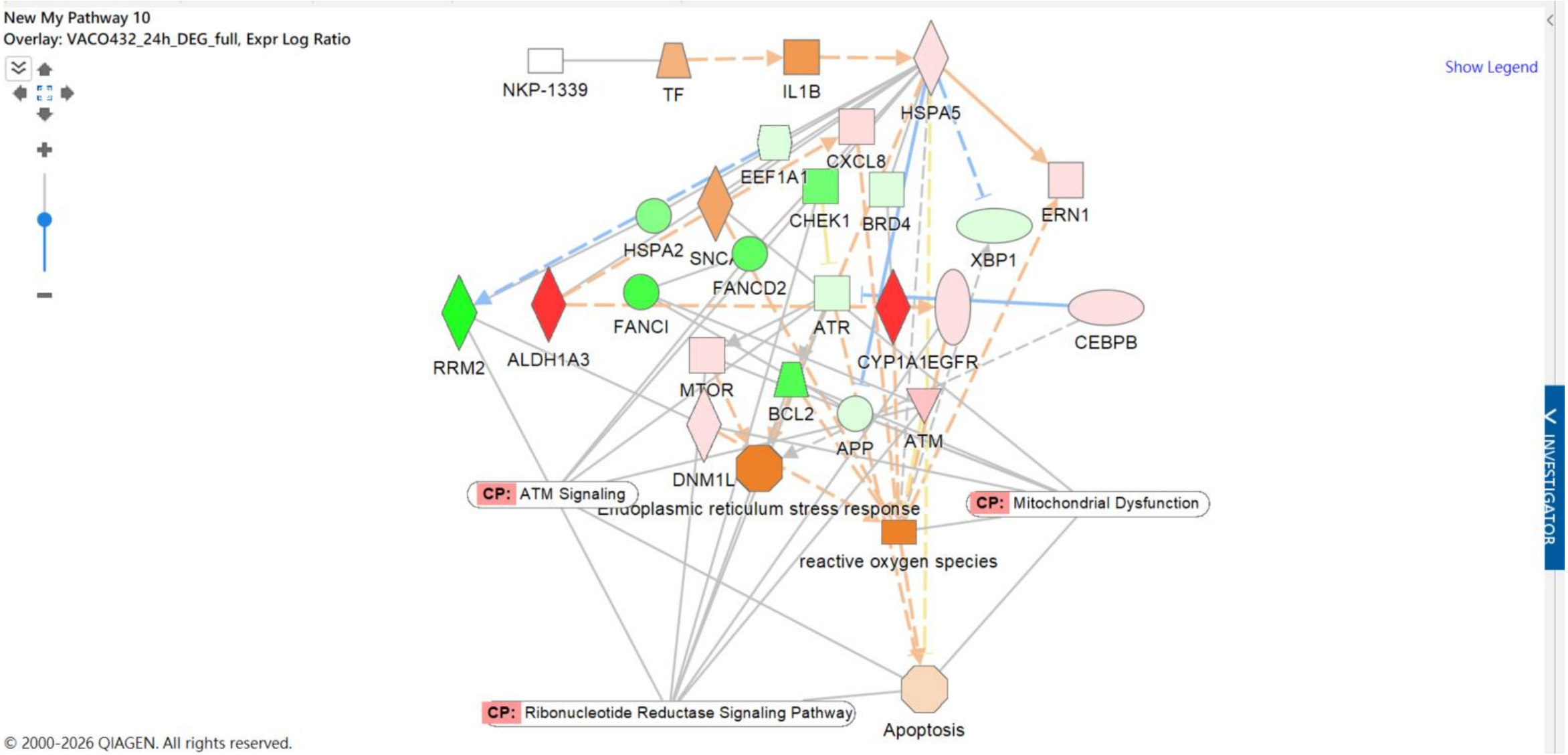
QIAGEN IPA – a dual approach to data analysis

With dataset	Without dataset
• Find connections in your data	• Search and explore the QIAGEN Knowledge Base
• Identify novel biomarkers	• Test hypothesis in silico
• Uncover key targets and regulators	• Identify degree of novelty in a hypothesis
• Discover novel disease mechanisms	
• Compare across experiments	

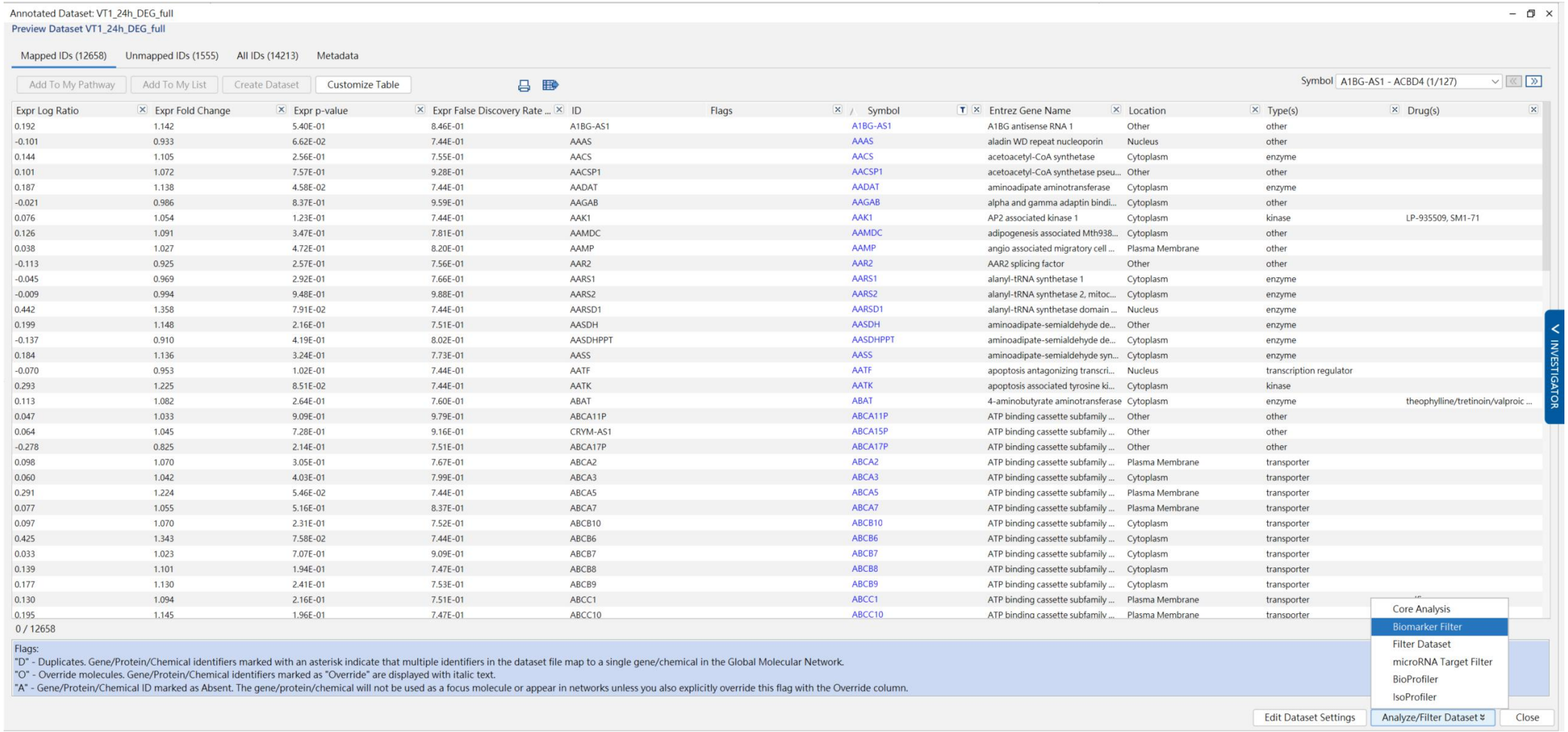
Search gene Disease and Function



Overlap Analysis

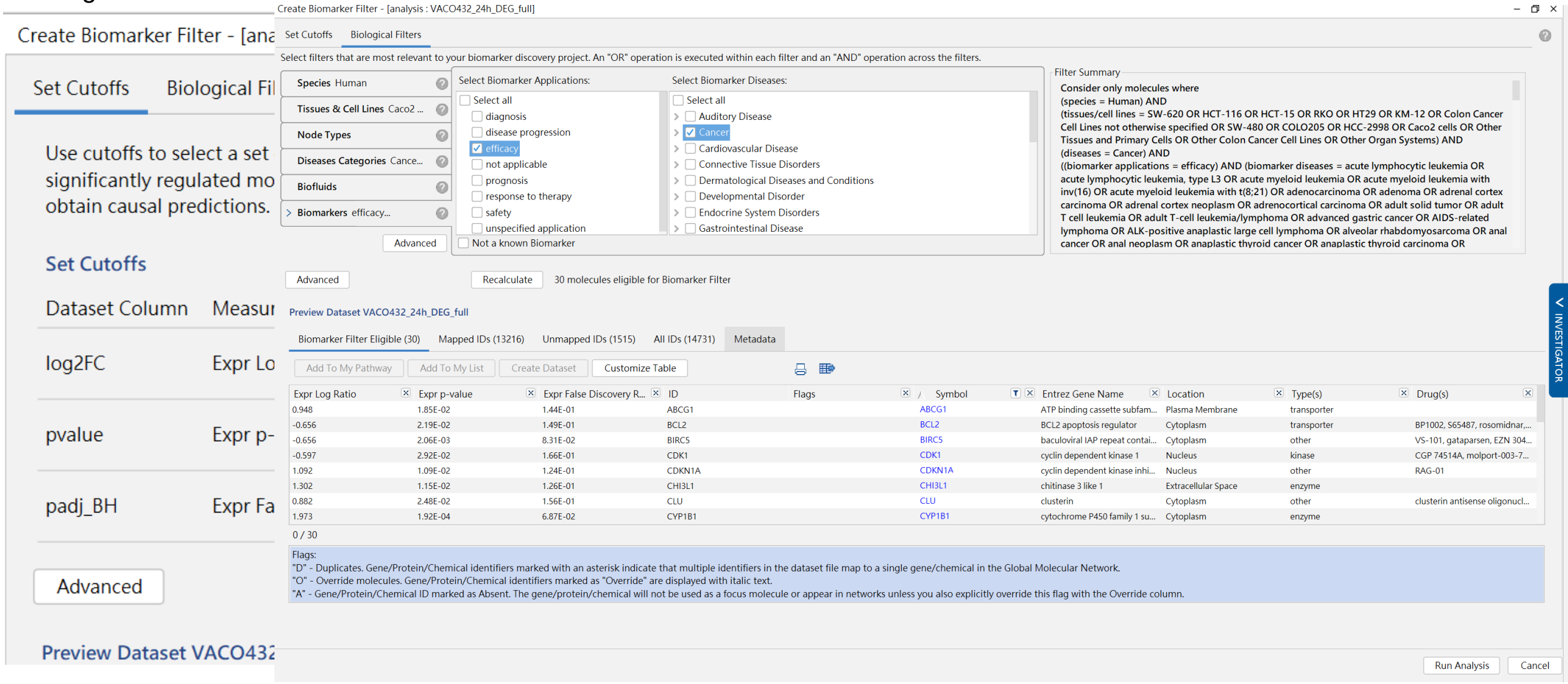


Analysis -> Biomarker



Set Cutoff and Biological Filter

Biological Filter and set cutoffs



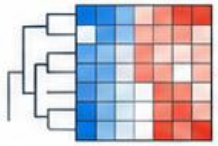
Biomarker filtered result

Symbol	Entrez Ge	Location	Family	Drug(s)	Gene Sym	Expr Log	Expr p-va	Expr Fals	Human	Other Org	Other Tiss	Caco2 cel	COLO205	Colon Car	HCC-299	HCT-116	HCT-15	HT29	KM-12	Other Col	RKO	SW-480	SW-620	Biomarker Applicat
ABCC3	ATP bindi	Plasma M	transporte		ABCC3	0.666	5.02E-03	1.01E-01	x	x	x	x	x		x		x	x					x	diagnosis,prognosis
ABCG1	ATP bindi	Plasma M	transporte		ABCG1	0.948	1.85E-02	1.44E-01	x	x	x		x					x						efficacy,unspecifie
AHNAK2	AHNAK r	Cytoplasm	other		AHNAK2	1.111	5.91E-04	7.29E-02	x	x						x								unspecified applicat
ALDH1A	aldehyde	Cytoplasm	enzyme	disulfiram	ALDH1A	1.083	2.56E-02	1.57E-01	x	x	x		x		x			x	x	x				diagnosis,disease pr
ALDH1A	aldehyde	Cytoplasm	enzyme		ALDH1A	1.898	1.97E-03	8.30E-02	x	x					x	x	x	x	x				x	unspecified applicat
ALDH3A	aldehyde	Cytoplasm	enzyme		ALDH3A	1.179	1.42E-02	1.32E-01	x	x	x		x		x		x	x	x				x	diagnosis,unspecifie
ALPP	alkaline p	Plasma M	phosphata	anti-ALPI	ALPP	1.45	1.26E-02	1.28E-01	x	x	x													diagnosis,unspecifie
ANXA1	annexin A	Plasma M	other	hydrocorti	ANXA1	0.696	3.19E-02	1.71E-01	x	x	x		x		x	x	x	x	x	x			x	diagnosis,prognosis
BCL2	BCL2 apo	Cytoplasm	transporte	BP1002, S	BCL2	-0.656	2.19E-02	1.49E-01	x	x	x		x	x	x	x	x	x	x	x	x	x	x	diagnosis,efficacy,p
BIRC5	baculovira	Cytoplasm	other	VS-101, g	BIRC5	-0.656	2.06E-03	8.31E-02	x	x	x	x	x		x	x	x	x		x	x	x	x	diagnosis,disease pr
CALB2	calbindin	Cytoplasm	other		CALB2	-0.66	2.82E-02	1.64E-01	x	x			x		x	x		x	x	x			x	unspecified applicat
CCNF	cyclin F	Nucleus	other		CCNF	-0.693	3.48E-05	6.87E-02	x	x		x	x		x	x	x	x	x				x	unspecified applicat
CD22	CD22 mol	Plasma M	transmem	pinatuzum	CD22	0.831	2.00E-02	1.47E-01	x	x	x		x		x	x	x	x	x				x	unspecified applicat
CDK1	cyclin dep	Nucleus	kinase	CGP 7451	CDK1	-0.597	2.92E-02	1.66E-01	x	x		x	x		x	x	x	x	x				x	efficacy
CDKN1A	cyclin dep	Nucleus	other	RAG-01	CDKN1A	1.092	1.09E-02	1.24E-01	x	x	x		x		x	x	x	x	x			x	x	diagnosis,efficacy,p
CHI3L1	chitinase 3	Extracellu	enzyme		CHI3L1	1.302	1.15E-02	1.26E-01	x	x														diagnosis,efficacy,p
CLU	clusterin	Cytoplasm	other	clusterin a	CLU	0.882	2.48E-02	1.56E-01	x	x	x		x		x	x	x	x	x				x	efficacy,unspecifie
CYP1B1	cytochrom	Cytoplasm	enzyme		CYP1B1	1.973	1.92E-04	6.87E-02	x	x	x							x	x					diagnosis,efficacy,p
CYP3A5	cytochrom	Cytoplasm	enzyme		CYP3A5	0.703	1.62E-02	1.37E-01	x	x			x		x			x		x				efficacy,safety,unsp
E2F1	E2F trans	Nucleus	transcripti		E2F1	-0.643	2.55E-02	1.57E-01	x	x	x	x	x		x	x	x	x	x	x			x	disease progression
FADS3	fatty acid	Plasma M	enzyme		FADS3	0.588	2.25E-02	1.50E-01	x	x					x	x	x	x	x				x	unspecified applicat
FAS	Fas cell su	Plasma M	transmem	APO010,	FAS	0.766	3.02E-02	1.68E-01	x	x	x					x	x	x	x	x		x		diagnosis,disease pr
FOXM1	forkhead b	Nucleus	transcripti		FOXM1	-0.661	1.77E-04	6.87E-02	x	x		x	x		x	x	x	x	x	x			x	prognosis
FTH1	ferritin he	Cytoplasm	enzyme		FTH1	0.833	3.78E-03	9.53E-02	x	x	x		x		x	x	x	x	x				x	unspecified applicat
GADD45(	growth arı	Nucleus	other		GADD45(	1.099	2.60E-03	8.46E-02	x	x	x													efficacy
GAST	gastrin	Extracellu	other		GAST	1.47	9.09E-03	1.19E-01	x	x								x		x				efficacy,safety
GDF15	growth dif	Extracellu	growth fa	AZD8853	GDF15	0.792	5.23E-03	1.02E-01	x	x	x		x		x	x	x	x	x				x	diagnosis,unspecifie
GMNN	geminin D	Nucleus	transcripti		GMNN	-0.706	7.89E-03	1.12E-01	x	x	x		x		x	x	x	x	x				x	unspecified applicat
H2AX	H2A X va	Nucleus	transcripti		H2AX	-0.63	3.99E-04	7.04E-02	x	x			x		x	x	x	x	x				x	efficacy

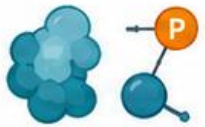
QIAGEN IPA | From Omics Data to Biological Mechanisms

Key functions we will introduce in this session

Input data



RNA-seq / transcriptomics



Proteomics / phosphoproteomics

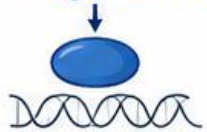
Metabolomics

miRNA

Non-model species via ortholog mapping

1 Canonical Pathways

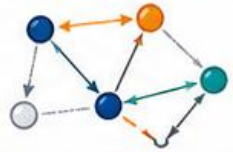
2 Upstream Regulators



3 Diseases & Functions

IPA Core Analysis

4 Regulator Effects / Causal Networks



5 Comparison Analysis

6 Molecule Activity Predictor

What IPA helps us do

- Convert omics results into biological mechanisms
- Identify key pathways and upstream drivers
- Compare groups, conditions, or time points
- Build mechanistic hypotheses
- Prioritize biomarkers or therapeutic targets
- Create clear summary figures for papers and presentations

IPA bridges diverse omics datasets and interprets them as pathways, regulators, functions, and networks—turning lists of molecules into an interpretable biological story.

Better Care with Better Knowledge

若有需要進一步的資訊或在使用軟體上遇到問題歡迎聯繫以下窗口:
熊嘉妮 資深專案副理 ChristineHsiung@gga.asia 02-2795 1777 #2505

Bioinfo@GGA.ASIA