

IPA 2023 Spring/Summer Release and Case Study

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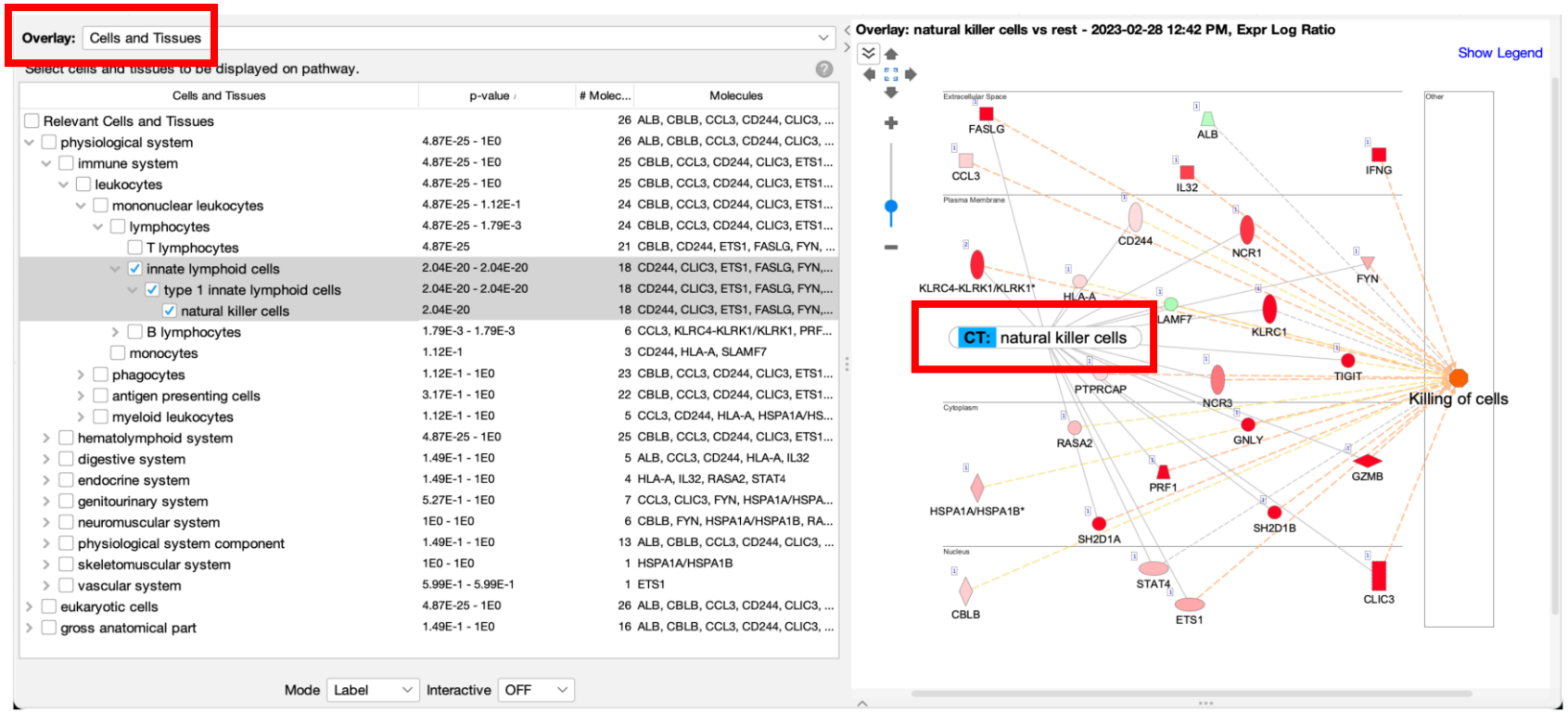
Agenda

- What’s new 2023 IPA Spring/Summer Release介紹
- 疾病與樣本 Metadata 整合分析
- 藥物潛在標的預測 IPA 與第三方軟體整合運用
- 你所不知道的 IPA 製圖技巧 外泌體研究案例分享

Identify potential cell types based on the set of genes on networks and pathways

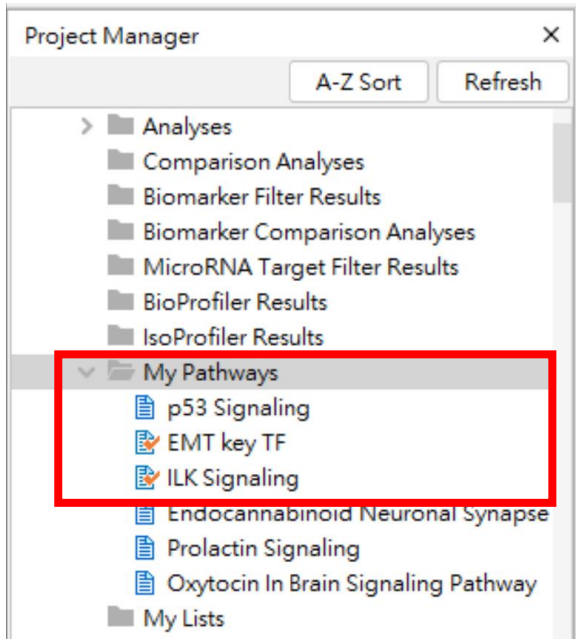
Overlay :Cell and Tissues

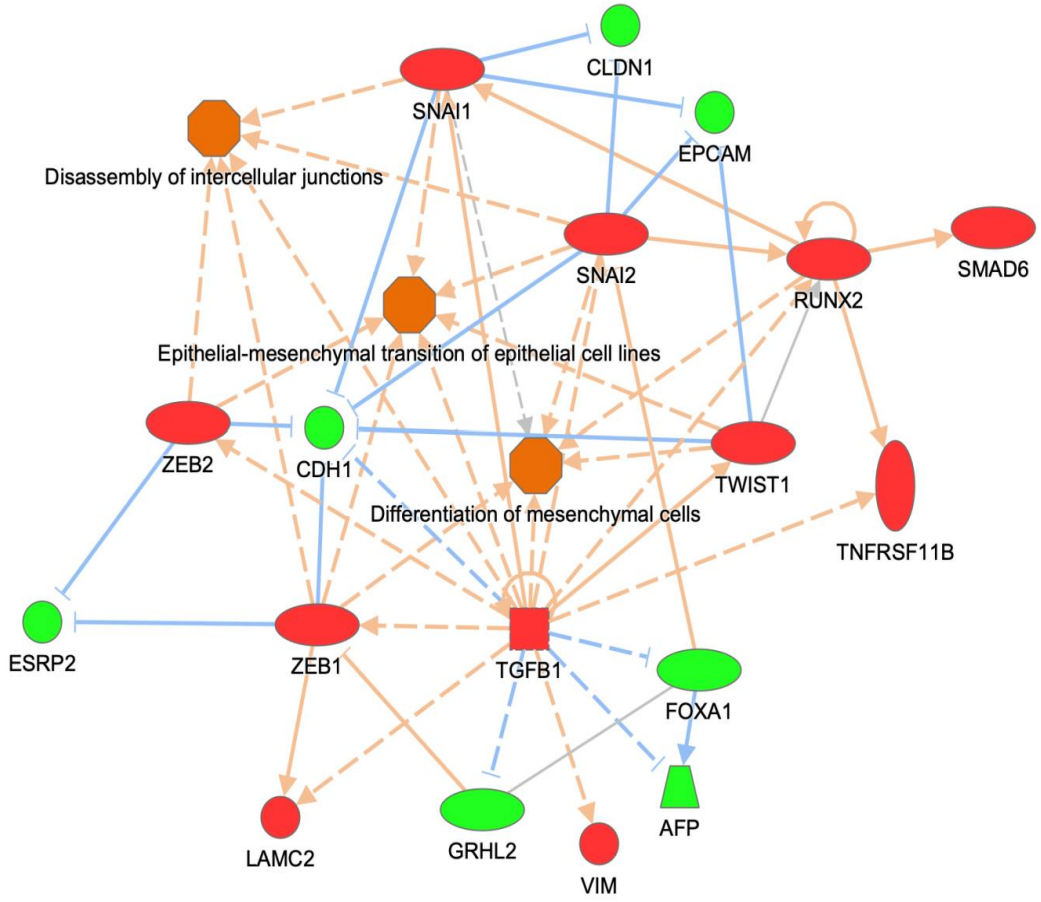
THE HUMAN PROTEIN ATLAS



Enrichment of natural killer enriched genes on a network.

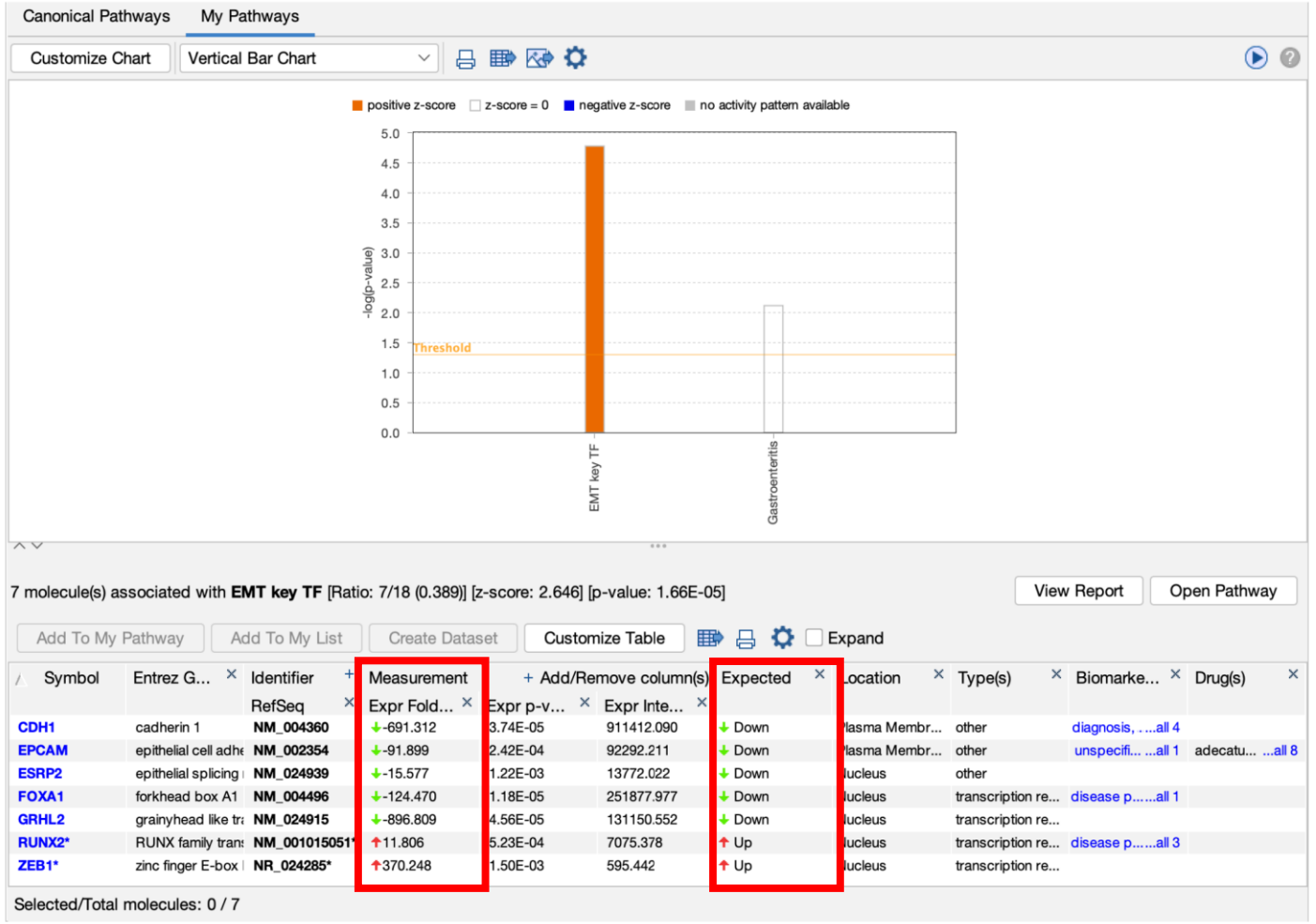
Causally score My Pathways in Core Analysis





A custom My Pathway with nodes assigned by the user as activated (red) or green (inhibited).

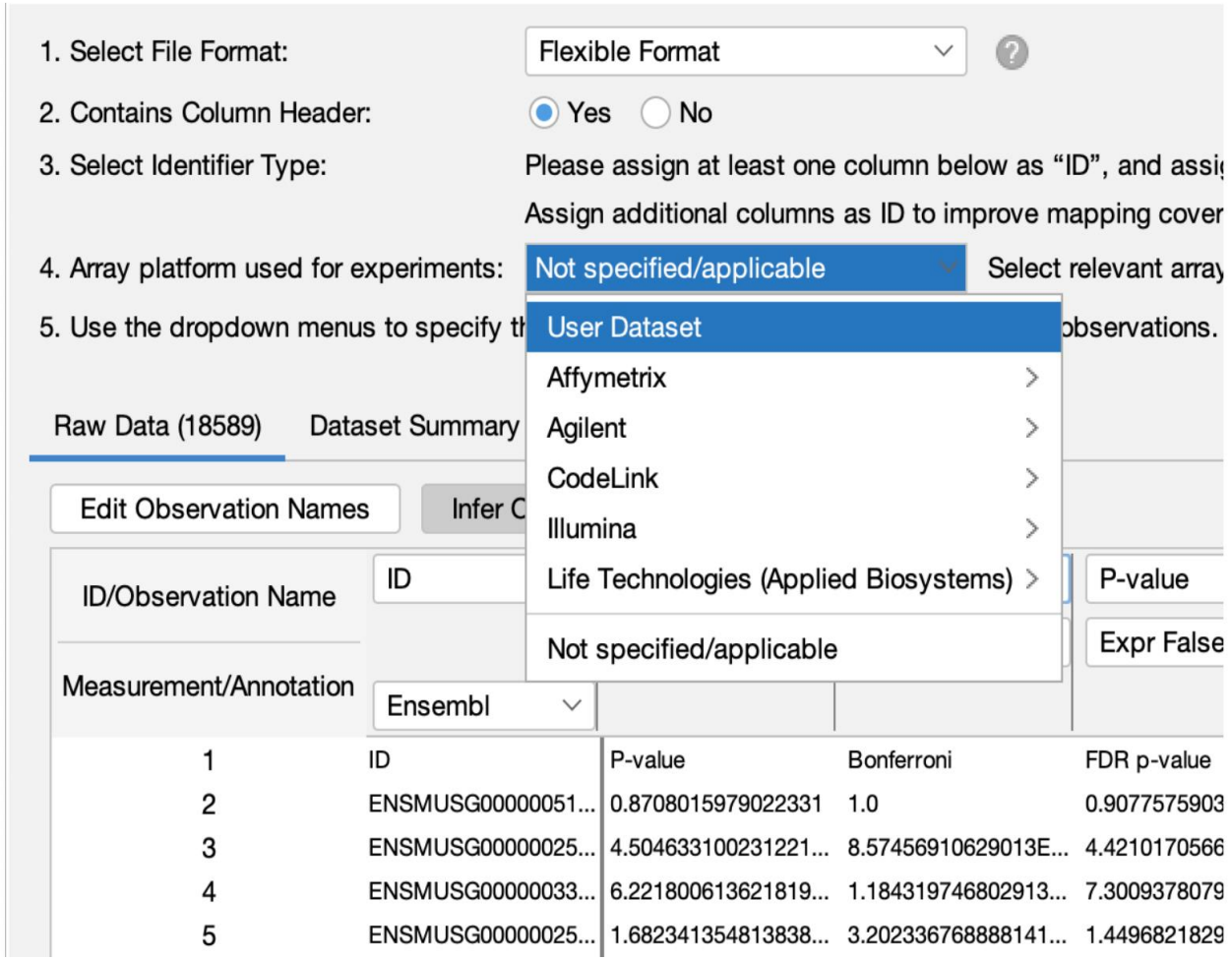
Causally score My Pathways in Core Analysis



Symbol	Entrez G...	Identifier	Measurement	Expr Fold...	Expr p-v...	Expr Inte...	Expected	Location	Type(s)	Biomarke...	Drug(s)
		RefSeq									
CDH1	cadherin 1	NM_004360		-691.312	3.74E-05	911412.090	Down	lasma Membr...	other	diagnosis, ...all 4	
EPCAM	epithelial cell adhe	NM_002354		-91.899	2.42E-04	92292.211	Down	lasma Membr...	other	unspecifi... ...all 1	adecatu... ...all 8
ESRP2	epithelial splicing	NM_024939		-15.577	1.22E-03	13772.022	Down	ucleus	other		
FOXA1	forkhead box A1	NM_004496		-124.470	1.18E-05	251877.977	Down	ucleus	transcription re...	disease p.....all 1	
GRHL2	grainyhead like tr	NM_024915		-896.809	4.56E-05	131150.552	Down	ucleus	transcription re...		
RUNX2*	RUNX family tran	NM_001015051*		11.806	5.23E-04	7075.378	Up	ucleus	transcription re...	disease p.....all 3	
ZEB1*	zinc finger E-box	NR_024285*		370.248	1.50E-03	595.442	Up	ucleus	transcription re...		

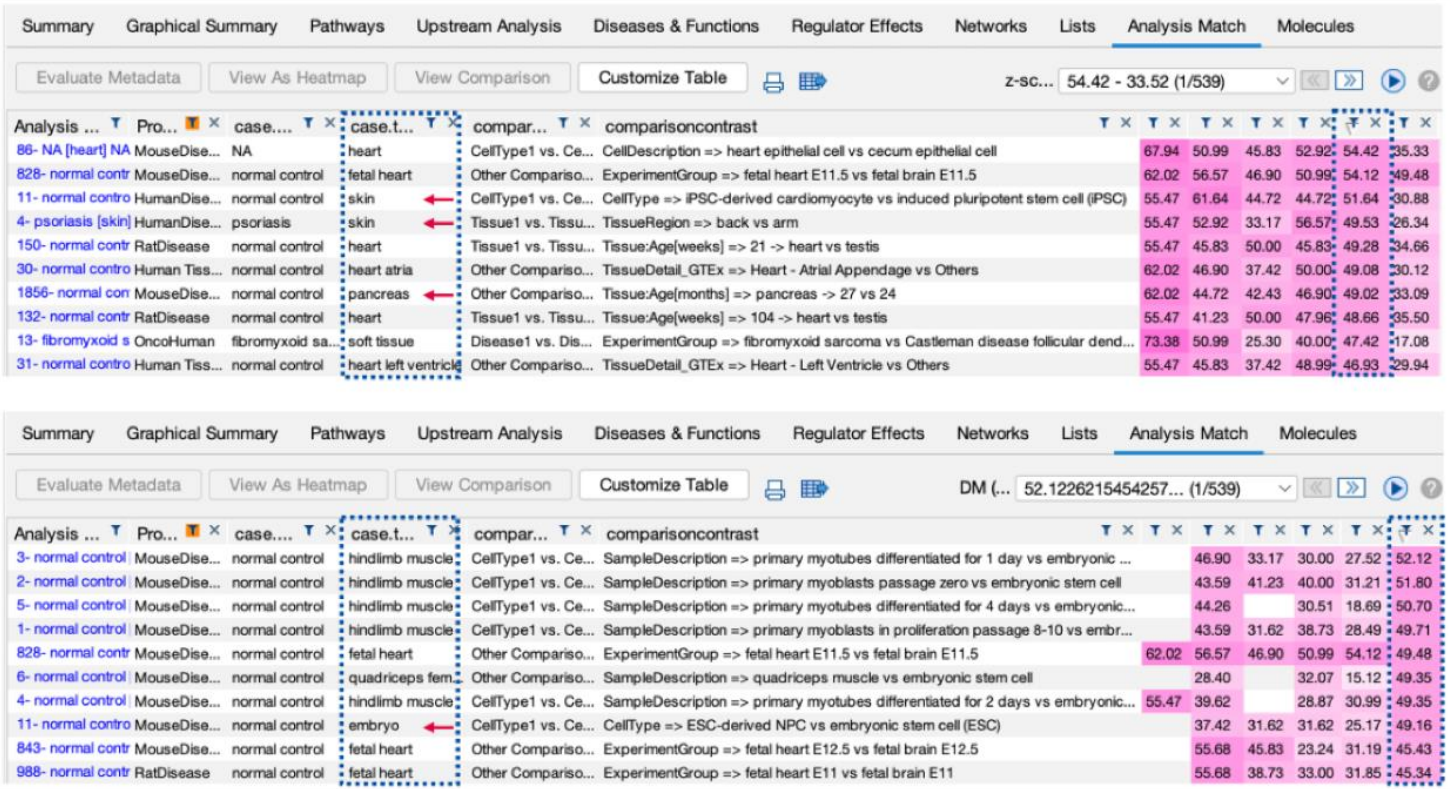
Causally scoring a My Pathway.

Set the "User Dataset" as the reference set when uploading a dataset



Setting the reference set to User Dataset reference during dataset upload.

Discover more precise matches in Analysis Match



Sorted by original overall z-score match

Matches to analyses from many tissue types, such as skin and pancreas

Sorted by new DM "dataset match" column

Results are more strictly heart or muscle cells vs embryonic cells

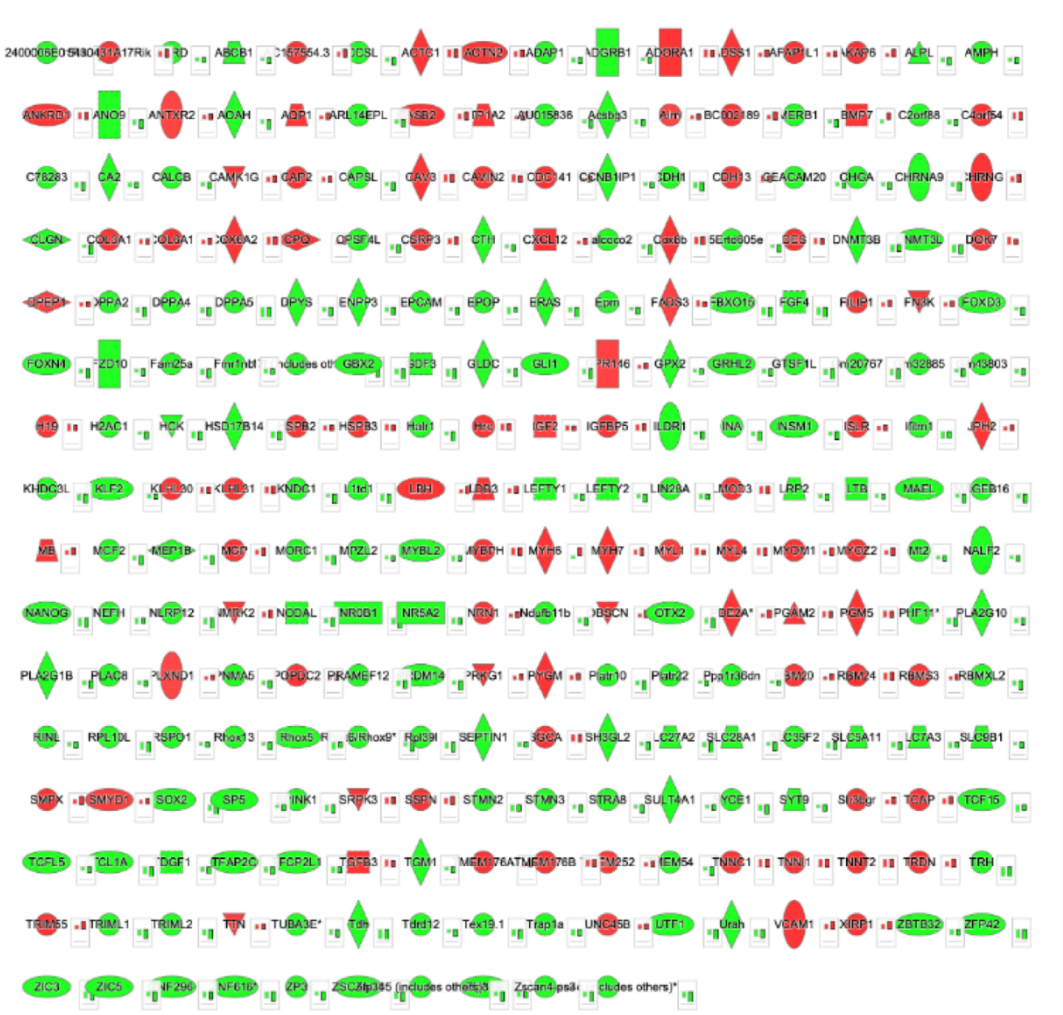
Analysis Match results sorted by the original score (top) and new score (bottom).

Heatmap of the top forty matching analyses



Heatmap of the top forty matching analyses. Each orange-colored square in the top row of the heatmap represents the z-score for that analysis versus the query

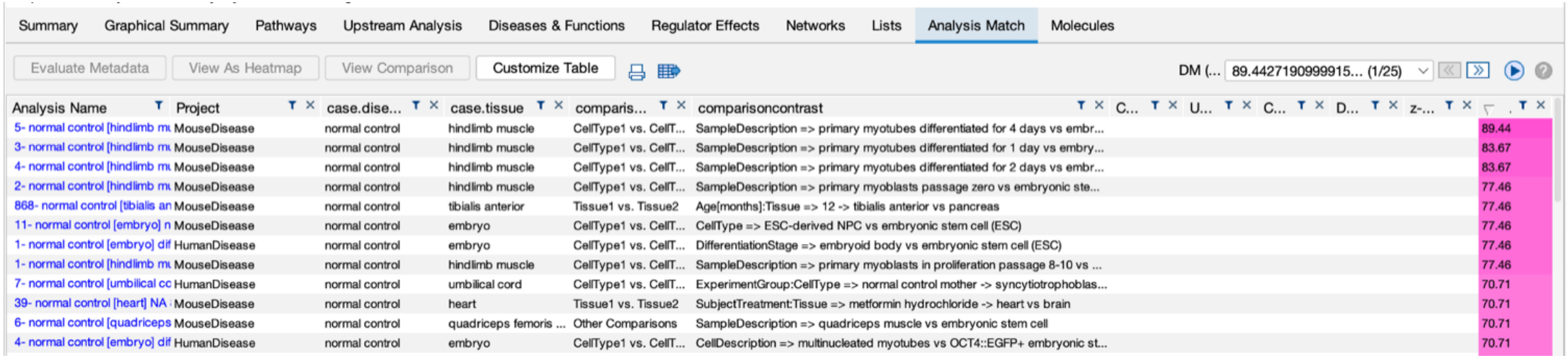
Heatmap of the top forty matching analyses



250 genes match between the cardiomyocyte analysis and its best matching analysis.

The new scoring method using a small dataset.

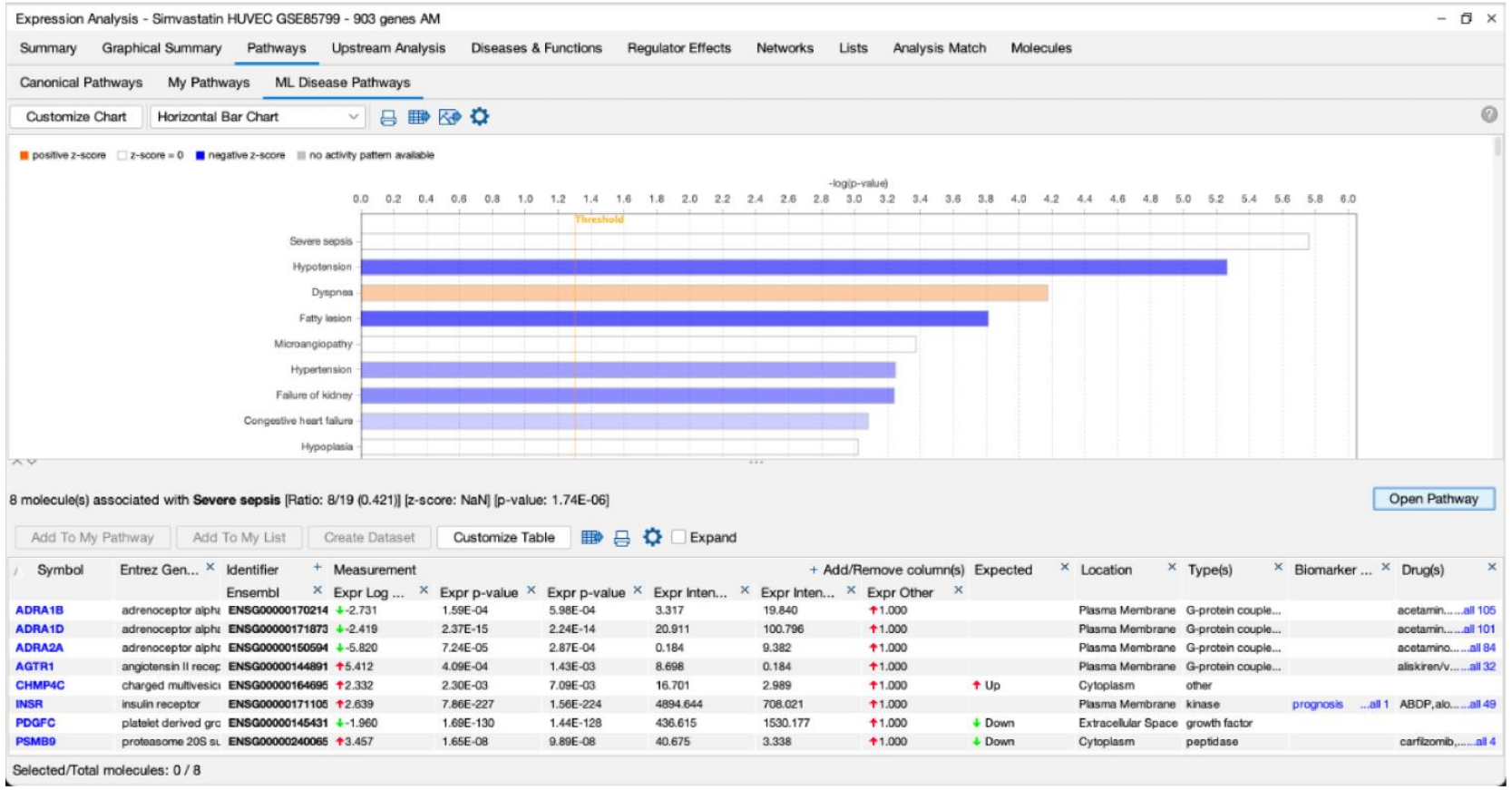
The new scoring method often works on small datasets, where there are typically too few genes to generate robust Upstream Regulator, Causal Network, Canonical Pathway, and Disease and Function signatures to match to other analyses.



Analysis Name	Project	case.dise...	case.tissue	comparis...	comparisoncontrast	C...	U...	C...	D...	z-...
5- normal control [hindlimb mu	MouseDisease	normal control	hindlimb muscle	CellType1 vs. CellT...	SampleDescription => primary myotubes differentiated for 4 days vs embr...					89.44
3- normal control [hindlimb mu	MouseDisease	normal control	hindlimb muscle	CellType1 vs. CellT...	SampleDescription => primary myotubes differentiated for 1 day vs embry...					83.67
4- normal control [hindlimb mu	MouseDisease	normal control	hindlimb muscle	CellType1 vs. CellT...	SampleDescription => primary myotubes differentiated for 2 days vs embr...					83.67
2- normal control [hindlimb mu	MouseDisease	normal control	hindlimb muscle	CellType1 vs. CellT...	SampleDescription => primary myoblasts passage zero vs embryonic ste...					77.46
868- normal control [tibialis an	MouseDisease	normal control	tibialis anterior	Tissue1 vs. Tissue2	Age[months]:Tissue => 12 -> tibialis anterior vs pancreas					77.46
11- normal control [embryo] n	MouseDisease	normal control	embryo	CellType1 vs. CellT...	CellType => ESC-derived NPC vs embryonic stem cell (ESC)					77.46
1- normal control [embryo] dif	HumanDisease	normal control	embryo	CellType1 vs. CellT...	DifferentiationStage => embryoid body vs embryonic stem cell (ESC)					77.46
1- normal control [hindlimb mu	MouseDisease	normal control	hindlimb muscle	CellType1 vs. CellT...	SampleDescription => primary myoblasts in proliferation passage 8-10 vs ...					77.46
7- normal control [umbilical cc	HumanDisease	normal control	umbilical cord	CellType1 vs. CellT...	ExperimentGroup:CellType => normal control mother -> syncytiotrophoblas...					70.71
39- normal control [heart] NA	MouseDisease	normal control	heart	Tissue1 vs. Tissue2	SubjectTreatment:Tissue => metformin hydrochloride -> heart vs brain					70.71
6- normal control [quadriceps	MouseDisease	normal control	quadriceps femoris ...	Other Comparisons	SampleDescription => quadriceps muscle vs embryonic stem cell					70.71
4- normal control [embryo] dif	HumanDisease	normal control	embryo	CellType1 vs. CellT...	CellDescription => multinucleated myotubes vs OCT4::EGFP+ embryonic st...					70.71

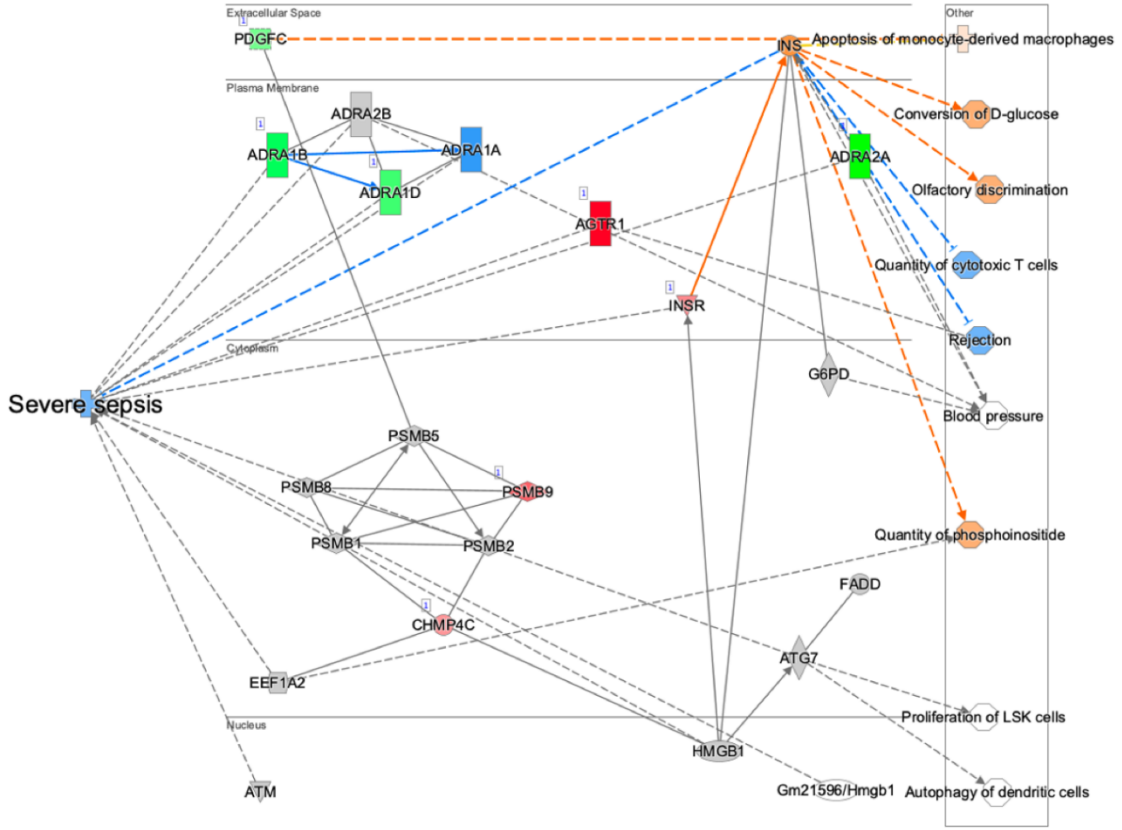
The analysis of a 10-gene dataset from the cardiomyocytes versus embryonic stem cells matches the expected types of analyses.

Find the unexpected with ML Disease Pathways in Core Analyses



ML Disease Pathways scored against simvastatin-treated rats (liver). The most significant result by Fisher's Exact Test (right-tailed) is "Severe sepsis".

Find the unexpected with ML Disease Pathways in Core Analyses



The severe sepsis ML pathway overlaid with simvastatin differential expression data. IPA predicts that simvastatin may decrease severe sepsis.

Other software changes

- The speed to upload and save a dataset has been improved, most noticeably for datasets with many columns.
- "Reactome" appears as a content source in certain filters in the UI in this release, however, there is currently only a minor addition of Reactome content in IPA. As we prepare to add Reactome pathways in a future release, that source currently only refers to new groups and complexes that have added from Reactome.

What's new in the IPA summer release?

New pathways

- Acetylcholine Receptor Signaling Pathway
- Adrenergic Receptor Signaling Pathway (Enhanced)
- Cachexia Signaling Pathway
- GABAergic Receptor Signaling Pathway (Enhanced)
- Glutaminergic Receptor Signaling Pathway (Enhanced)
- ISGylation Signaling Pathway
- Microautophagy Signaling Pathway
- NFKBIE Signaling Pathway
- Orexin Signaling Pathway
- Sertoli Cell Germ Cell Junction Signaling Pathway (Enhanced)

Existing pathways updated to include an activity pattern

- IL-17A Signaling in Fibroblasts
- Sertoli Cell-Sertoli Cell Junction Signaling
- TR/RXR Activation

What's new in the IPA summer release?

Addition of >400,000 new findings (bringing the total in IPA to over 12.6 million)

>29,000 protein-protein interaction findings from BioGrid
>407,000 cancer mutation findings from ClinVar
>1,800 target-to-disease findings from ClinicalTrials.gov
>1,700 drug-to-disease findings from ClinicalTrials.gov
>800 Gene Ontology findings
>220 mappable chemicals
> 3,800 Lipid Maps IDs

What's new in the IPA summer release?

141,323 expression datasets (5,689 added)

Land	Repository	Datasets Q1 2023	Datasets Q2 2023	Increase
DiseaseLand	HumanDisease	32,680	33,672	992
	MouseDisease	25,070	25,253	183
	RatDisease	8,226	8,226	
	LINCS	28,234	28,234	
OncoLand	OncoHuman (Formerly OncoGEO)	15,147	17,125	1,978
	OncoMouse	1,054	1,054	
	TCGA	4,438	4,438	
	MetastaricCancer	81	81	
	Hematology	4,267	4,267	
	Pediatrics	444	444	
	ENCODE RNA Binding*	486	486	
Single Cell Land	SingleCellHuman	194	194	
	SingleCellHumanUmi	8,636	11,049	2,413
	SingleCellHumanUmiLite	603	603	
	SingleCellHumanHCL	1,476	1,469	-7
	SingleCellMouse	81	81	
	SingleCellMouseUmi	3,097	3,220	123
	SingleCellMouseUmiLite	115	115	
Normal Cell and Tissues	Human Tissues (GTEx)	1,312	1,312	

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- 你所不知道的 IPA 製圖技巧 外泌體研究案例分享

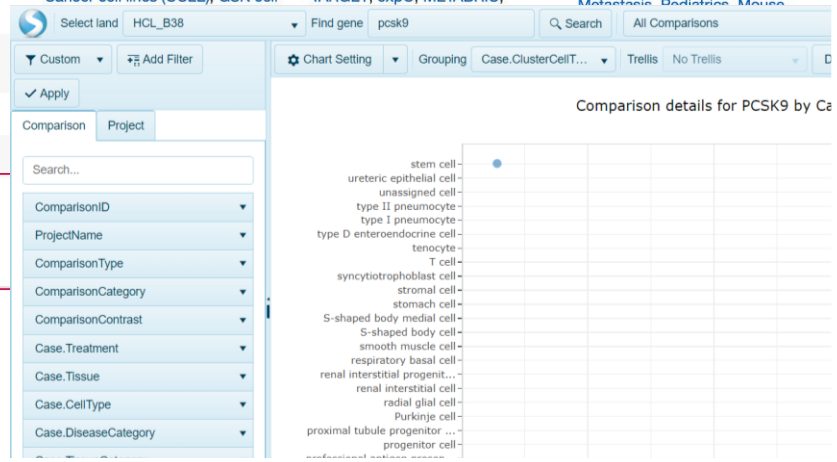
Visualize OmicSoft single cell data in Land Explorer

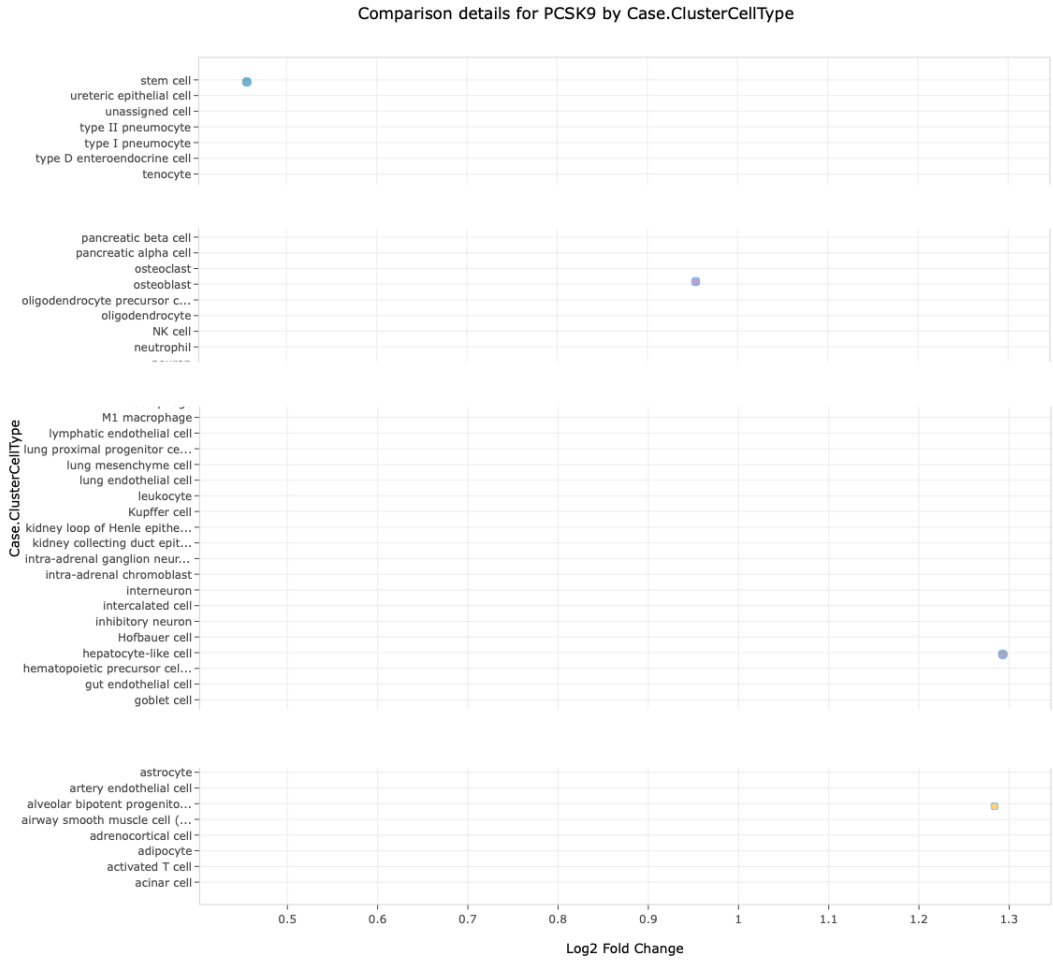
*Land Explorer for IPA license is required to view the linked pages

Now you can easily explore single cell expression for any gene among the public data curated by OmicSoft. These single cell views are available via new links on IPA Gene Views

OmicSoft Land Explorer: Sample-level experimental data

Data Type / Data Source	Normal Tissue	Cell Lines	Oncology Consortia	Oncology Studies
RNA-seq expression:	Solid tissue (GTEx), Solid tissue (HPA), Blueprint	Cancer cell lines (CCLE)	TCGA, TARGET, BeatAML, ICGC, CGCI, CCLE+GTEx+TCGA, ENCODE RNA-associated gene knockdown	General oncology, Hematology, Pediatrics, Mouse studies
Microarray expression:	Solid tissue (GTEx)	Cancer cell lines (CCLE), GSK cell	TARGET, expO, METABRIC,	General oncology, Hematology,
Differential regulation:	Solid tissue (GTEx)			
Alteration frequency:				
Survival by expression:				
Single Cell differential regulation:	Human Cell Landscape (HCL), Tabula Sapiens			

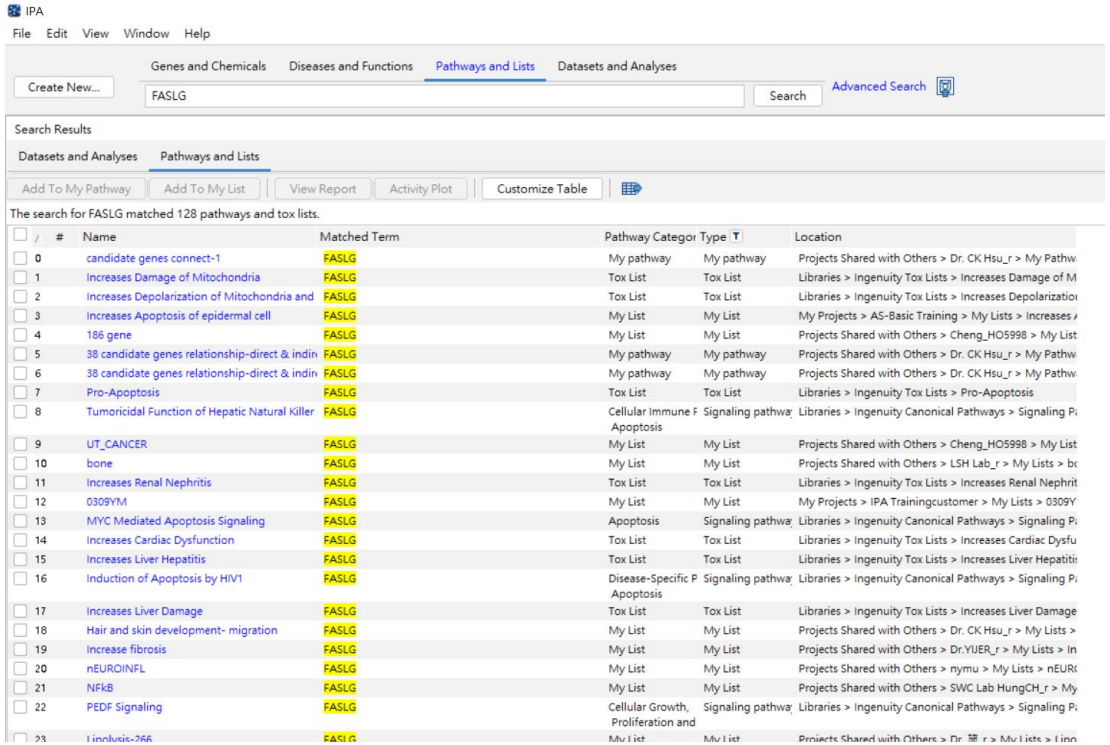


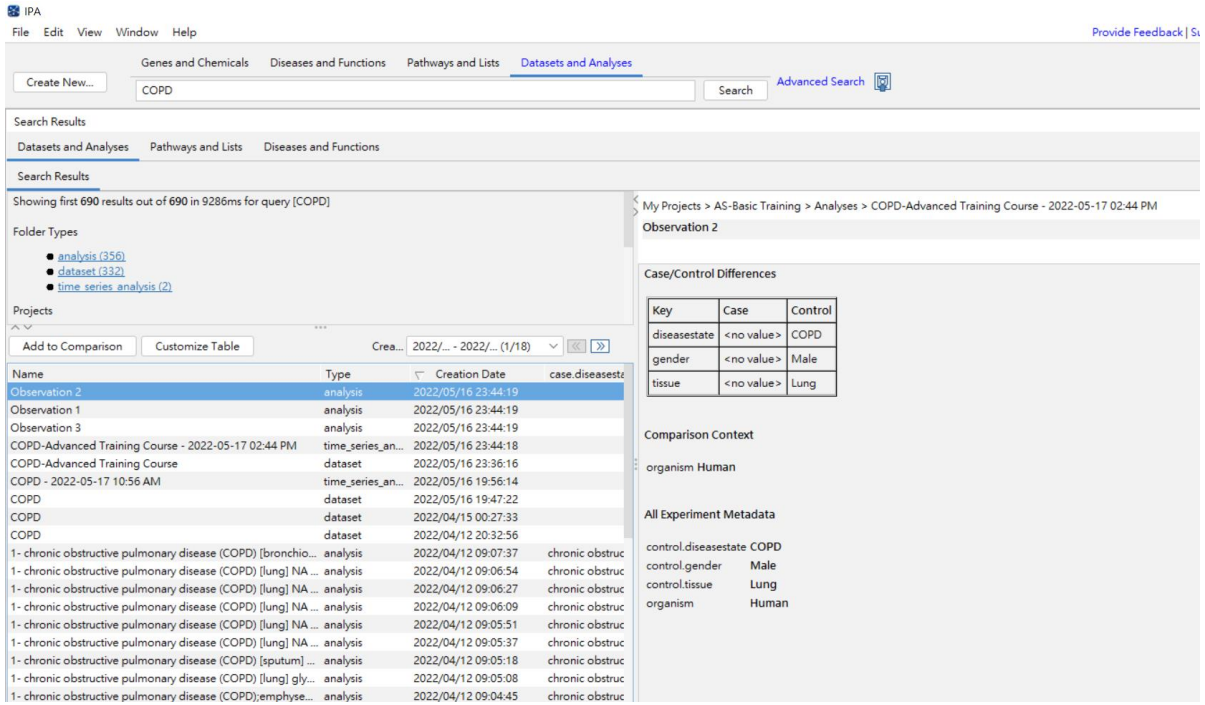


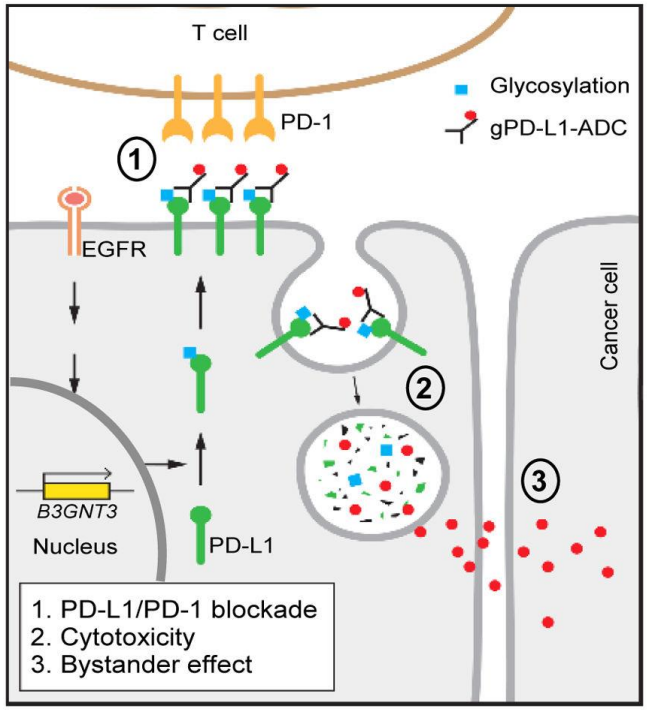
The figure shows how PCSK9 is overexpressed in hepatocyte-like cells, and less so in stem cells and osteoblasts

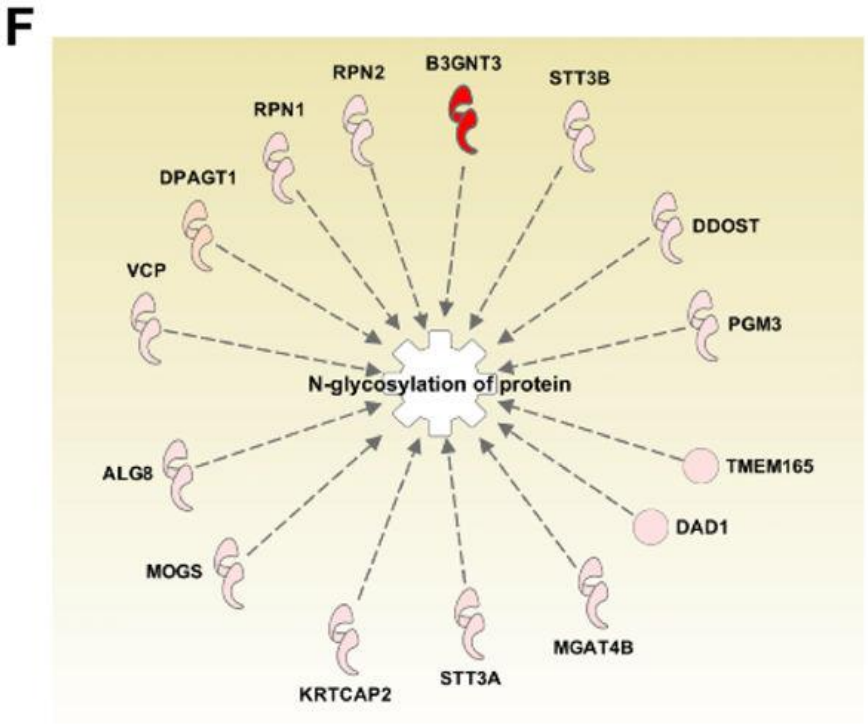
Improved ease of use and increased capabilities of search

- The Search tool in IPA is now easier to use because all search options have been consolidated to the main tool bar. Furthermore, you can speed up your research by finding entities (i.e., genes, chemicals, diseases, and functions) of interest inside Canonical Pathways and Tox Lists.
- You can also search for your own custom pathways and lists either by name or by entities within them, even in notes you have added to the pathways.



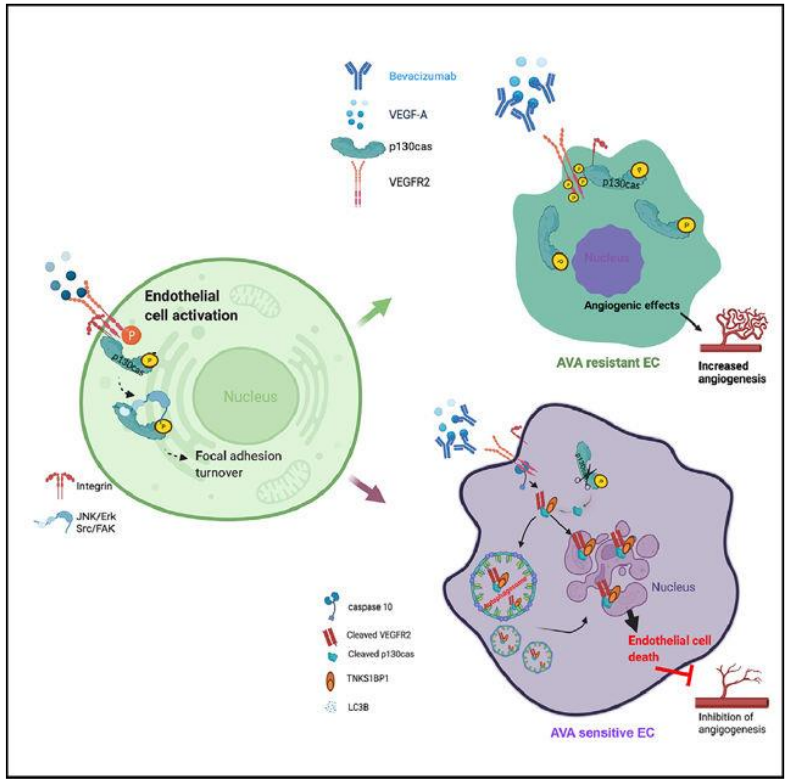






PD-L1 bound N-linked glycosylation-associated proteins shown by Ingenuity Pathway Analysis (IPA). PD-L1 bound proteins were identified from Flag-PD-L1 co-immunoprecipitated protein complex using MS/MS analysis followed by IPA

Endothelial p130cas confers resistance to anti-angiogenesis therapy

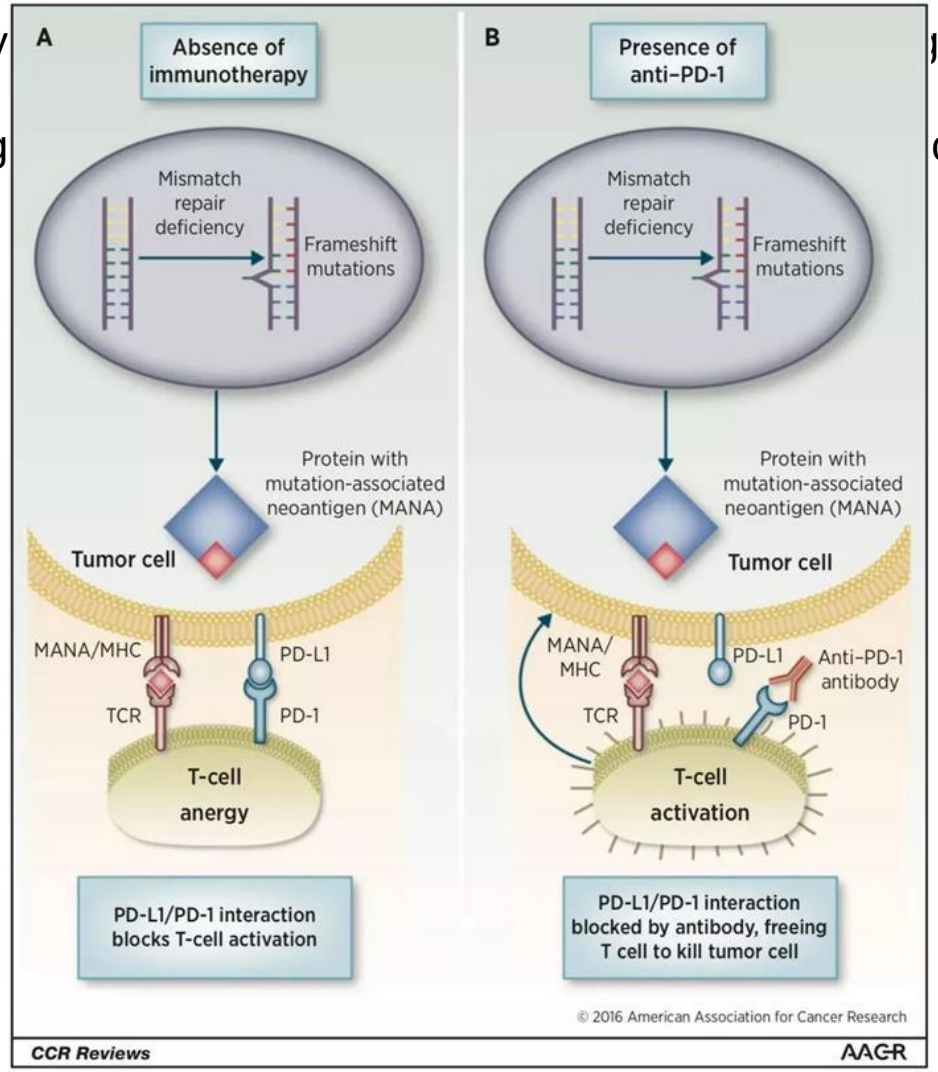




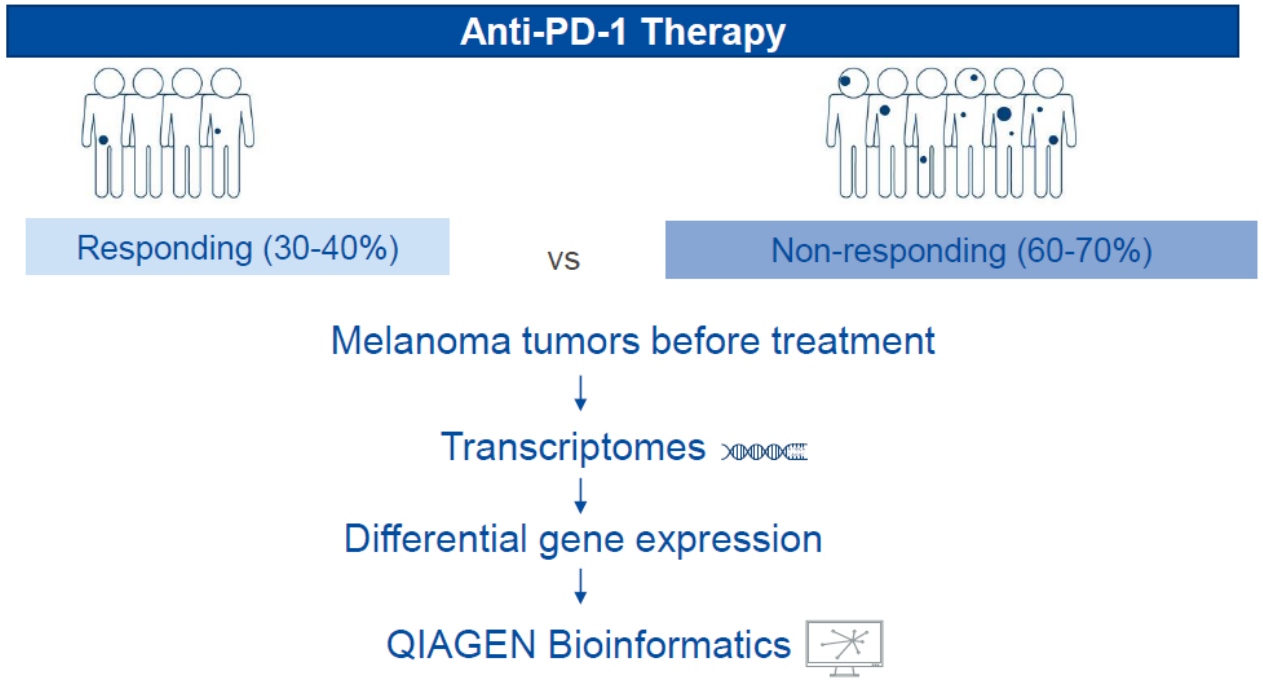
- Schematic representing Ingenuity Pathway Analysis of a cDNA microarray of ECs isolated from anti-VEGF-A antibody (B20)-sensitive ID8 tumors and B20-resistant ID8 tumors.

Understanding innate resistance to anti PD1 in melanoma

- Immunoassay ... and inhibiting receptors located on effector T cells
- Anti-PD1 drug ... cells, killing cancer cells



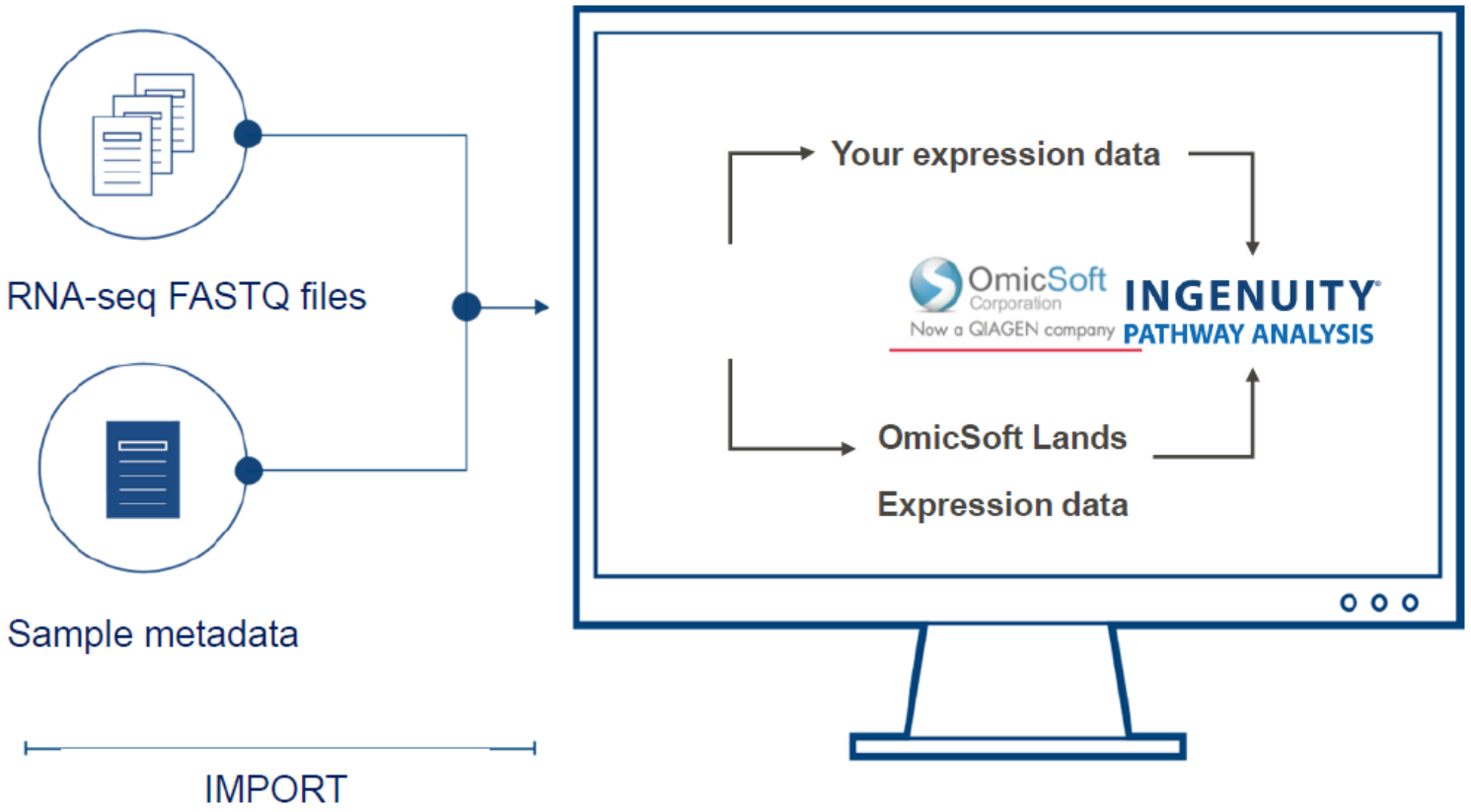
Metastatic melanoma RNA-seq data analysis



SUMMARY

PD-1 immune checkpoint blockade provides significant clinical benefits for melanoma patients. We analyzed the somatic mutanomes and transcriptomes of pretreatment melanoma biopsies to identify factors that may influence innate sensitivity or resistance to anti-PD-1 therapy. We find that, while overall high mutational loads associate with improved survival both in responding and non-responding patients, responding tumors are specifically enriched for mutations in the DNA repair gene *BRCA2*. Innately resistant tumors display a transcriptional signature (referred to as the IPRES or Innate anti-PD-1 Resistance) indicating concurrent upexpression of genes involved in the regulation of mesenchymal transition, cell adhesion, ECM remodeling, angiogenesis and wound-healing. Notably, MAPK-targeted therapy (MAPKi) induces similar signatures in

Ingenuity Pathway Analysis (IPA) FASTQ to insight



Upstream Regulator Analysis: Transcriptional Regulators

Upstream Regulators | Causal Networks

ADD TO MY PATHWAY | ADD TO MY LIST | DISPLAY AS NETWORK | CUSTOMIZE TABLE | MECHANISTIC NETWORKS

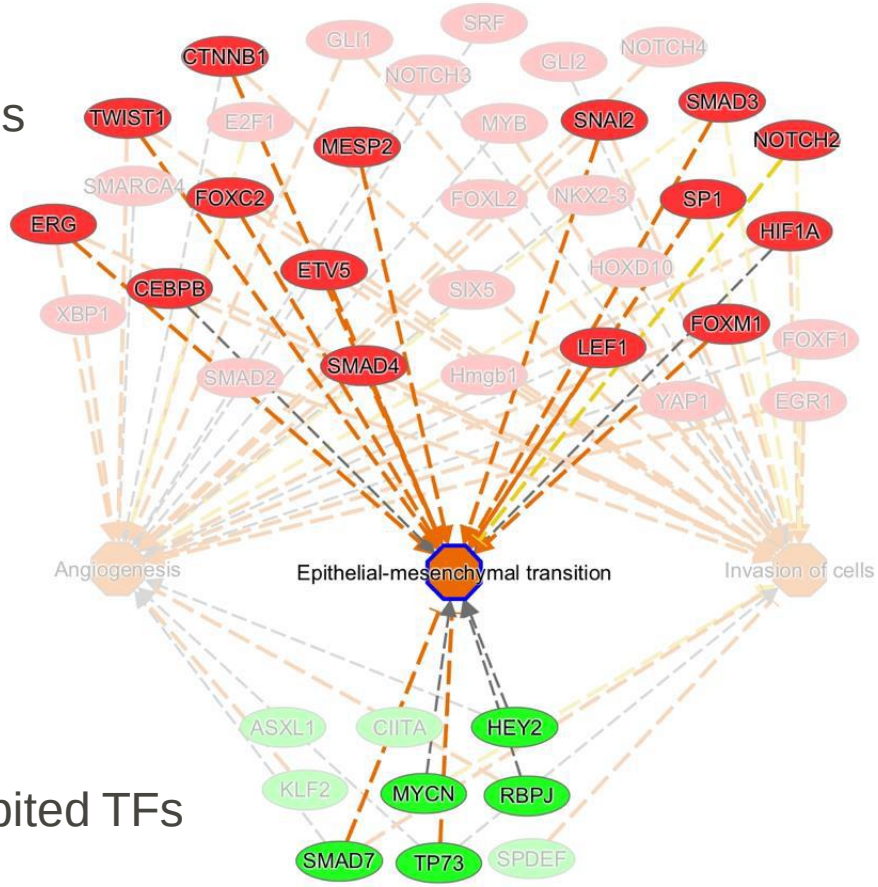
DISPLAY AS NETWORK

Upstream Reg...		lecule Type	Predicted Activati...	Activation z-s...	p-value of overlap	Target molecu...	Mechanistic N...
SMAD2		transcription regulator	Activated	3.750	5.23E-06	↑ACTA2, ↑...all 21	490 (15)
GLI1	↑1.875	transcription regulator	Activated	3.678	7.62E-07	↓BCL2L1, ↓...all 39	209 (7)
SMAD3	↑3.847	transcription regulator	Activated	3.606	9.09E-06	↑ACTA2, ↑...all 40	510 (17)
CTNNB1	↓-3.182	transcription regulator	Activated	3.258	3.97E-07	↑ACTA2, ↑...all 100	485 (19)
ERG	↑2.067	transcription regulator	Activated	3.144	4.14E-03	↓ADGRG1, ↑...all 29	
FOXM1	↑3.106	transcription regulator	Activated	3.033	3.03E-03	↑ACE, ↑AU... ...all 20	476 (17)
YAP1	↓-2.683	transcription regulator	Activated	2.970	2.31E-03	↑ACTA2, ↑...all 18	423 (17)
SMARCA4	↑2.255	transcription regulator	Activated	2.922	1.13E-04	↑ACE, ↑AC... ...all 80	507 (19)
SNAI2	↑2.033	transcription regulator	Activated	2.784	1.23E-02	↑AXL, ↑BSG, ...all 10	
FOXL2	↑3.923	transcription regulator	Activated	2.779	2.11E-02	↑BMP2, ↑C... ...all 11	
MYB	↑2.771	transcription regulator	Activated	2.534	2.24E-03	↓BCL2L1, ↑...all 21	
ETV5	↓-2.478	transcription regulator	Activated	2.433	1.28E-02	↓CDH1, ↓CL... ...all 9	
GLI2	↑1.910	transcription regulator	Activated	2.385	1.60E-01	↑CCL3L3, ↓...all 12	
CEBPA	↓-1.884	transcription regulator	Activated	2.277	2.34E-02	↓AKR1C1/... ...all 47	
TWIST1	↑1.837	transcription regulator	Activated	2.277	3.06E-12	↑ACAN, ↑A... ...all 42	351 (7)
LEF1	↑1.908	transcription regulator	Activated	2.219	5.50E-02	↓CDH1, ↑C... ...all 9	
FOXC2	↑6.493	transcription regulator	Activated	2.219	4.16E-01	↓CDH1, ↑M... ...all 5	
NOTCH4	↑1.832	transcription regulator	Activated	2.217	1.12E-03	↑ACTA2, ↑C... ...all 8	198 (6)
HDAC6	↑2.330	transcription regulator	Activated	2.201	2.07E-02	↓CDH1, ↑G... ...all 8	
NOTCH3	↑2.797	transcription regulator	Activated	2.105	1.06E-03	↑ACTA2, ↓...all 12	
PLAG1	↑2.287	transcription regulator	Activated	2.097	9.49E-04	↑CDKN1C, ↑...all 13	
FOXF1	↑1.846	transcription regulator	Activated	2.000	1.28E-02	↑CACNA1C, ↑...all 4	
POU5F1	↑1.930	transcription regulator		1.977	1.93E-01	↓BFAR, ↓C... ...all 31	

This is a transcriptional regulator signature of epithelial to mesenchymal transition (EMT)

Transcriptional program drives epithelial mesenchymal transition

All activated TFs



All inhibited TFs

Statistically significant functions overlapping the TF network:

Epithelial-mesenchymal transition
p-value 5.06E-29

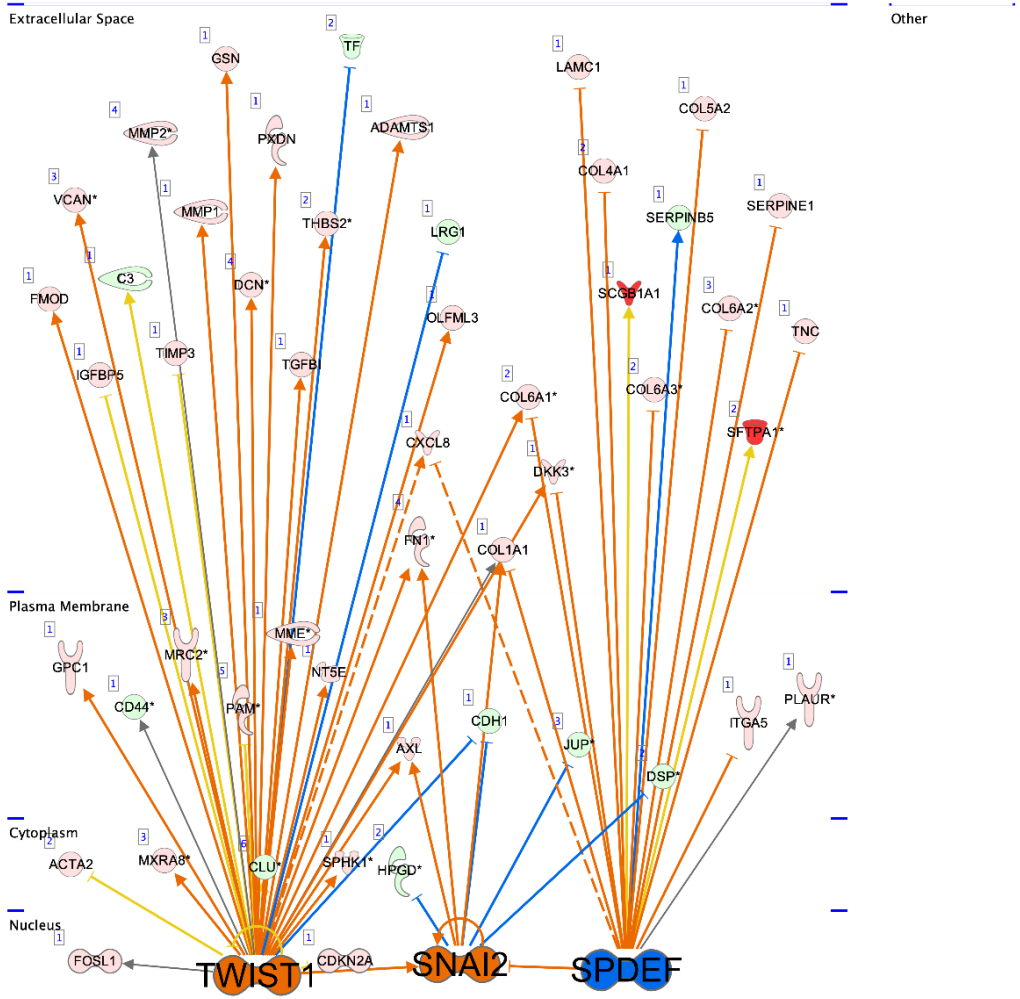
Angiogenesis
p-value 3.72E-25

Invasion of cells
p-value 4.81E-23

EMT is regulated by at least two transcription factors: SNAI2 and TWIST1

SNAI2 and TWIST1 = **activated** in non-responders

SPDEF = **inhibited** in non-responders. Normal activity is as tumor suppressor.

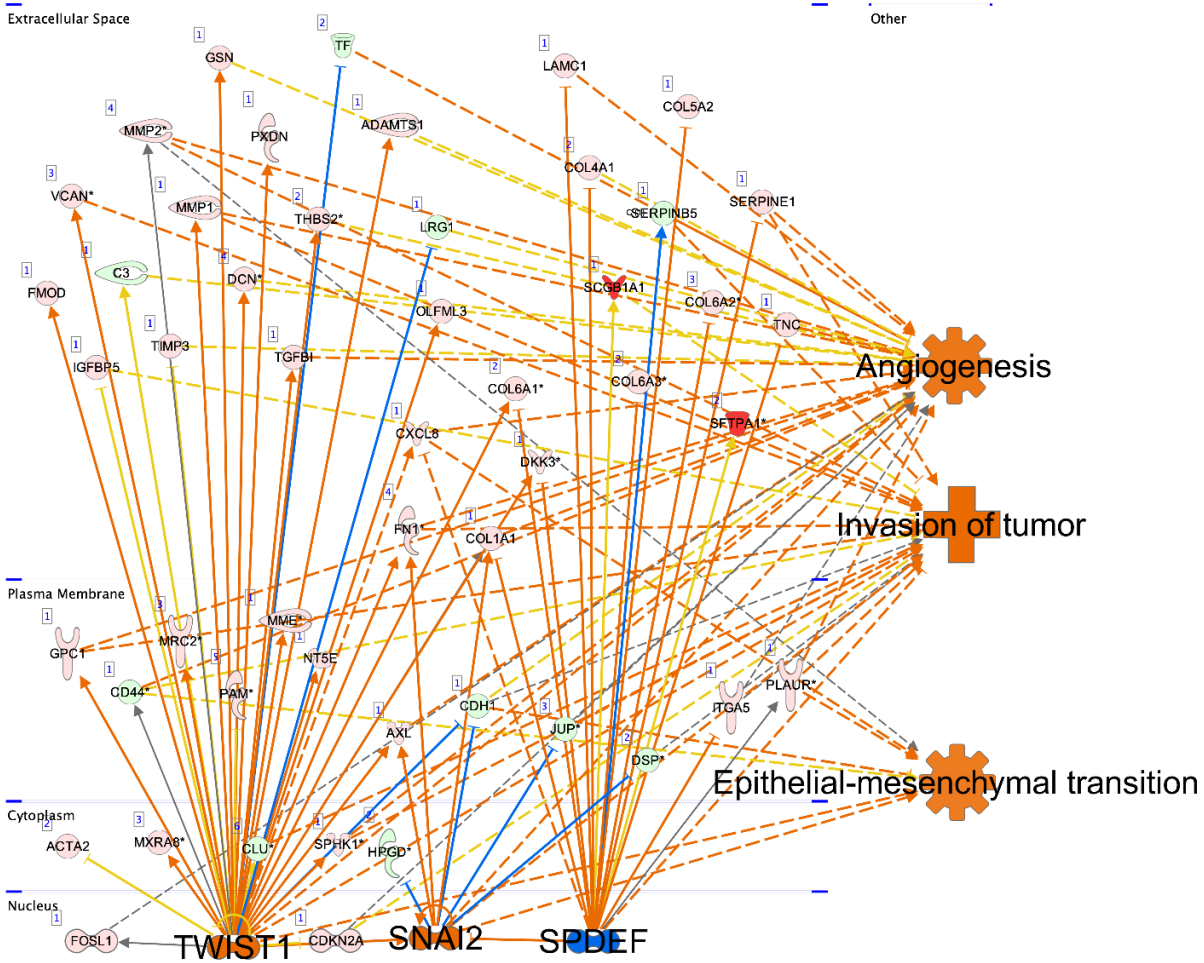


EMT is regulated by at least two transcription factors: SNAI2 and TWIST1

SNAI2 and TWIST1 = **activated** in non-responders

SPDEF = **inhibited** in non-responders. Normal activity is as tumor suppressor.

They drive increases in EMT, angiogenesis, and invasion.



Causal Network Analysis to find chemicals to augment treatment (hypotheses)

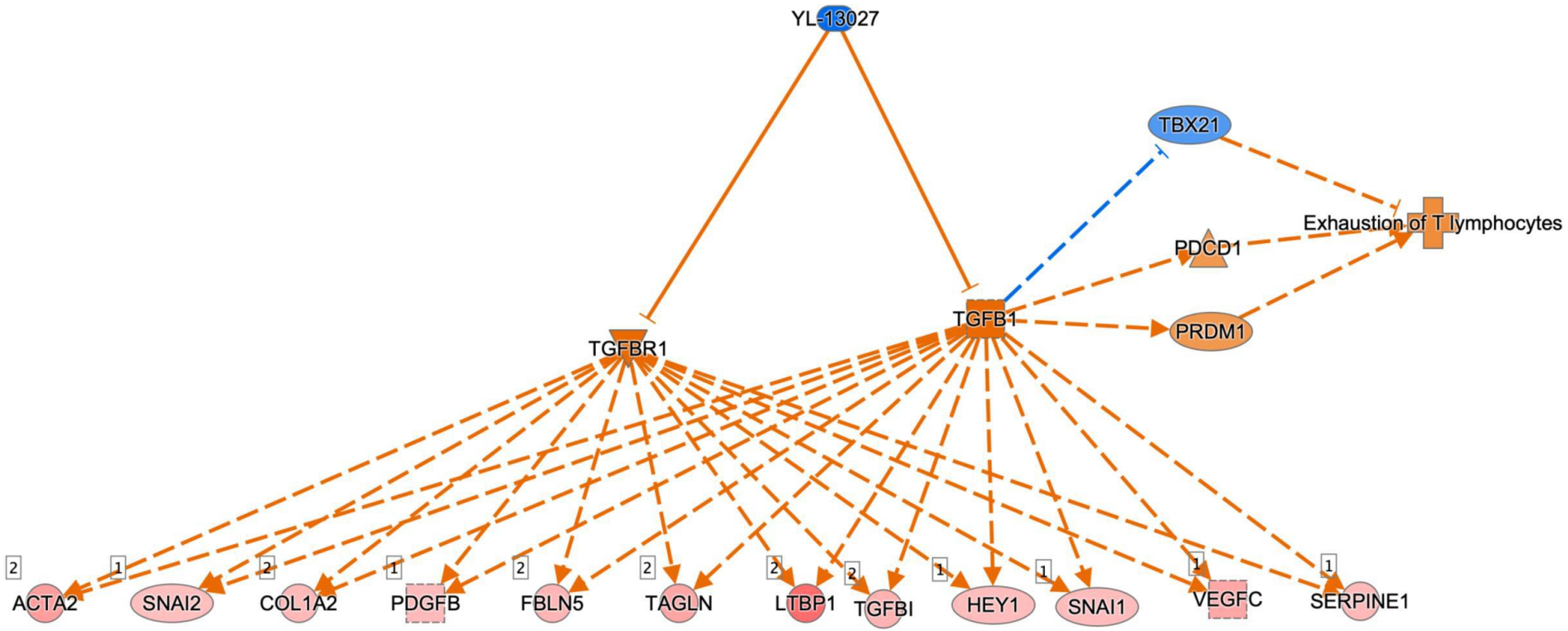
Upstream Regulators | Causal Networks

ADD TO MY PATHWAY | ADD TO MY LIST

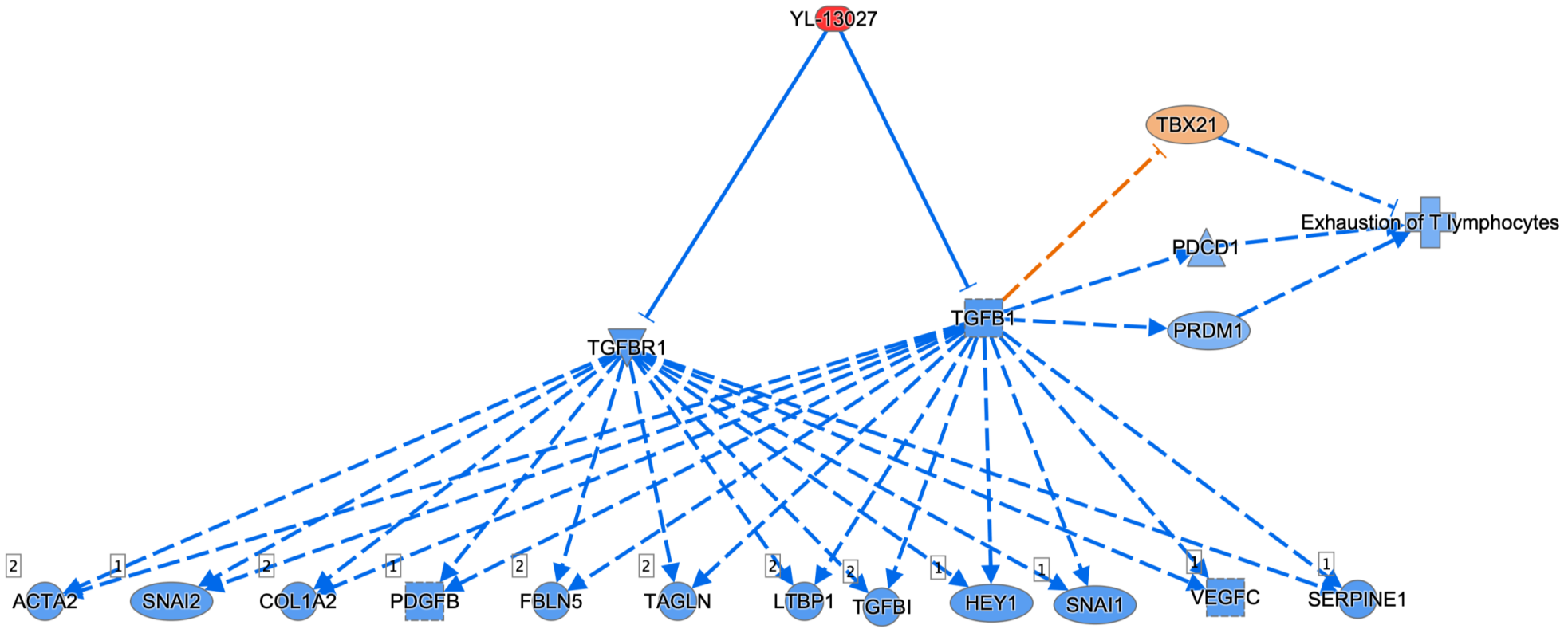
More I

								Add/Remove column(s)	Exhaustion of T lymphocytes [exhaust...		Advanced melanoma [advance...		Invasion of cell	
Master Regulator	Molecule Type	De...	Pre...	..	p-...	Net...	Tar...	Ca...	Len...	Path Types	Len...	Path Types	Len...	Pa
YL-13027	chemical drug	2	Inhibited	-7.054	7.70E-20	1.00E-04	...all 205	205 (3)	3 | 6	DU(3), IU(3)	3 | 4	DU(1), IU(3)	2 | 2	IU
ganglioside GD1b	chemical - endogen...	2	Inhibited	-5.630	1.14E-07	3.05E-02	...all 92	92 (6)	3 | 18	DU(11), IU(7)	3 | 15	DU(9), IU(6)	2 | 6	IU
argatroban	chemical drug	2	Inhibited	-5.334	1.04E-09	6.00E-04	...all 62	62 (4)	3 | 3	DU(2), IU(1)	3 | 4	DU(1), IU(3)	2 | 4	IU
arachidonyltrifluorometh	chemical reagent	2	Inhibited	-5.023	5.21E-11	4.50E-02	...all 235	235 (9)	3 | 14	DU(9), IU(5)	3 | 23	DU(9), IU(14)	2 | 12	IU
galunisertib	chemical drug	2	Inhibited	-4.950	2.35E-08	2.00E-04	...all 32	32 (3)			3 | 1	DU(1)	2 | 2	IU
bivalirudin	biologic drug	2	Inhibited	-4.808	2.39E-07	6.60E-03	...all 53	53 (3)	3 | 3	DU(2), IU(1)	3 | 6	DU(2), IU(4)	2 | 4	D
cytochalasin B	chemical toxicant	2	Inhibited	-4.734	8.14E-13	5.00E-04	...all 145	145 (10)	2 | 1	DU(1)	2 | 1	DU(1)	1 | 1	IU
SC68376	chemical - kinase in...	2	Inhibited	-4.589	1.16E-06	4.90E-02	...all 65	65 (4)	3 | 6	DU(4), IU(2)	3 | 10	DU(6), IU(4)	2 | 6	D
plerixafor	chemical drug	2	Inhibited	-4.530	6.47E-08	3.94E-02	...all 117	117 (10)	2 | 1	IU(1)	2 | 1	DU(1)	1 | 1	IU
mrs2179	chemical reagent	2	Inhibited	-4.529	2.27E-07	2.90E-02	...all 78	78 (5)	3 | 6	DU(5), IU(1)	3 | 5	DU(1), IU(4)	2 | 5	D
antithrombin alfa	biologic drug	2	Inhibited	-4.522	1.13E-07	2.10E-03	...all 47	47 (3)	3 | 1	DU(1)	3 | 4	DU(1), IU(3)	2 | 1	IU
graptopetalum paragua	chemical - endogen...	2	Inhibited	-4.522	1.27E-07	2.70E-03	...all 47	47 (2)	3 | 9	DU(4), IU(5)	3 | 19	DU(6), IU(13)	2 | 4	D
LMT-28	chemical reagent	3	Inhibited	-4.522	6.33E-16	7.30E-03	...all 414	414 (61)	3 | 9	DU(3), IU(6)	3 | 9	DU(2), IU(7)	2 | 3	IU
stearylamine	chemical reagent	2	Inhibited	-4.429	9.58E-08	2.10E-03	...all 49	49 (3)	3 | 2	DU(1), IU(1)	3 | 4	DU(1), IU(3)	2 | 2	D
aclarubicin	chemical drug	3	Inhibited	-4.419	1.77E-08	1.43E-02	...all 118	118 (15)			3 | 2	DU(1), IU(1)	2 | 2	IU
sphinganine	chemical - kinase in...	2	Inhibited	-4.417	2.79E-08	2.80E-03	...all 74	74 (5)	3 | 4	DU(3), IU(1)	3 | 9	DU(5), IU(4)	2 | 3	D
bevacizumab	biologic drug	2	Inhibited	-4.383	4.31E-09	1.69E-02	...all 125	125 (6)	3 | 17	DU(6), IU(11)	1 | 1	IU(1)	2 | 15	D
axitinib	chemical drug	2	Inhibited	-4.346	5.70E-10	8.00E-04	...all 89	89 (8)	3 | 8	DU(3), IU(5)	3 | 9	DU(2), IU(7)	2 | 4	D
ulinastatin	chemical drug	2	Inhibited	-4.330	1.24E-07	2.20E-03	...all 48	48 (5)	3 | 2	DU(2)	3 | 4	DU(1), IU(3)	2 | 2	IU
nebivolol	chemical drug	2	Inhibited	-4.281	9.22E-09	2.30E-03	...all 83	83 (10)	3 | 3	DU(3)	3 | 15	DU(9), IU(6)	2 | 10	D
emodin	chemical drug	2	Inhibited	-4.127	7.70E-12	1.80E-02	...all 233	233 (20)	3 | 34	DU(20), IU(14)	2 | 2	IU(2)	1 | 1	IU
leptomycin B	chemical drug	2	Inhibited	-4.110	2.71E-12	8.00E-04	...all 148	148 (8)	3 | 20	DU(9), IU(11)	3 | 24	DU(4), IU(20)	2 | 13	D

Prediction: Absence of YL13027 can lead to increased T cell exhaustion

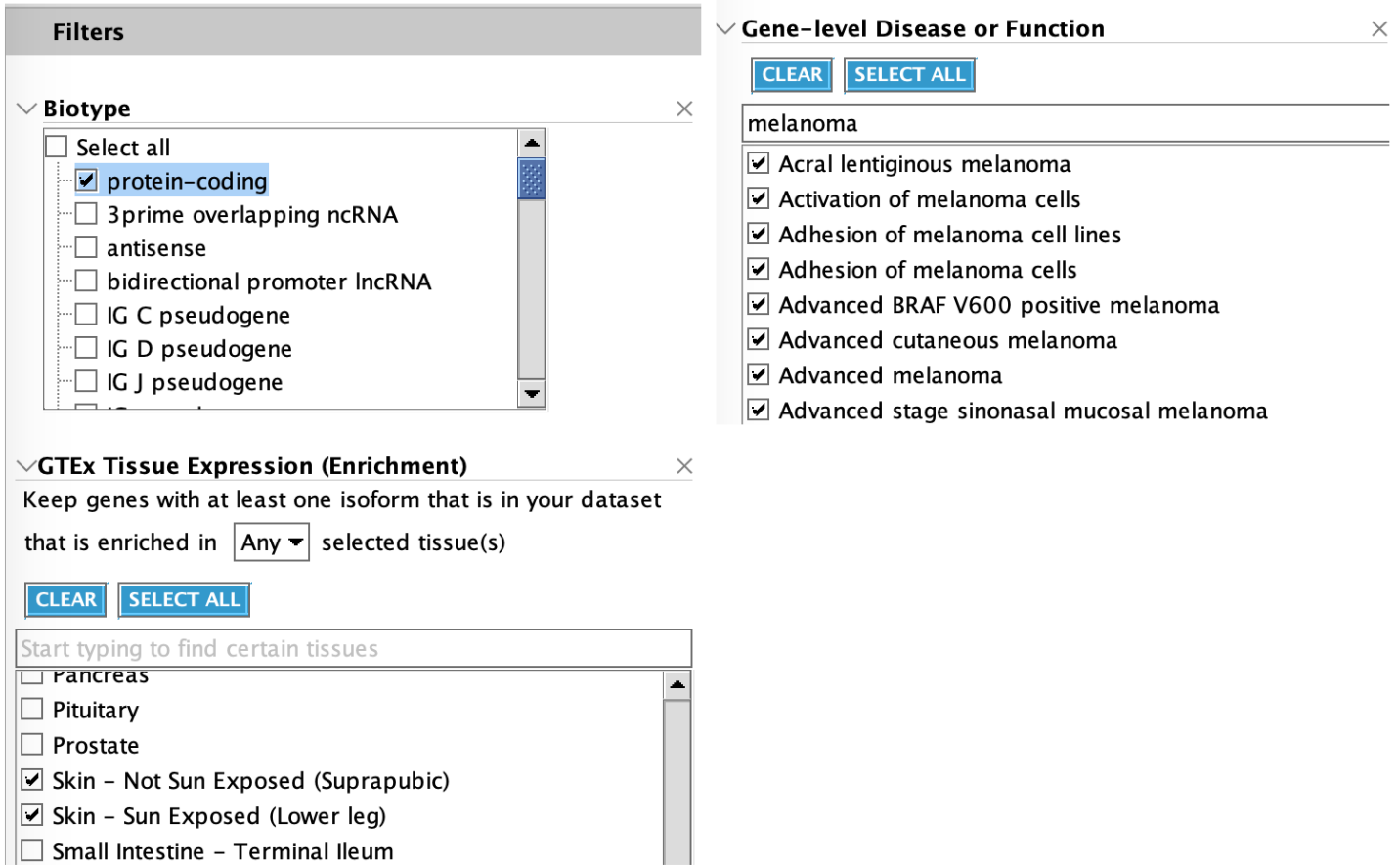


Hypothesis: adding YL13027 will decrease T cell exhaustion

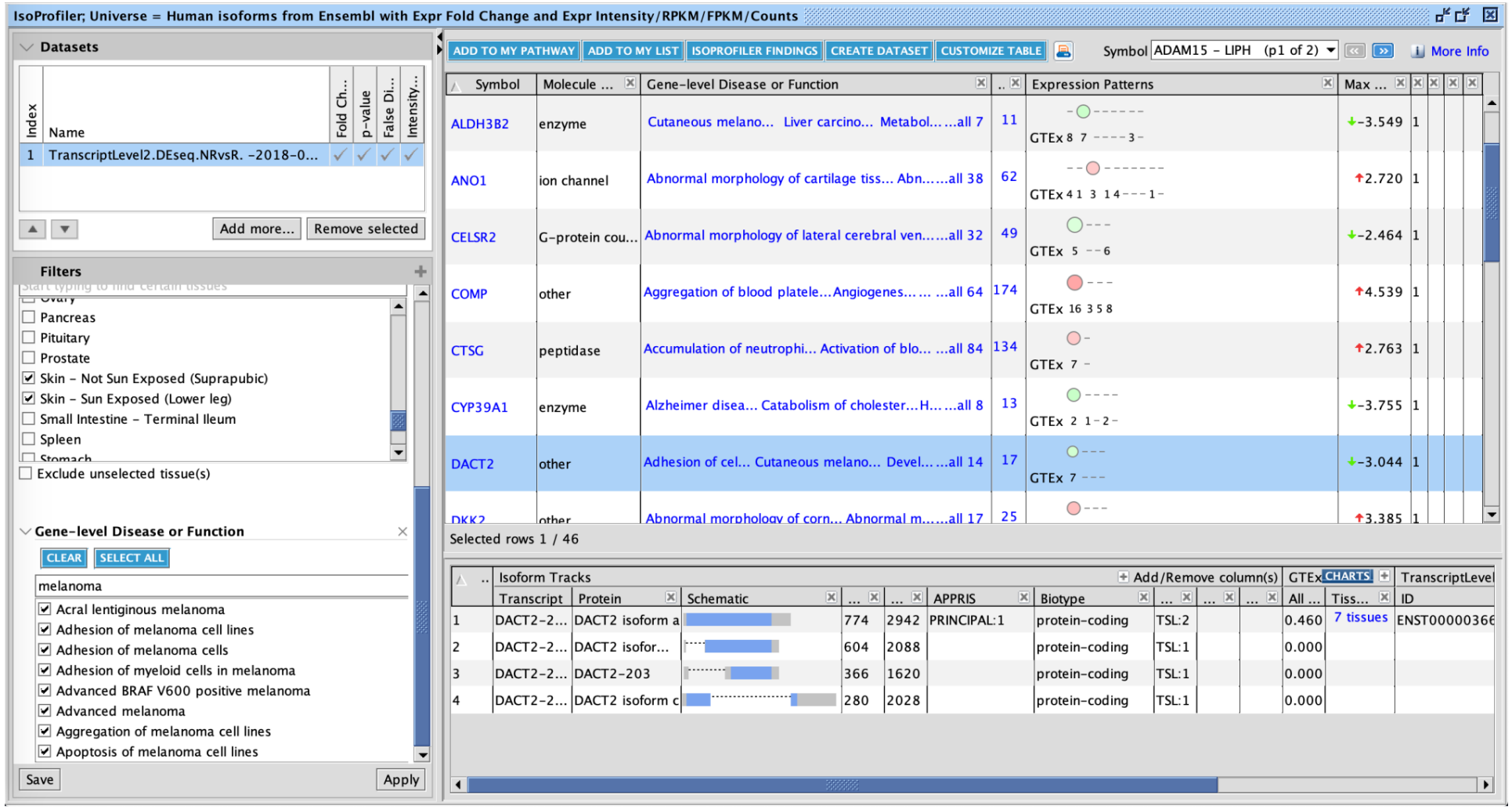


Searching for skin enriched protein coding isoforms with melanoma association

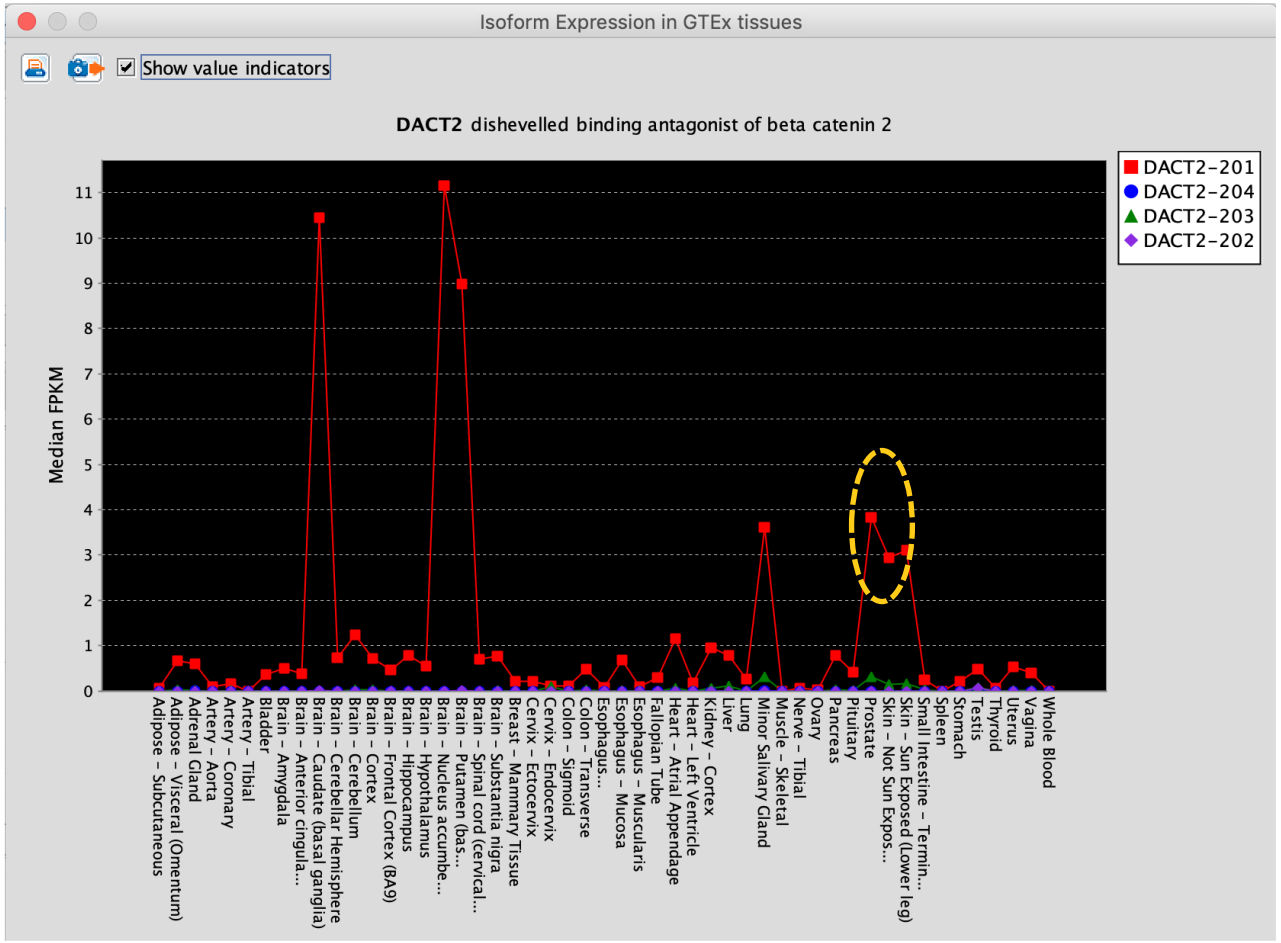
IsoProfiler filters



IsoProfiler: 46 genes have isoforms that meet all criteria

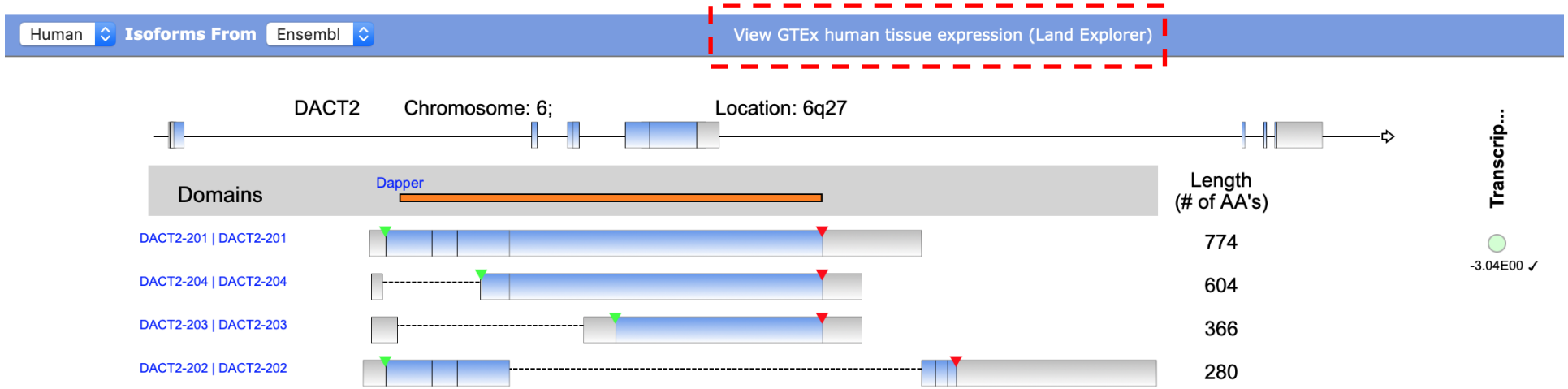


DACT2 isoform expression across GTEx tissues. Enriched in skin tissue



Transcript name: DACT2-201
ID: ENST00000366795
Tissue name: Prostate
All tissue median FPKM: 0.460
Median FPKM: 3.825
Ratio: 7.003x (Enriched)

DACT2 is a tumor suppressor enriched in normal skin tissues



DACT2 decreases proliferation of lung cancer.

22806826 Jia Y, Yang Y, Brock MV, Zhan Q, Herman JG, Guo M. Epigenetic regulation of DACT2, a key component of the Wnt signalling pathway in human lung cancer. J Pathol. 2013 Jun;230(2):194-204.

Source: Ingenuity ExpertAssist Findings

Original Sentence: DACT2 inhibits lung cancer proliferation by suppressing the Wnt signalling pathway in lung cancer.

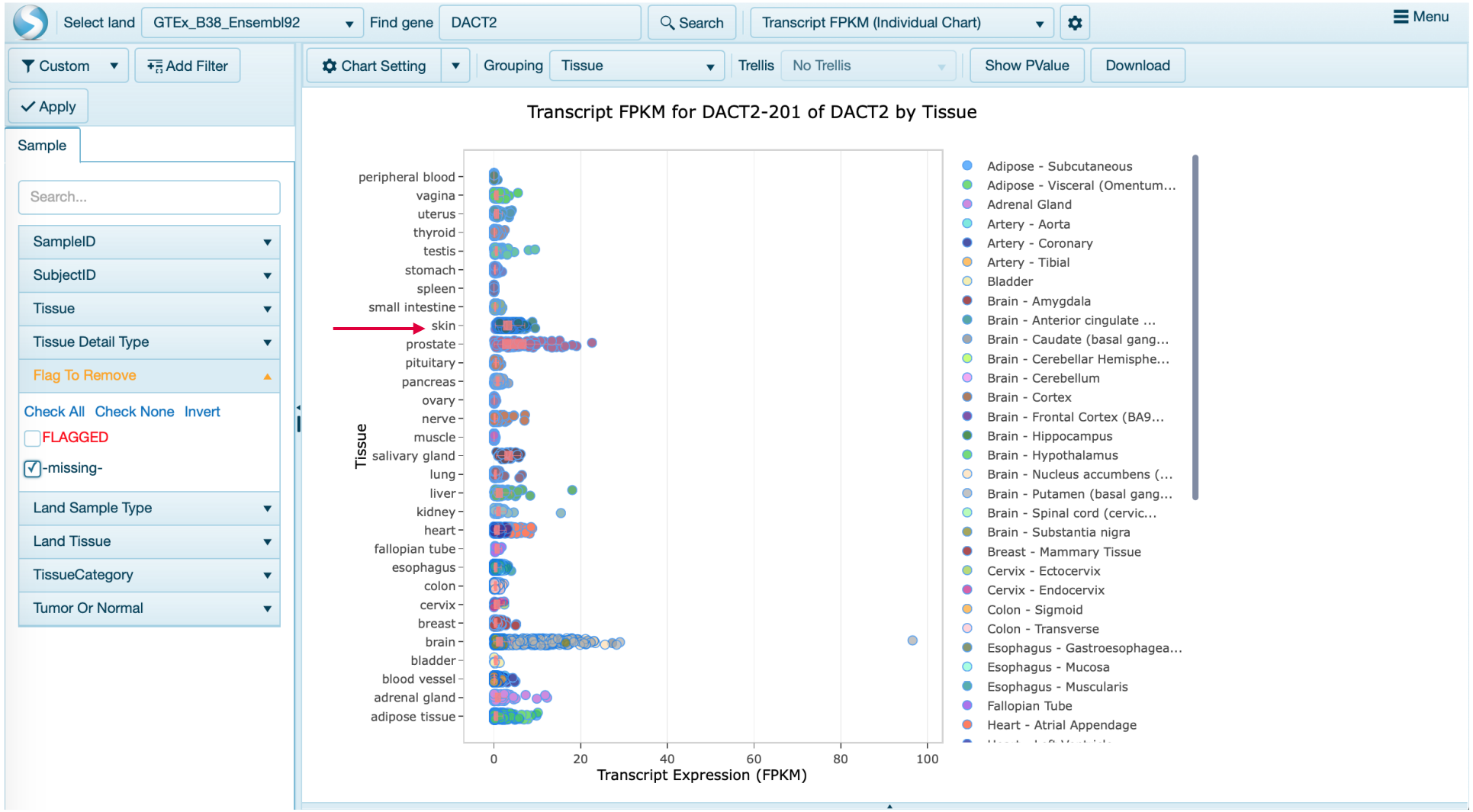
Mutant **human DACT2 gene** (substitution c.1132C>T translating to p.R378* [somatic nonsense]) **is observed with adenocarcinoma** in human prostate gland (COSMIC: observed in 2 of 141 samples).

26928463 Kumar A, Coleman I, Morrissey C, Zhang X, True LD, Gulati R, Etzioni R, Bolouri H, Montgomery B, White T, Lucas JM, Brown LG, Dumpit RF, DeSarkar N, Higano C, Yu EY, Coleman R, Schultz N, Fang M, Lange PH, Shendure J, Vessella RL, Nelson PS. Substantial interindividual and limited intraindividual genomic diversity among tumors from men with metastatic prostate cancer. Nat Med. 2016 Apr;22(4):369-78. Epub 2016 Feb 29.

COSMIC: 5996714

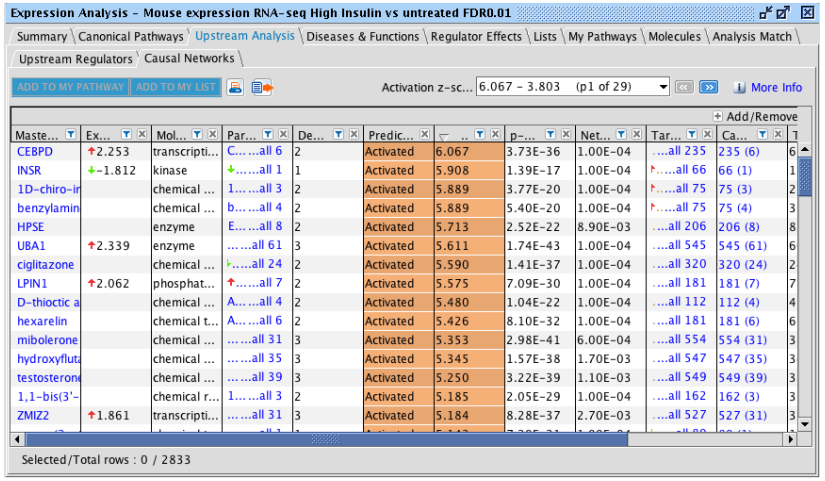
Source: Catalogue Of Somatic Mutations In Cancer (COSMIC)

Land Explorer for IPA (browser window), for sample-level exploration



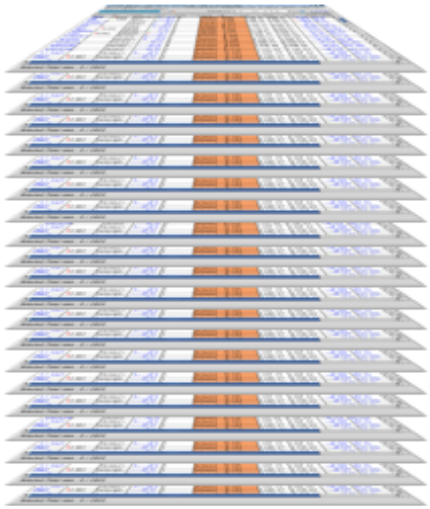
Analysis Match

How can you discover which analyses look like yours, to uncover insights from mechanistic similarities and differences?



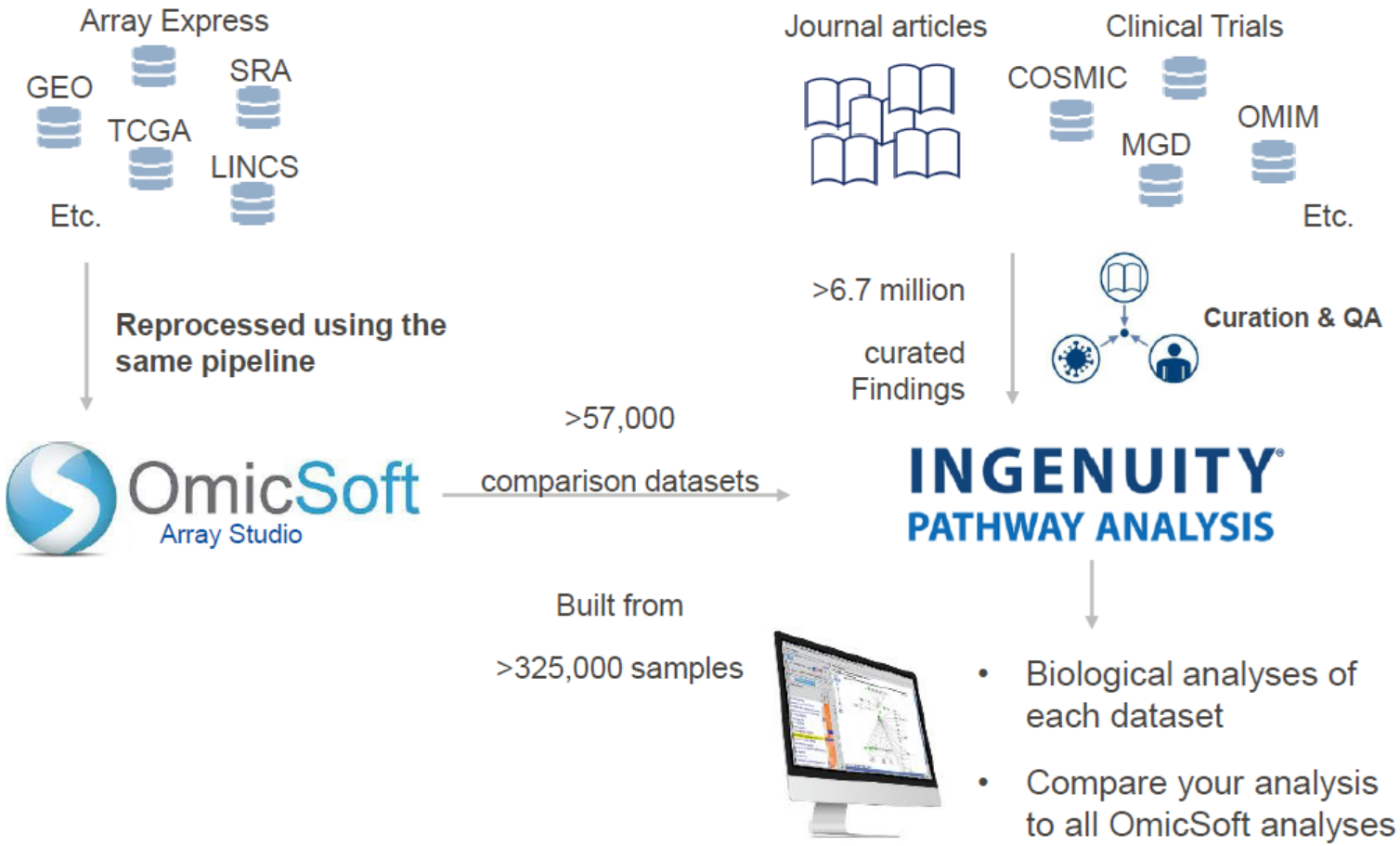
Match against

>57,000 analyses

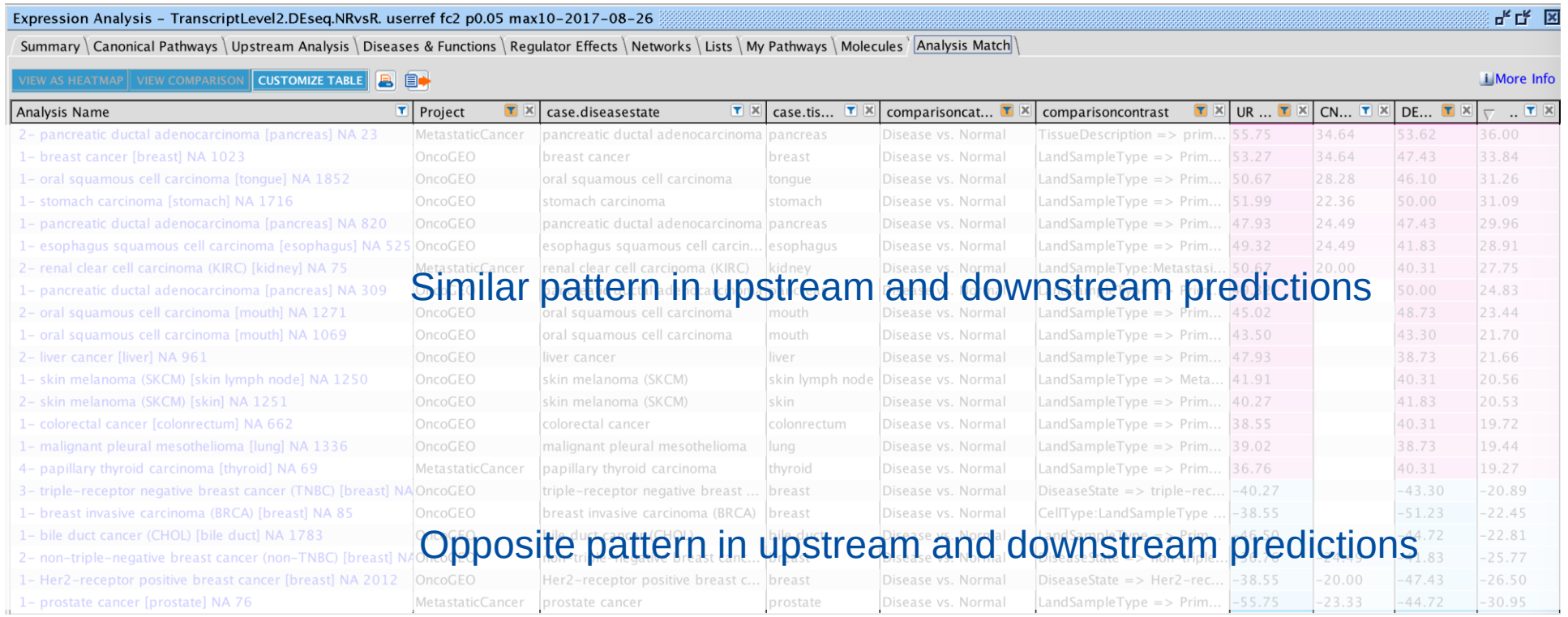


Which analyses have similar Upstream Regulators, Canonical Pathways, Diseases and Functions, etc?

Analysis Match combines knowledge with data

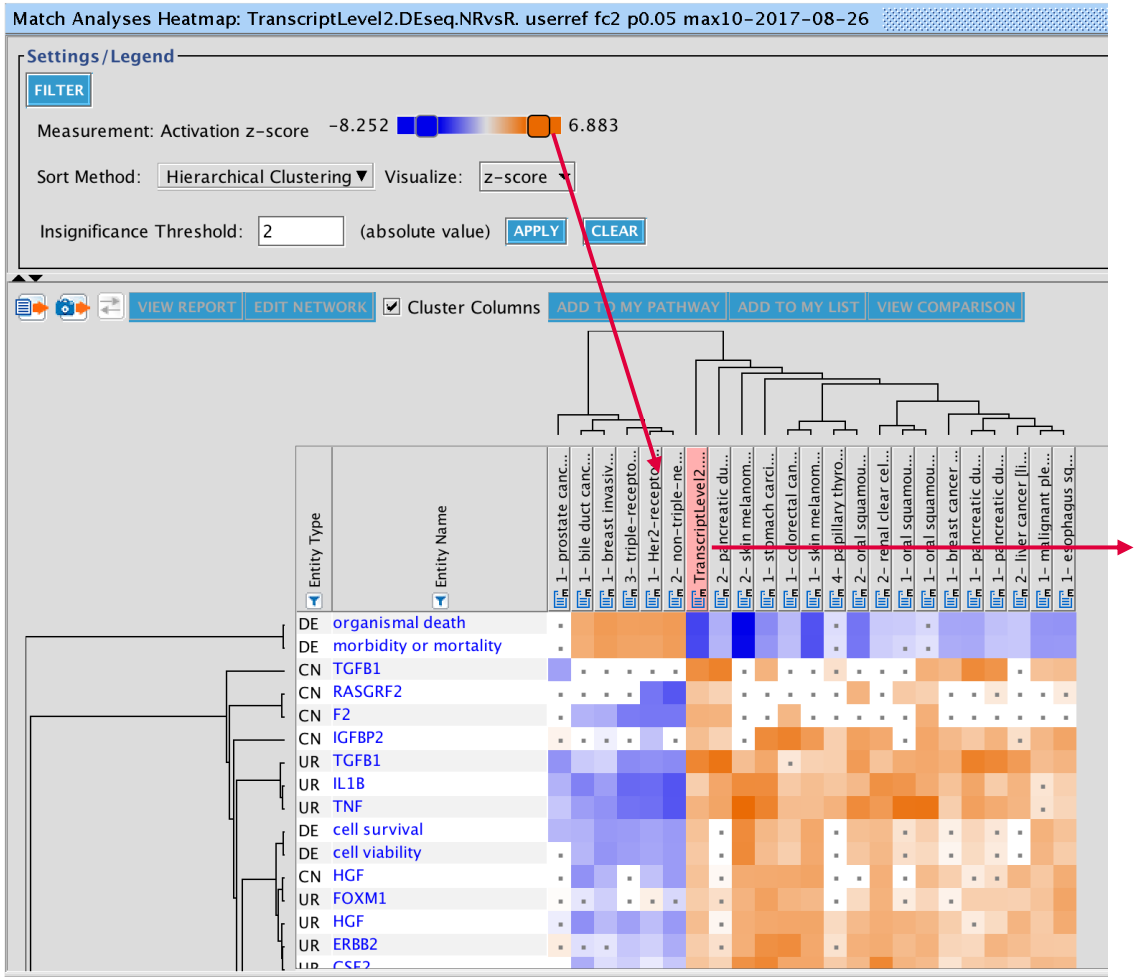


Analysis Match: Melanoma vs. precomputed datasets and your own



Analysis Match: Melanoma vs. precomputed datasets and your own

Heatmap of the selected analyses

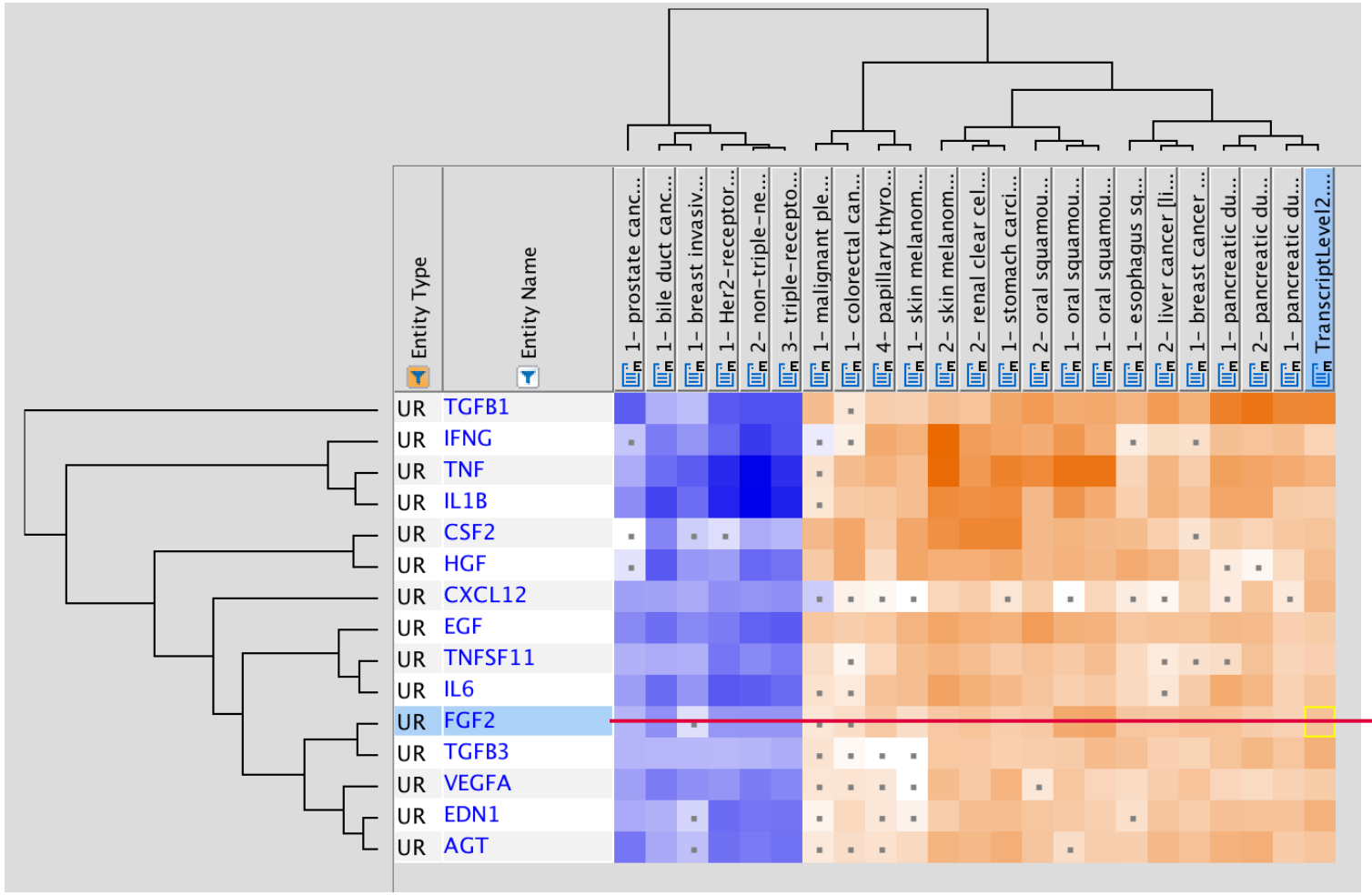


Metadata

1- colorectal cancer [colonrectum] NA 662

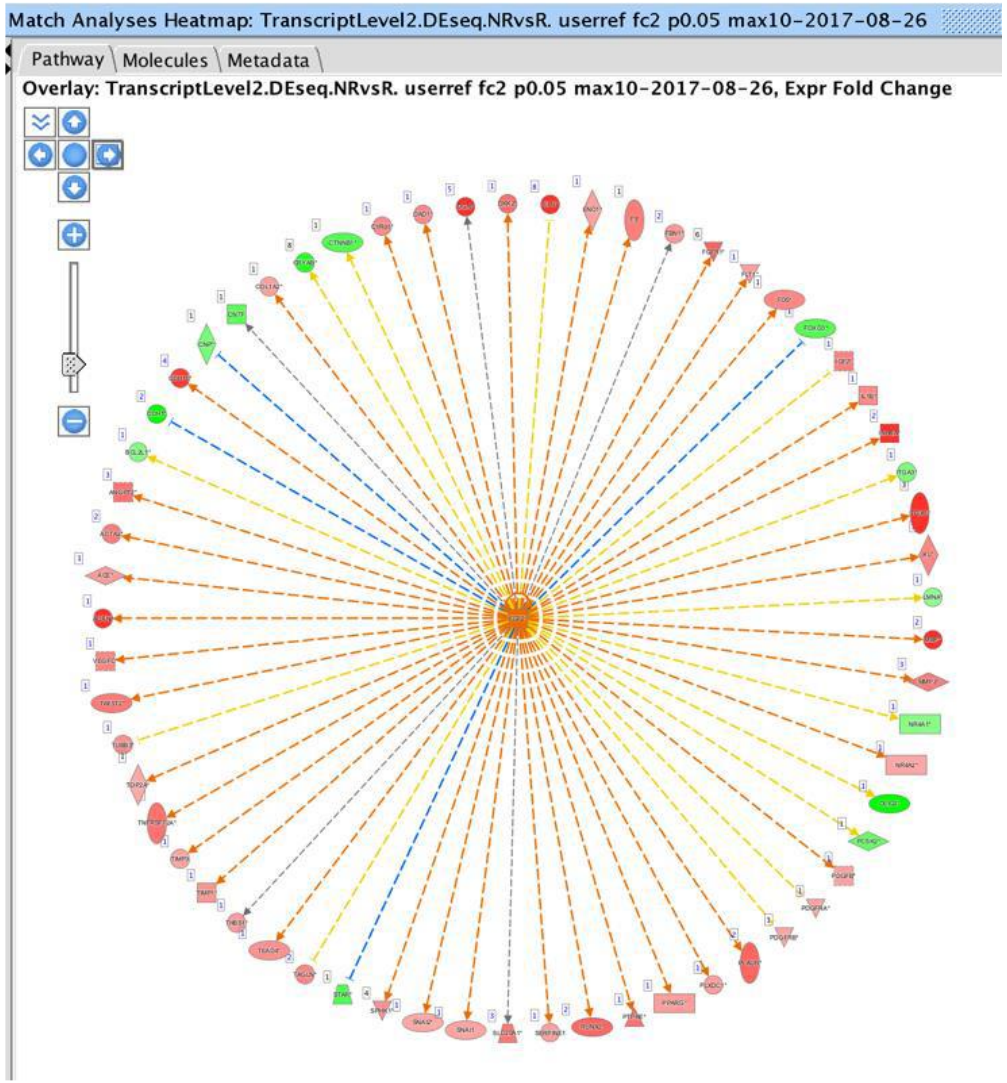
KEY	VALUE
case.diseasestate	colorectal cancer
case.sampleids	GSM588828;GSM588829;...
case.samplesource	colonrectum
case.tissue	colonrectum
case.treatment	NA
comparisoncategory	Disease vs. Normal
comparisoncontrast	LandSampleType => Prima...
comparisonid	GSE23878.GPL570.test1
comparisonindex	662
comparisontype	glm
control.diseasestate	colorectal cancer
control.sampleids	GSM588863;GSM588864;...
control.samplesource	colonrectum
control.tissue	colonrectum
control.treatment	NA
downregulated log2 cutoff	-1.6211
genemodelid	OmicsoftGene20130723
length	30373
observation name	1- colorectal cancer [colonr...
organism	human
platformname	Affymetrix.HG-U133_Plus_2
projectname	GSE23878
sampledatamode	Expression_Intensity_Probes
upregulated log2 cutoff	0.9543
weblink	https://www.ncbi.nlm.nih.g...

Upstream regulator signature related to tumor progression



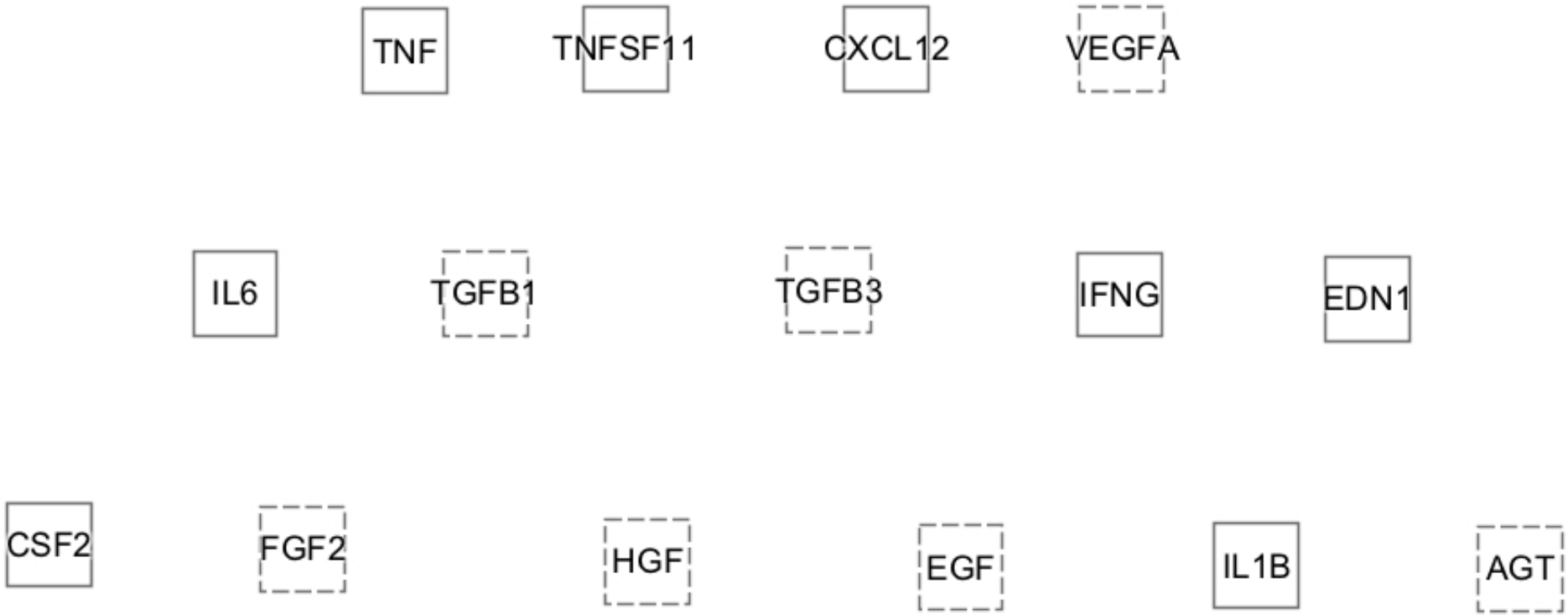
UR filtered by molecule type:
Cytokines and growth factors

Upstream regulator signature related to tumor progression

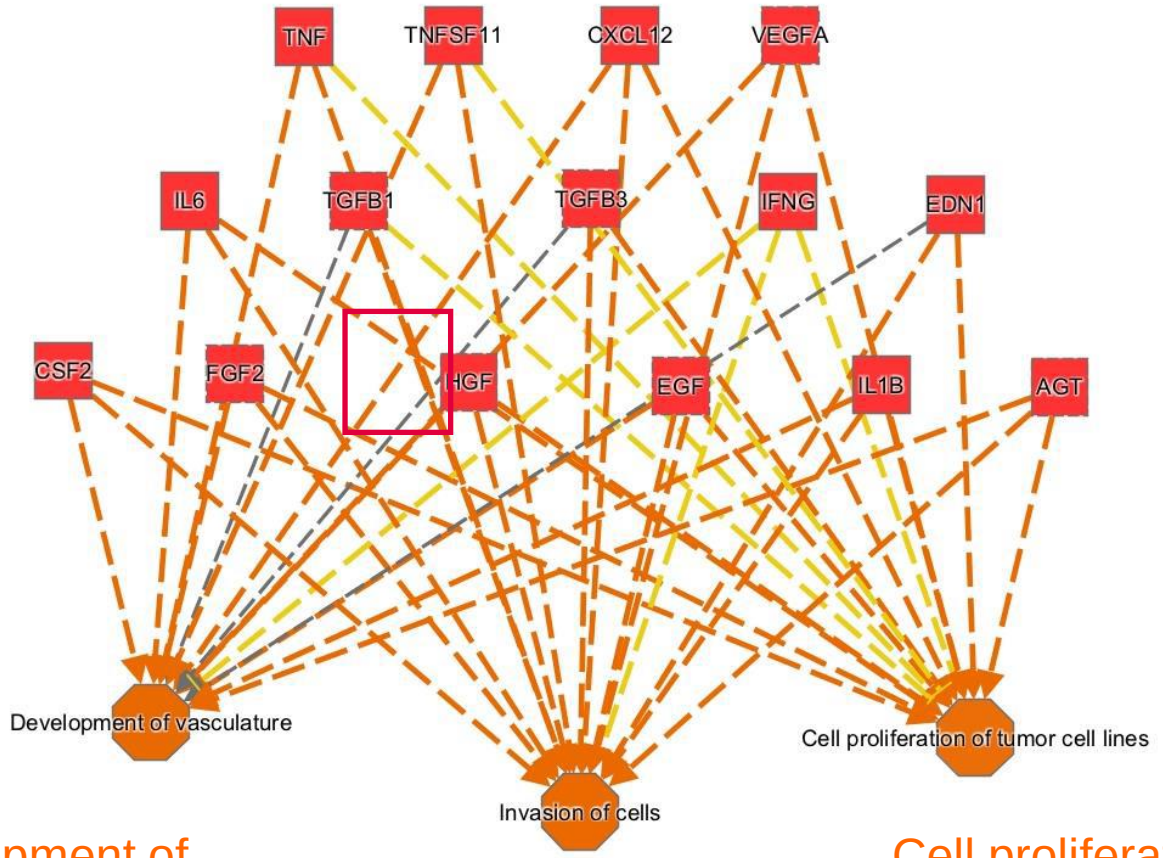


FGF2 is an upstream regulator predicted to be activated in non-responder vs responder

Upstream regulator signature related to tumor progression



Upstream regulator signature related to tumor progression



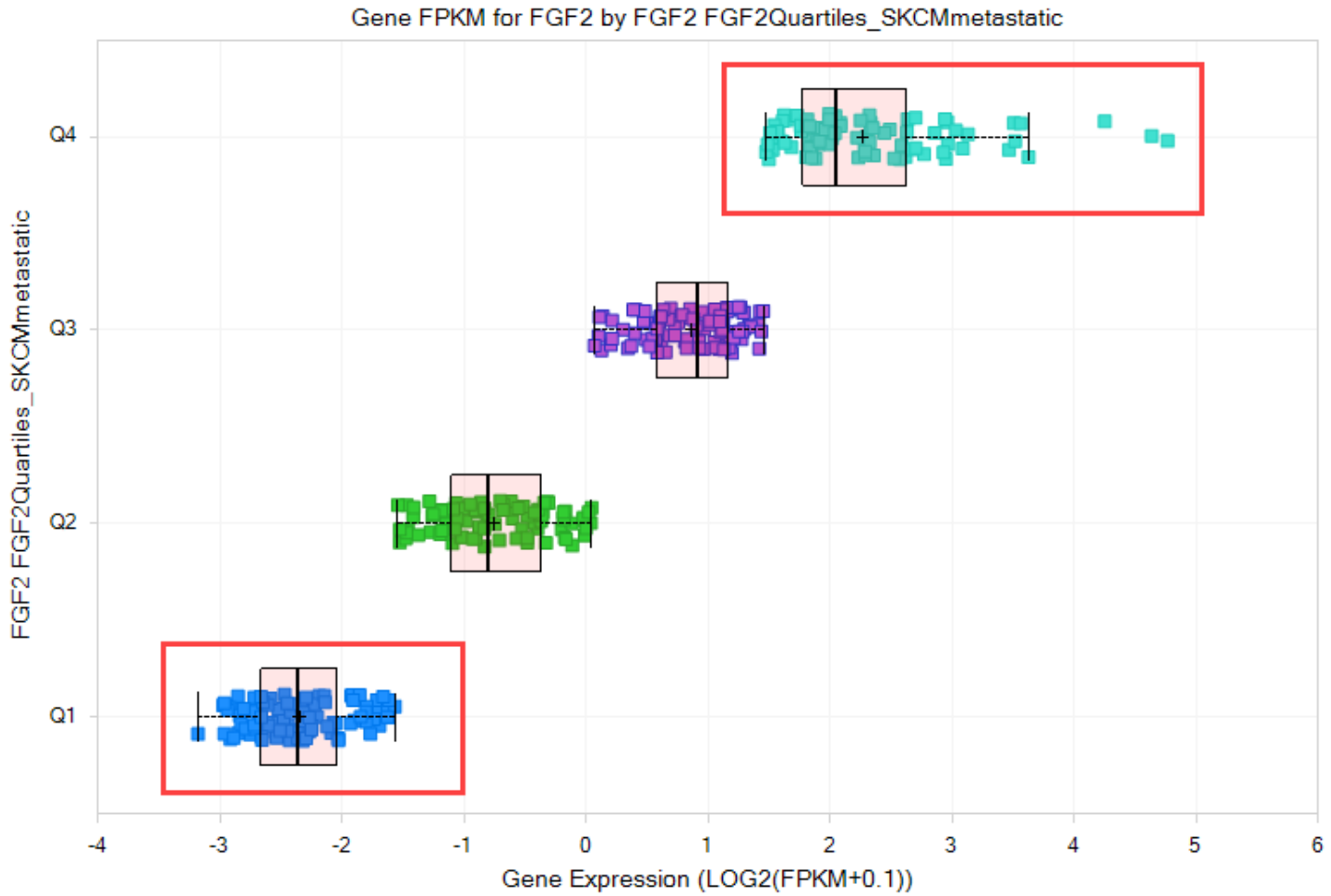
Next: Explore FGF2 in OncoLand

Development of vasculature
p-value: 1.43 E-18

Invasion of cells
p-value: 1.28 E-19

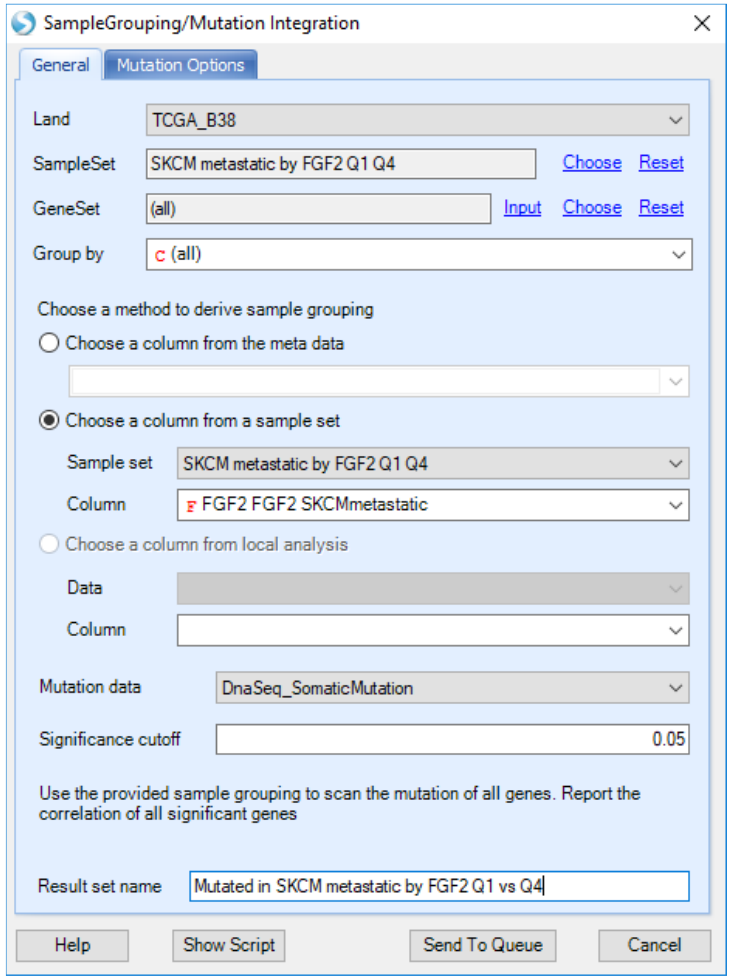
Cell proliferation of tumor cell lines
p-value: 6.37 E-15

Subset data for comparison by expression and metadata



Compare metastatic skin melanoma samples with low versus high expression of FGF2

Rapidly compare custom groupings for significant associations

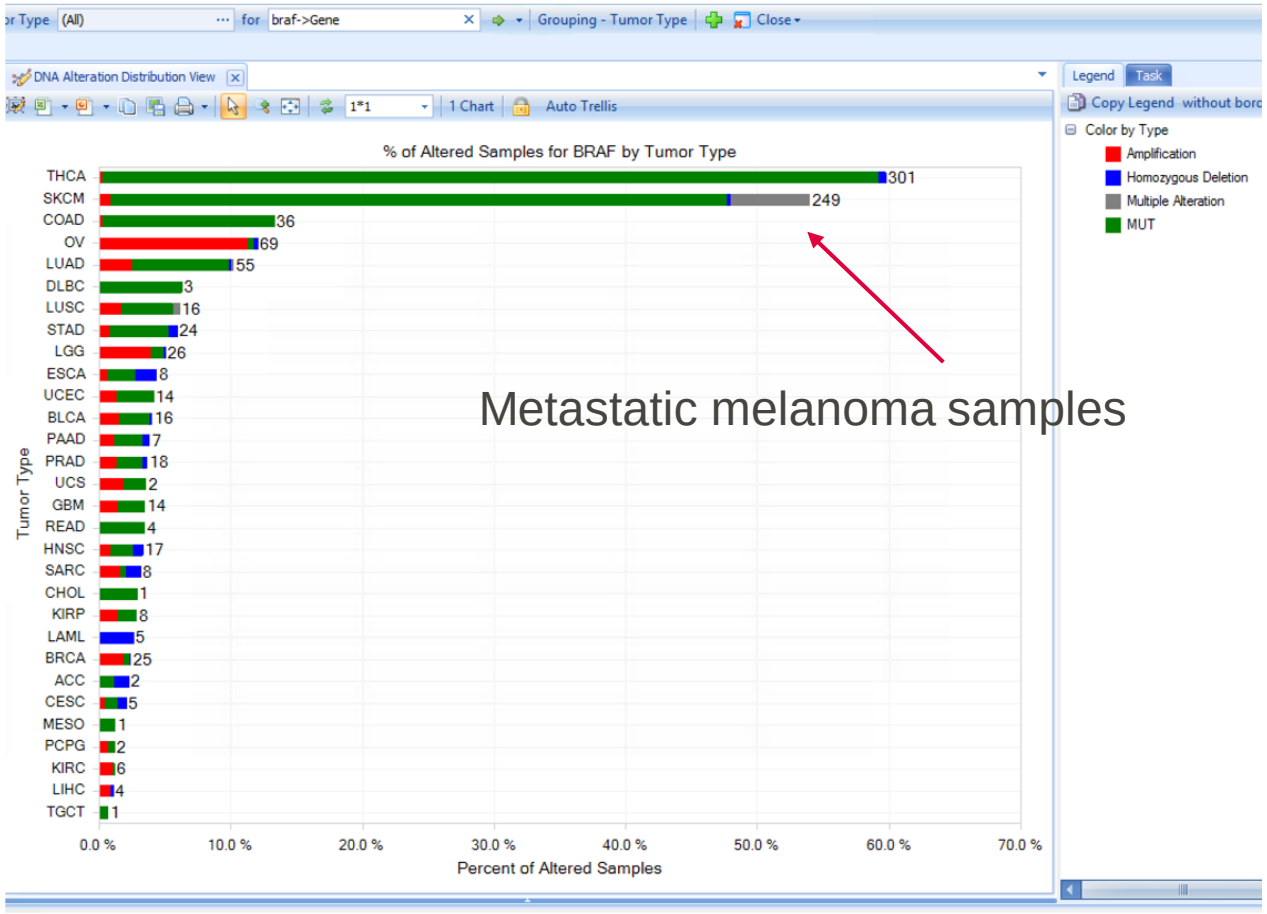


Compare groups for differences in expression, splicing, mutation, copy number, clinical metadata and survival

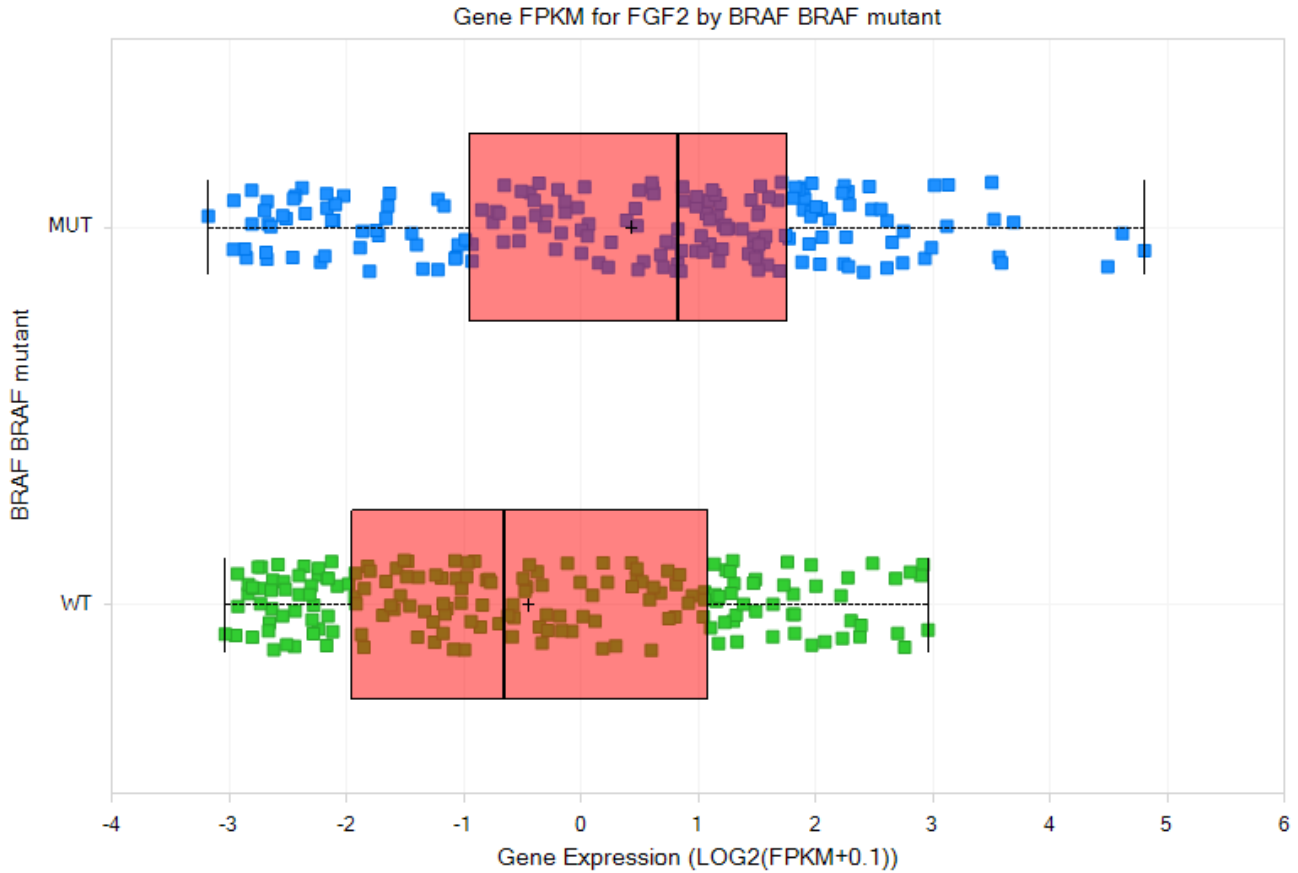
GeneID	Gene name	Gene exon length	P value [Fisher-Exact]	FDR BH
SULF1	*SULF1*	7194	1.495635474290e-005	0.0071
SVEP1	*SVEP1*	15269	3.718107130026e-005	0.0071
ENPEP	*ENPEP*	4995	4.673739698216e-005	0.0071
EPHA7	*EPHA7*	7489	5.273445707259e-005	0.0071
BRAF	*BRAF*	2946	5.700041690929e-005	0.0071
TLR4	*TLR4*	5781	0.0001	0.0107
TSHZ2	*TSHZ2*	12581	0.0001	0.0120
SMOC1	*SMOC1*	3698	0.0002	0.0120
ANO2	*ANO2*	5092	0.0002	0.0129
CGNL1	*CGNL1*	7339	0.0002	0.0129
MYO18B	*MYO18B*	8982	0.0002	0.0130
DOCK3	*DOCK3*	8755	0.0003	0.0130
IGDCC4	*IGDCC4*	6751	0.0003	0.0130

Leveraging vast amounts of public data in OmicSoft'sOncoLand

BRAF alteration frequency by tumor

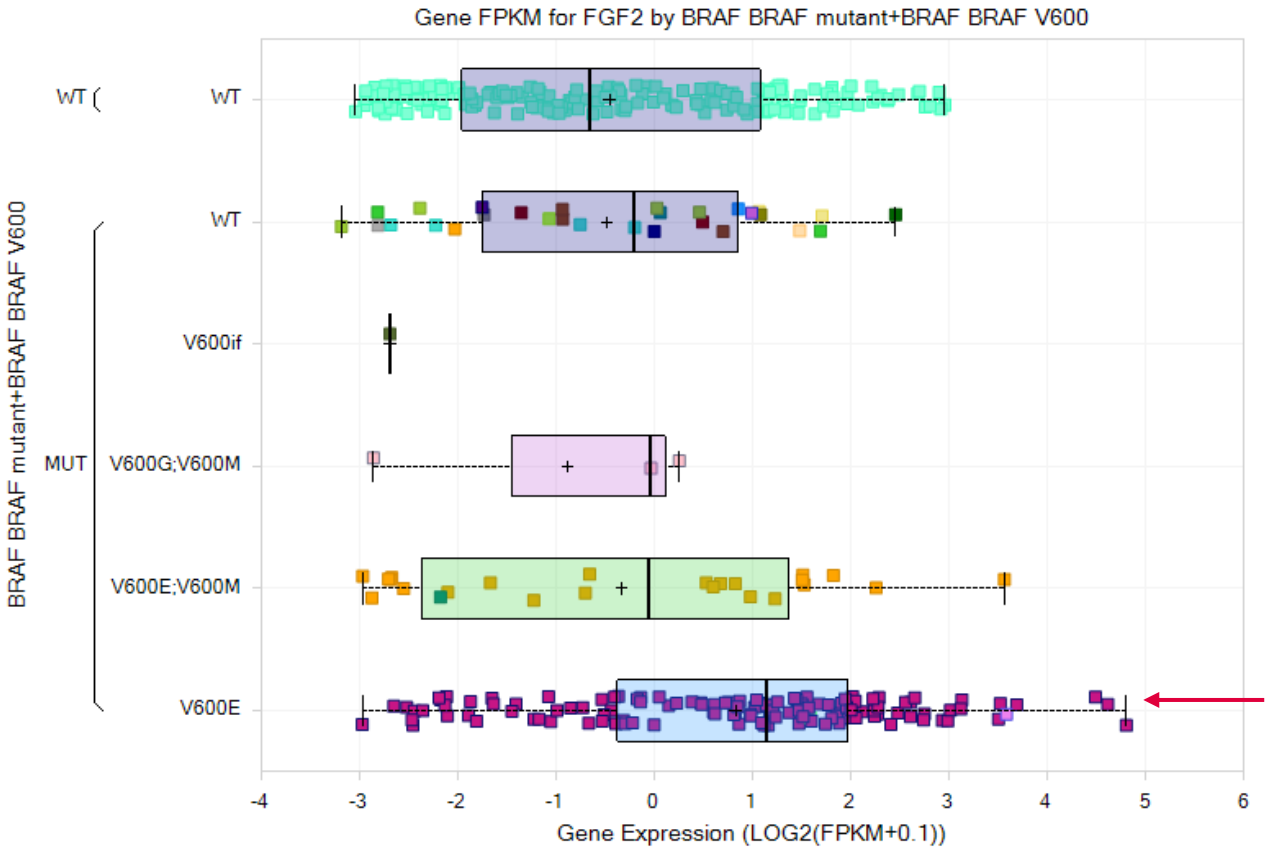


BRAF mutation (all) in comparison to FGF2 expression



FGF2 expression is higher in BRAF mutant samples

FGF2 significantly upregulated in SKCM with BRAF V600E mutation



FGF2 expression is highest in BRAF V600E mutant samples

Conclusion: Understand innate anti-PD1 resistance

- A potential transcriptional program with TFs (SNAI2, TWIST1, SPDEF, etc.) is detected and drives the EMT phenotype in the anti-PD1 non-responders
- Chemicals (or drug targets) can be predicted as therapeutic to ameliorate non-responsive patients
- The isoform DACT2-201, that functions as a tumor suppressor and which is enriched in normal skin tissues, is downregulated in the non-responders
- A shared set of cytokines and growth factors may drive tumor progression across multiple cancer datasets
- At least two genes (FGF2, BRAF) are correlated and play key roles in advanced melanoma

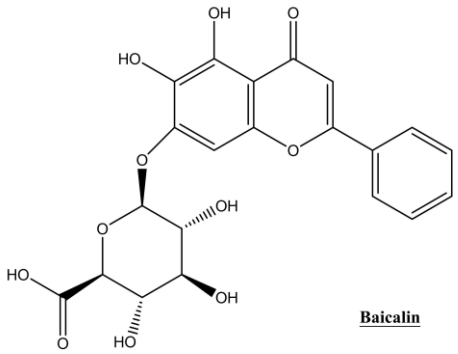
Agenda

- What’s new 2023 IPA Spring/Summer Release介紹
- 疾病與樣本 Metadata 整合分析
- 藥物潛在標的預測 IPA 與第三方軟體整合運用
- 你所不知道的 IPA 製圖技巧 外泌體研究案例分享

結合多體學與模擬技術，應用於抗COVID19中草藥藥效分析



Fig. 1. The components of traditional Chinese medicine (TCM) formula NRICM101.



Baicalin

① In silico and in vitro studies of Taiwan Chingguan Yihau (NRICM101) on TNF-α/IL-1β-induced Human Lung Cells

② In Silico Target Analysis of Treatment for COVID-19 Using Huang-Lian-Shang-Qing-Wan, a Traditional Chinese Medicine Formula.

③ Study of Baicalin towards COVID-19 treatment: In silico target analysis and in vitro inhibitory effects on SARS-CoV-2 proteases.

以虛擬藥物模擬工具，大量比對中草藥方科學成份潛在作用標的，再輔以多體學系統生物分析技術，組織出作用標的影響的細胞功能，進而解釋並優化**中草藥方、清冠一號對抗COVID19療效**。研究已於2021年陸續發表於**Natural Product Communications**, **Biomedicine**等期刊。

BIONET 訊聯生技　GGA 訊聯基因數位　分子數位中心 Molecular Sciences & Digital Innovation　BIONET 訊聯細胞智藥

西藥標靶藥物概念應用於中藥科學成份

西藥



標靶藥物:標靶藥物包含所有可鎖定腫瘤細胞的療法，像是： 荷爾蒙療法：鎖定驅動癌細胞生殖的荷爾蒙，阻斷其生成機制、受體、或下游訊息傳遞路徑

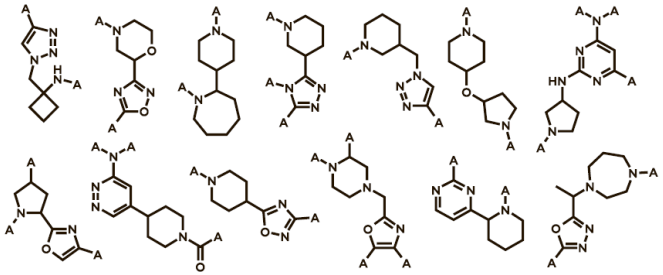
中藥



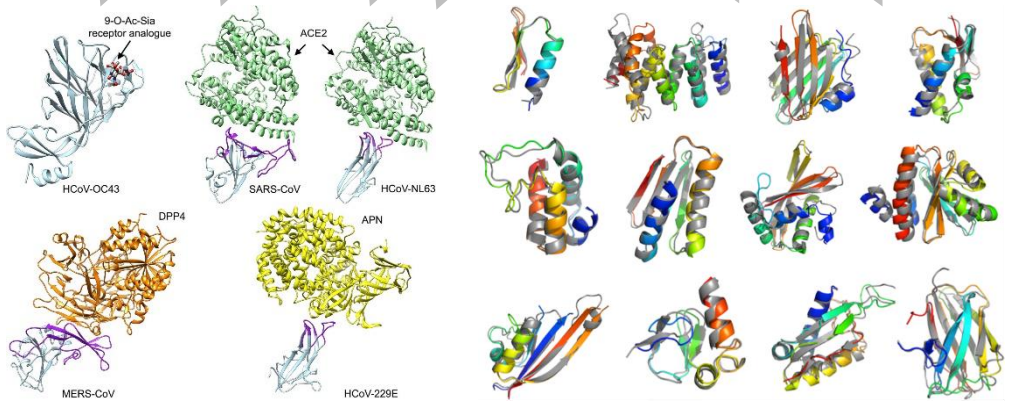


複方是由多味中藥材所組成的處方，以中醫典籍中的成方，或經驗成方來製成藥粉，由多種藥物搭配，得到更好的治療效果，經驗累積後，慢慢形成複方。

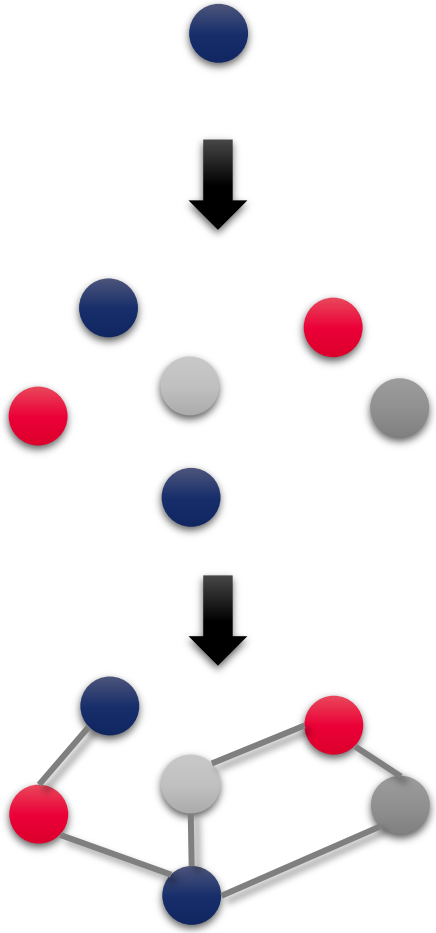
大量科學成份及其標靶作用方式



中草藥科學成份化合物



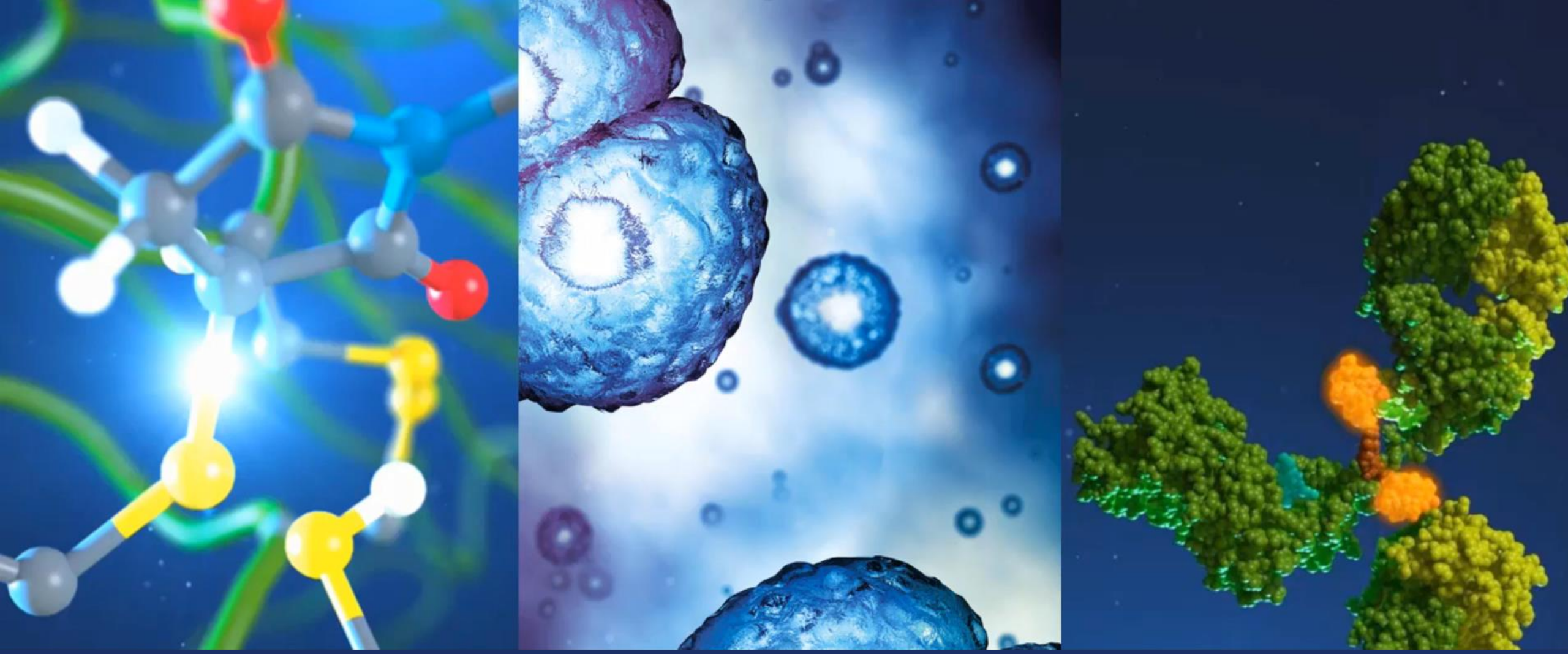
病源蛋白質標靶　　人體蛋白質標靶



單一標靶

科學成份標靶

科學成份標靶
系統性功能

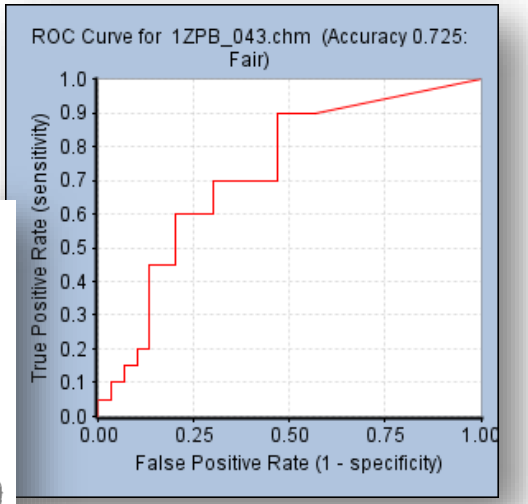


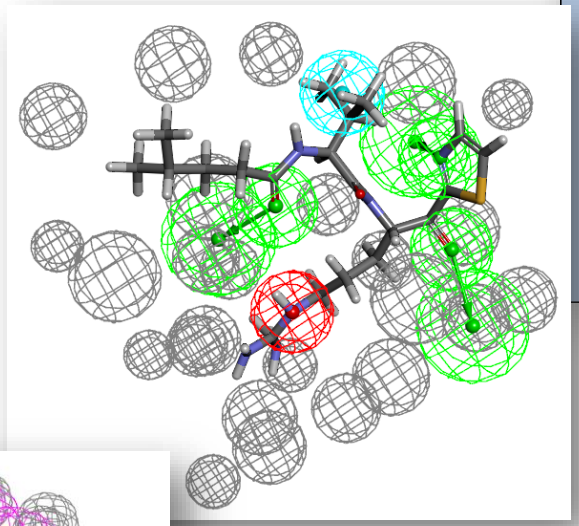
Discovery Studio

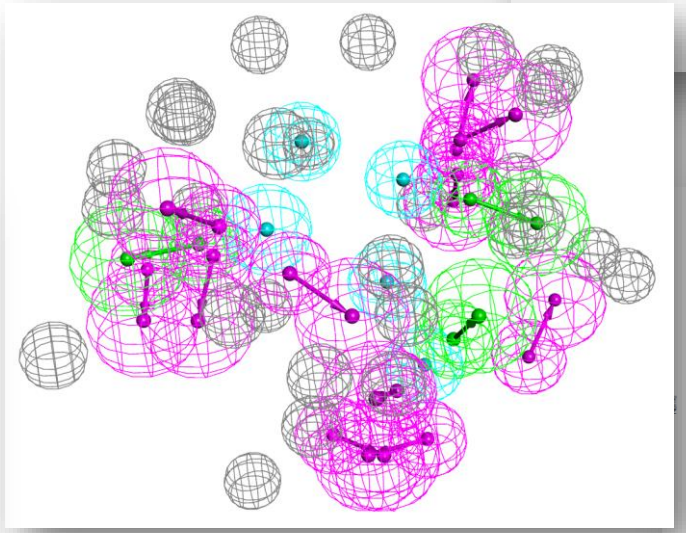
Small Molecule and Biologics Lead Identification & Optimization

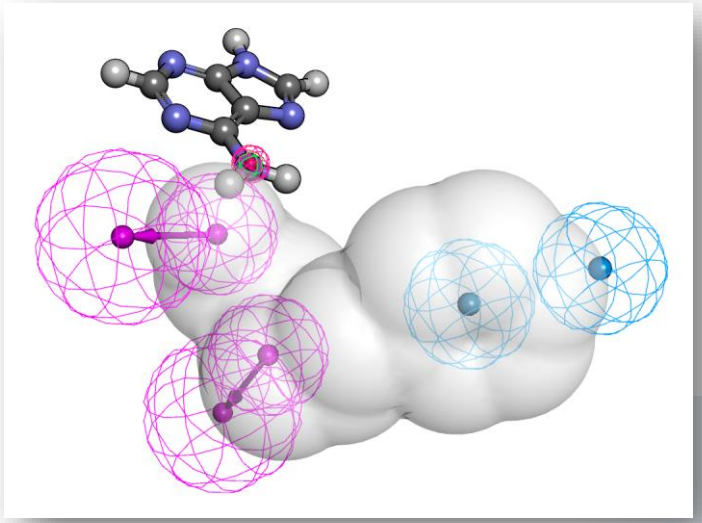
Structure-Based Pharmacophores

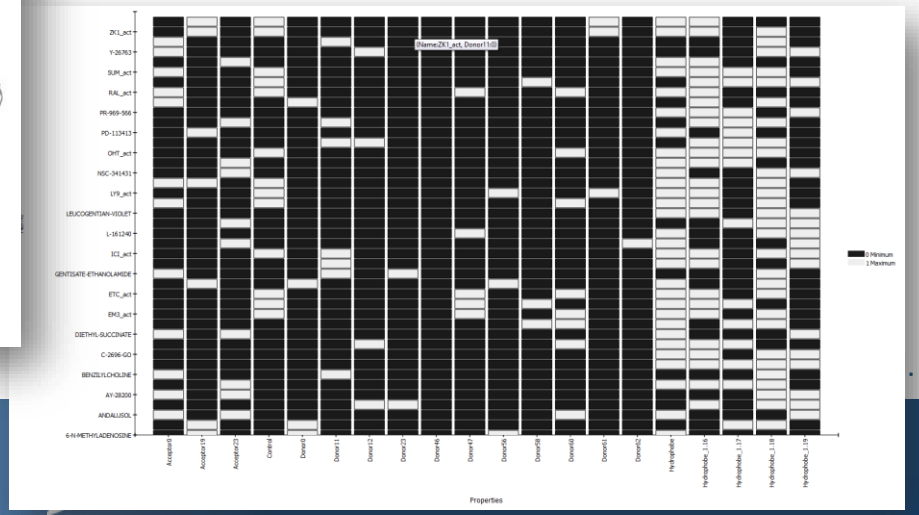
- Automatic
  - Receptor-Ligand complex
  - Interactions from a binding site
- Manual
  - Interaction map
  - Fragment-based





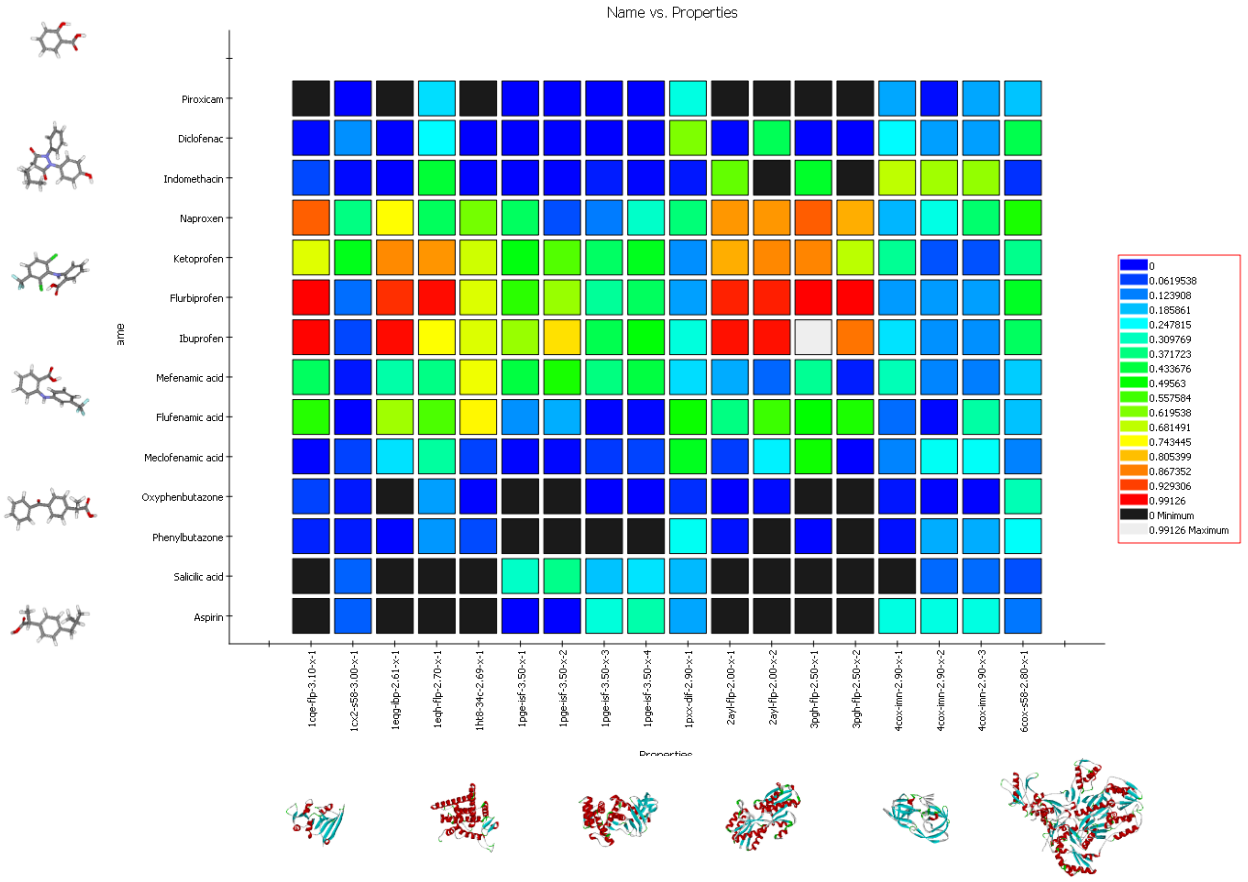






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透過電腦模擬計算，篩選科學成份作用標靶



Pharmacophore ID	Fit value	Gene Name	KEGG ID	Target class	Class	Function
3hcn	0.93	HEMH_HUMAN	K01772	Enzymes	Lyases	Sole sub-subclass for lyases that do not belong in the other subclasses
2xxz	0.91	KDM6B_HUMAN	K11448	Enzymes	Oxidoreductases	Acting on paired donors, with O_2 as oxidant and incorporation or reduction of oxygen.
3d9z	0.87	CAH2_HUMAN	K01672	Enzymes	Lyases	Carbonate dehydratase
1uu3	0.85	PDPK1_HUMAN	K06276	Enzymes	Transferases	Protein-serine-threonine kinases
2w0x	0.84	HIF1N_HUMAN	K00476	Enzymes	Oxidoreductases	Acting on paired donors, with O_2 as oxidant and incorporation or reduction of oxygen. The oxygen incorporated need
1w0h	0.83	ERI1_HUMAN	not found	Others	Others	Others
3iai	0.82	CAH9_HUMAN	K01672	Enzymes	Lyases	Carbonate dehydratase
2ivs	0.81	RET_HUMAN	K05126	Cytokine receptors	Receptor tyrosine kinase	RTK class XIV (RET receptor family)
2va6	0.81	BACE1_HUMAN	K04521	Enzymes	Hydrolases	Acting on peptide bonds (peptidases)
2w4o	0.80	KCC4_HUMAN	K05869	Enzymes	Transferases	Ca^{2+}-calmodulin-dependent protein kinase
2xht	0.80	HS90A_HUMAN	K04079	Proteasome	Eukaryotic proteasome	HSP90A; molecular chaperone ; Assembling factors
3csj	0.79	GSTP1_HUMAN	K00799	Enzymes	Transferases	Glutathione transferase ; Transferring alkyl or aryl groups, other than methyl groups

標靶篩選

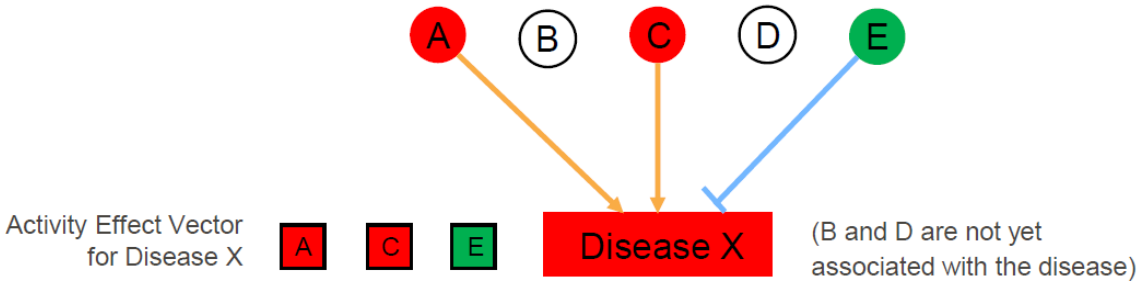
① 24小時內完成40個科學成份 vs 17000多個人體與COVID19蛋白質標的配對

② 共挑選出200個可能的潛在作用蛋白質

Enhancing the KB through Machine Learning

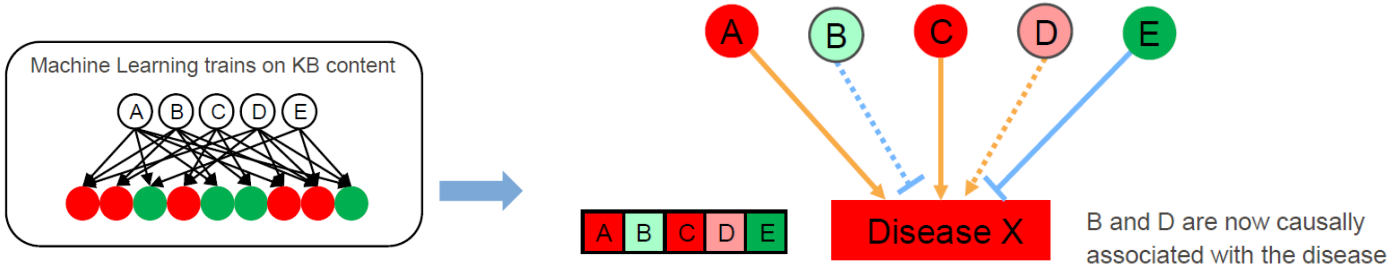
Standard KB

- Relationships between Disease X and neighboring genes can be described as an Activity Effect Vector built only from KB findings.



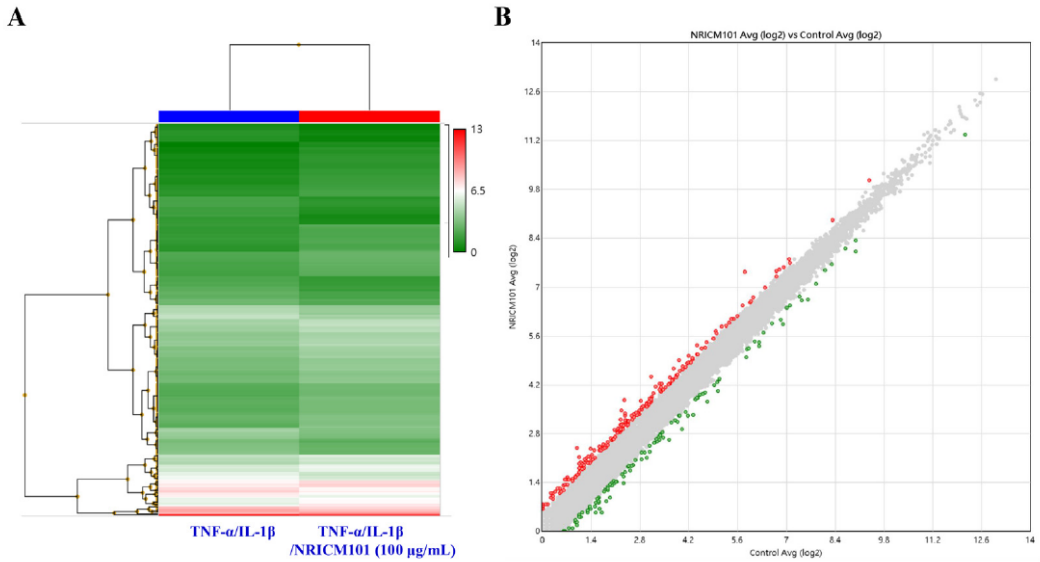
Enhanced KB

- Machine Learning builds richer Activity Effect Vectors by identifying molecules that have similar activity effects. Such vectors enable the inference of new associations and prioritization of relationships.
- In short, if two genes regulate the expression of a similar set of genes, but only one is associated with the disease, then the other likely has a similar biological impact as well.

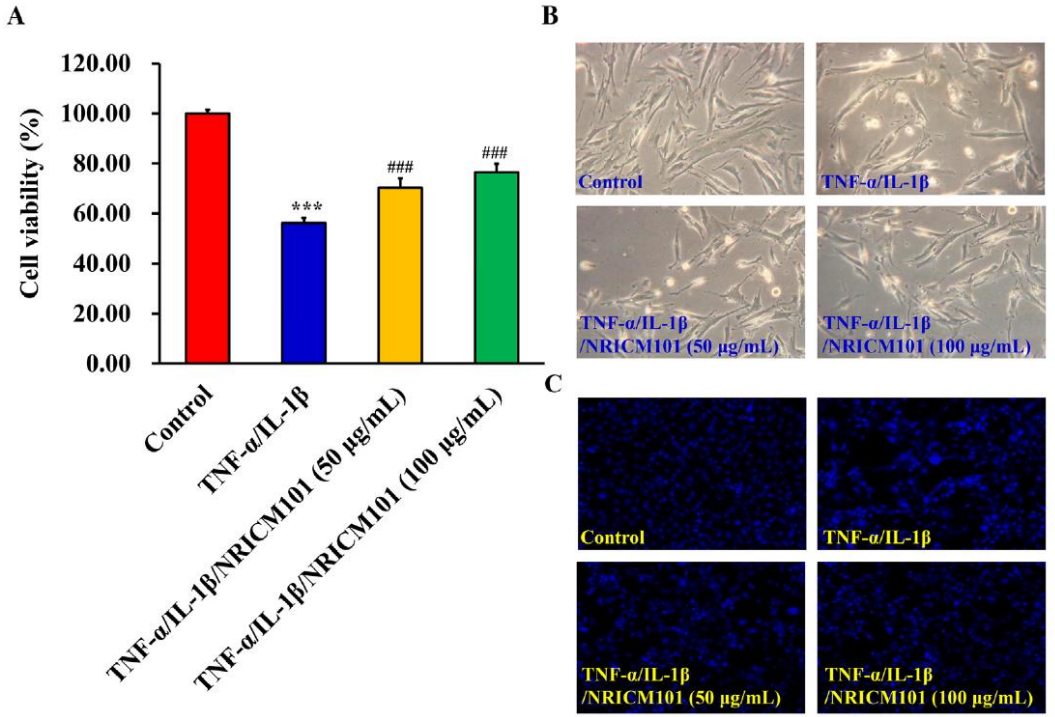


Activity Effect Vectors consist of thousands of molecules in the KB. The approach has been validated by “rediscovering” known, curated findings in the KB.

搭配NGS RNA-Sequencing技術，整合基因體表現資訊



Comparison	Up-regulation	Down-regulation
NRICM101 vs TNF-α/IL-1β	213	118

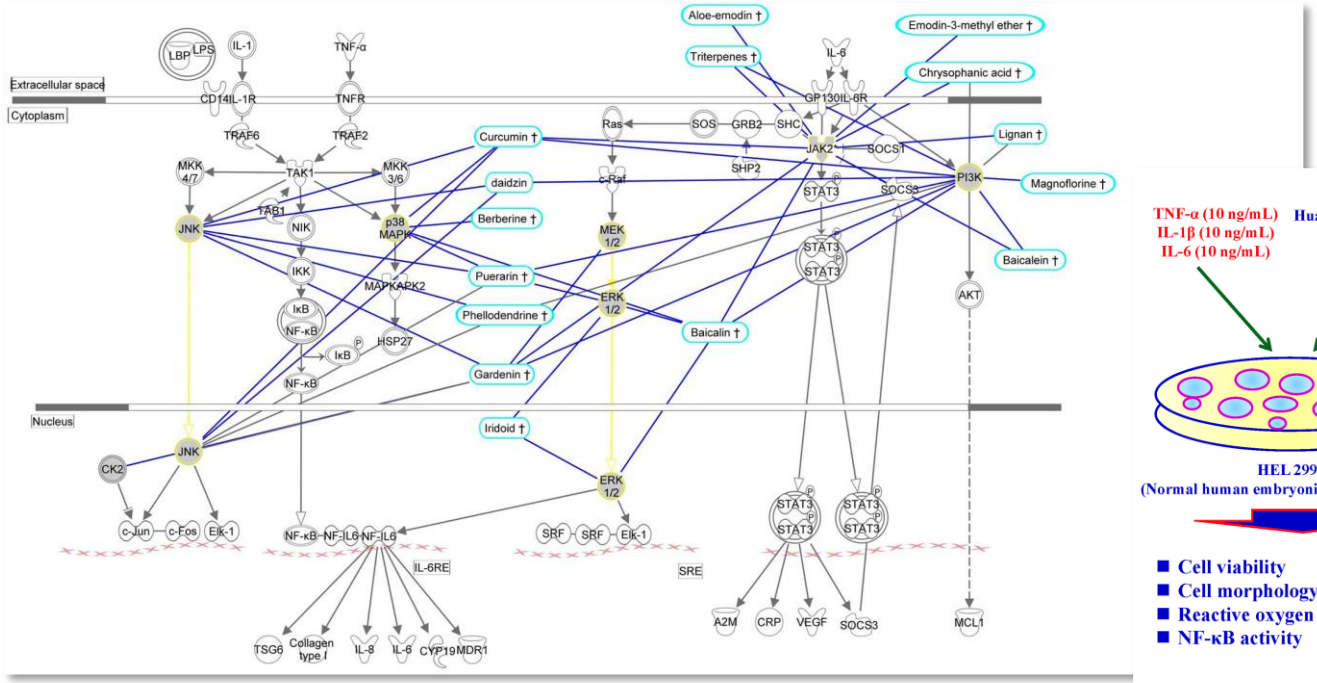


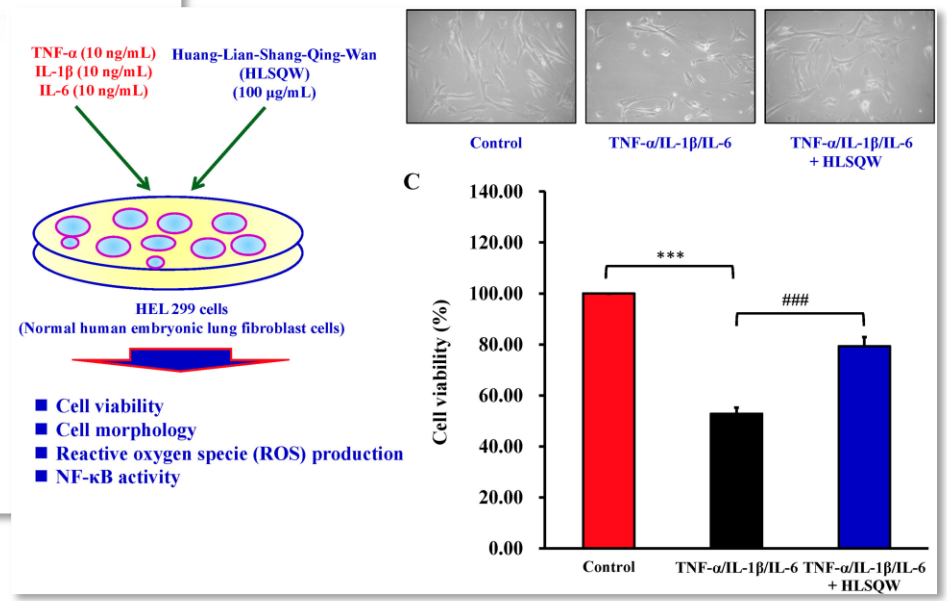
標靶篩選

① 利用QIAGEN IPA從RNA-Seq結果中找出TNF-α為上游調控因子

② 細胞實驗證實清冠一號可透過調控TNF-α/IL-1β增加細胞存活率

建構多體學作用機制，作為治療策略參考





機制確認

① 8小時內找出多個科學成份可抑制IL-6引發的Cytokine Storm

② 於IL-6 induced細胞實驗中證實這些科學成份能有效降低發炎反應，提升細胞存活率

Agenda

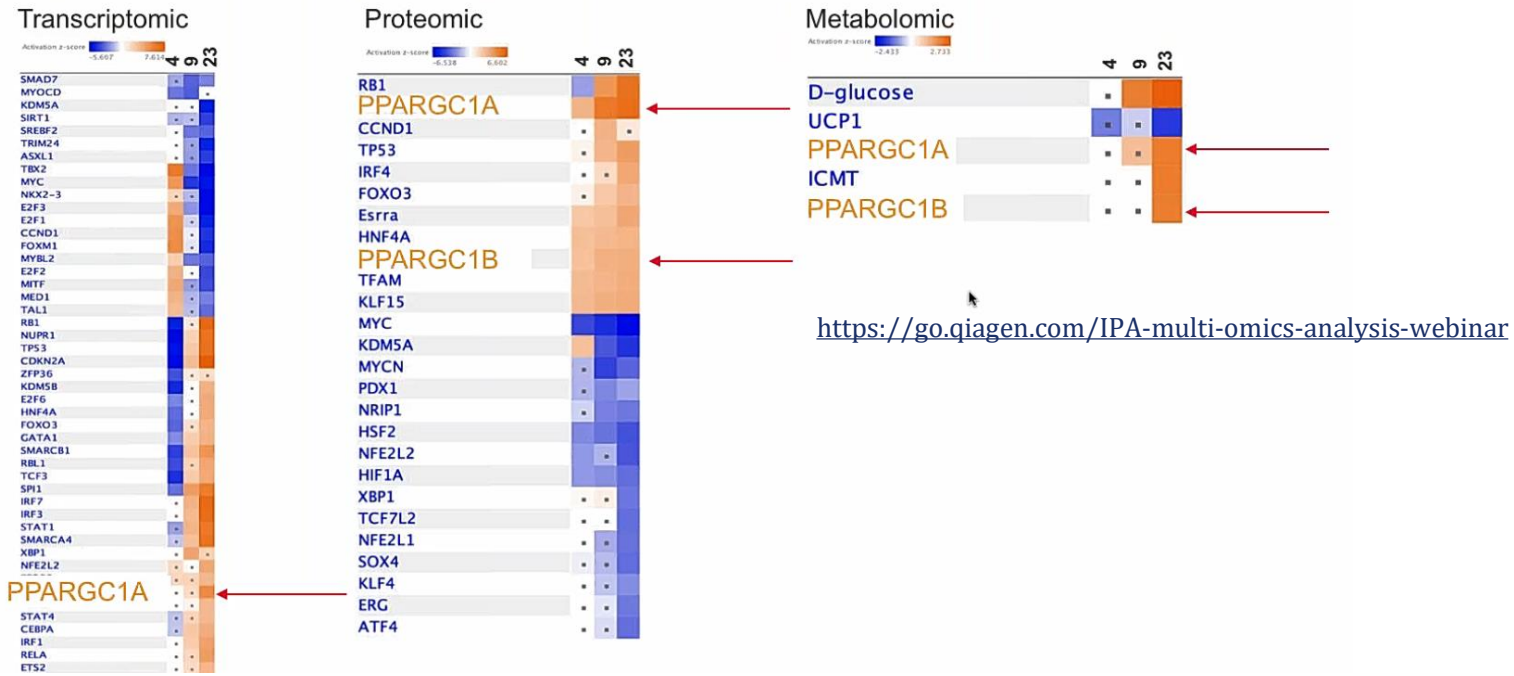
- What’s new 2023 IPA Spring/Summer Release介紹
- 疾病與樣本 Metadata 整合分析
- 藥物潛在標的預測 IPA 與第三方軟體整合運用
- 你所不知道的 IPA 製圖技巧 外泌體研究案例分享

Integrate and compare genomics, transcriptomics, proteomics and metabolomics data to see the big picture on your focus research

Transcriptomics, proteomics and metabolic changes in the postnatal mouse heart identified by QIAGEN IPA and OmicSoft

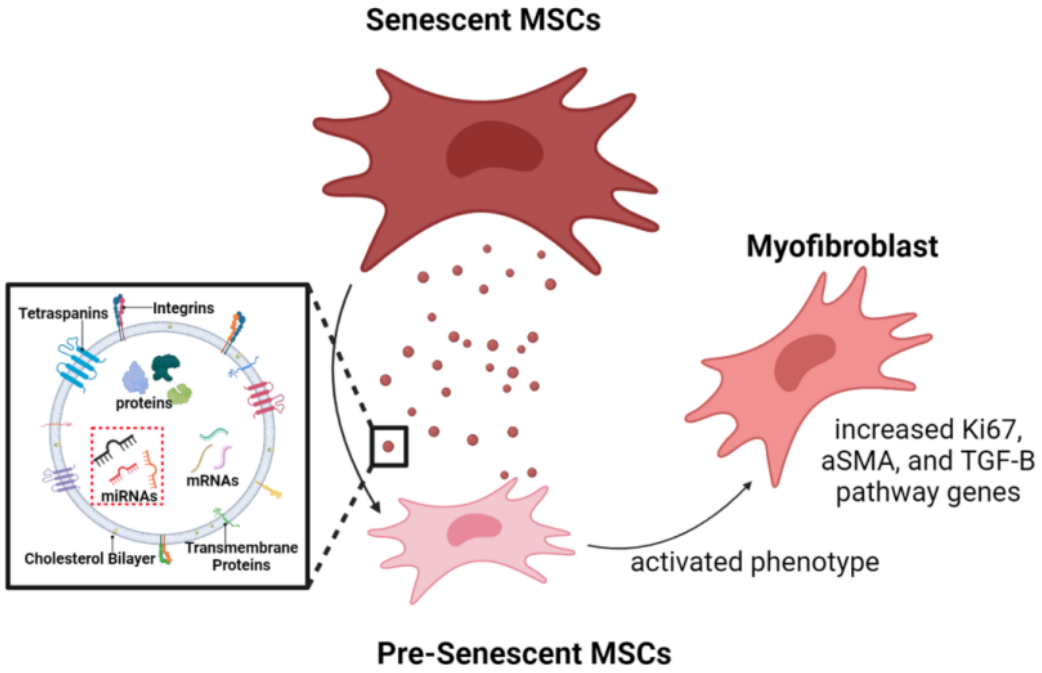
Multi-omics analysis indicate similar transcriptional drivers

Upstream Analysis of transcriptomic, proteomic, and metabolomic data show induction of fatty oxidation regulation by PPARG coactivators.



https://go.qiagen.com/IPA-multi-omics-analysis-webinar

Senescence-associated exosomes transfer miRNA-induced fibrosis to neighboring cells. *AGING*, 2023, Vol. 15, No. 5

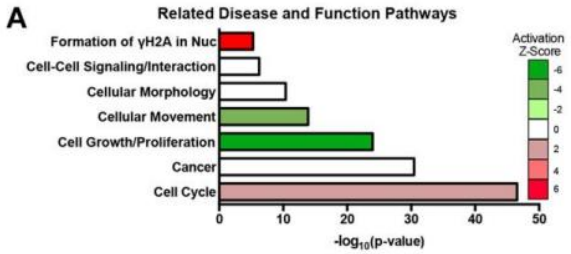


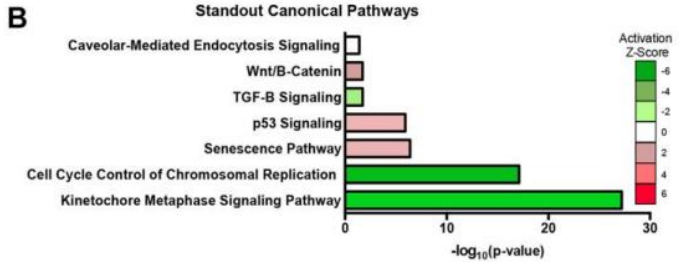
- Senescent MSCs如何影響周遭細胞?
- 主要關鍵成分是什麼?

放射療法導致間質幹細胞衰老，其所分泌出來的Exosome，會激活周遭的間質幹細胞，促使分化成肌纖維母細胞。

Senescent MSC
gamma-irradiation

Pre-senescent MSC
Control





D Cell Adhesion & Focal Adhesion

Sen/Pre-Sen			Sen	Pre-Sen	Gene Sym
Fold	p-value	FDR			
-3.5	4.09E-05	4%	11.52	15.02	TNC
-1.7	2.00E-04	9%	5.42	7.14	HLA-DPB1
-1.3	3.00E-04	10%	5.14	6.4	ITGB3
-1.2	1.40E-03	19%	4.65	5.89	CDH4
-1	1.20E-03	18%	13.59	14.62	PDGFRB
1.09	7.00E-04	15%	11.13	10.04	JAM3
1.17	1.10E-03	17%	17.68	16.51	LAMC1
1.39	2.10E-03	23%	11.85	10.46	NFASC
1.45	2.00E-04	8%	17.65	16.2	CCND1
3.48	4.53E-06	2%	14.85	11.37	LAMC2

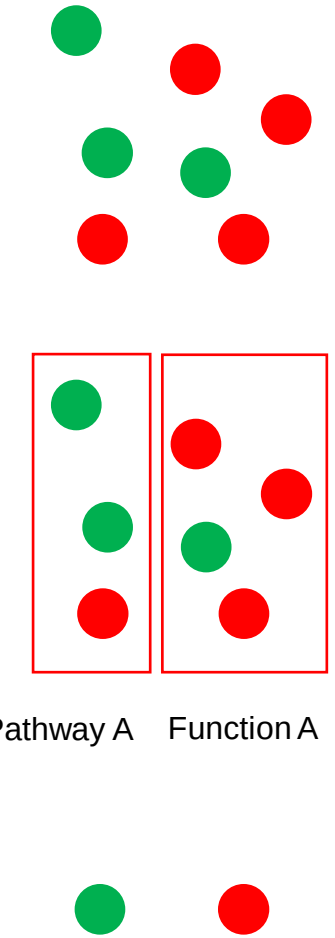
E TGFβ

Sen/Pre-Sen			Sen	Pre-Sen	Gene Sym
Fold	p-value	FDR			
-1.8	3.00E-04	9%	7.95	9.78	RBL1
-1.4	1.50E-03	20%	10.2	11.55	E2F4
-1.1	2.40E-03	24%	11.17	12.29	TFDP1
-1	9.00E-04	16%	12.29	13.33	SP1
1.19	2.30E-03	24%	15.8	14.61	SMURF2

Expression data from Transcriptome Analysis

Find related Function/Phenotypes by pathway analysis

Allocate specific gene in related pathway/function



與Cell cycle, TGF-β, and vesicle-mediated pathways高度相關

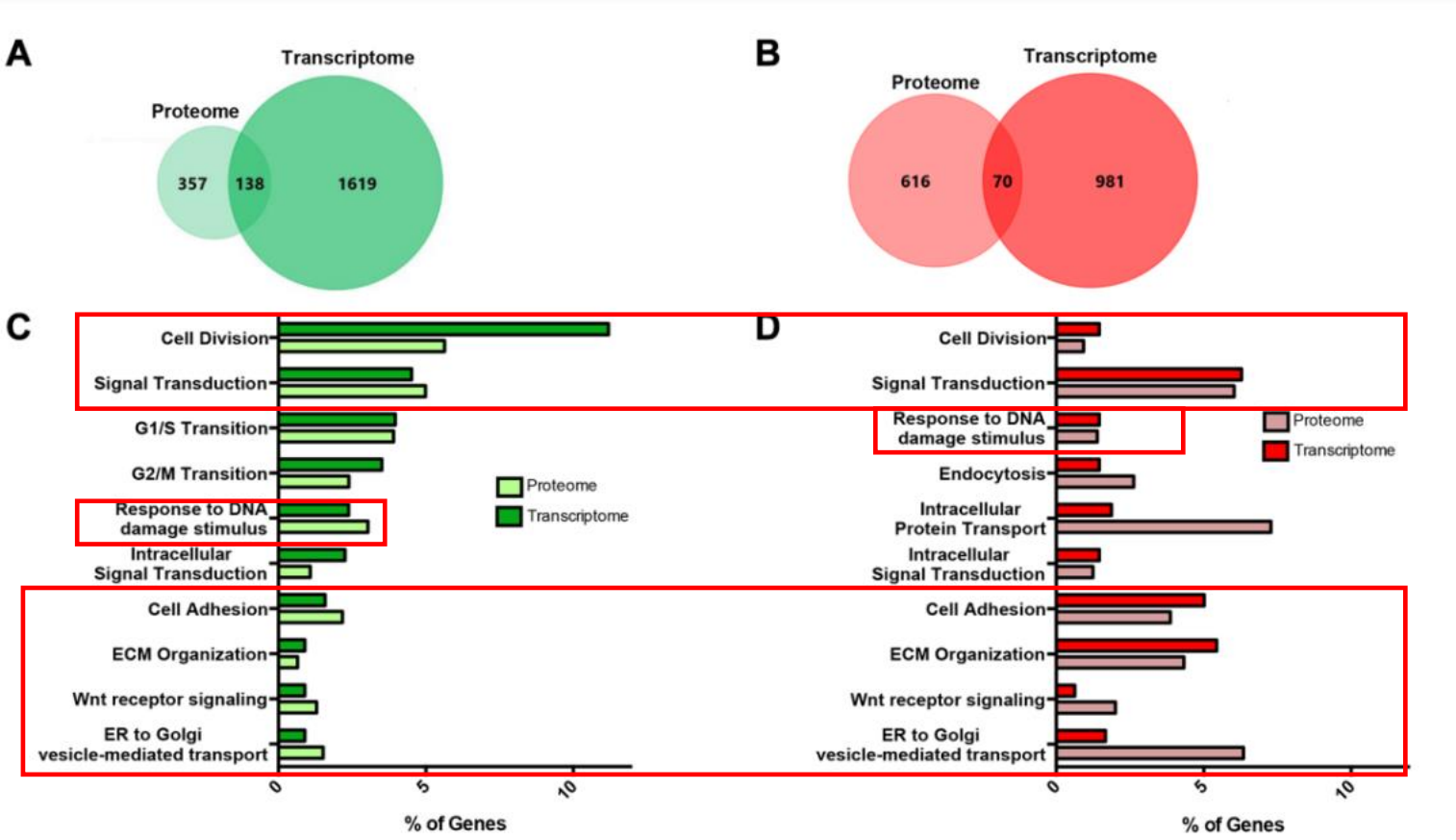
Senescent MSC
gamma-irradiation

Pre-senescent MSC
Control

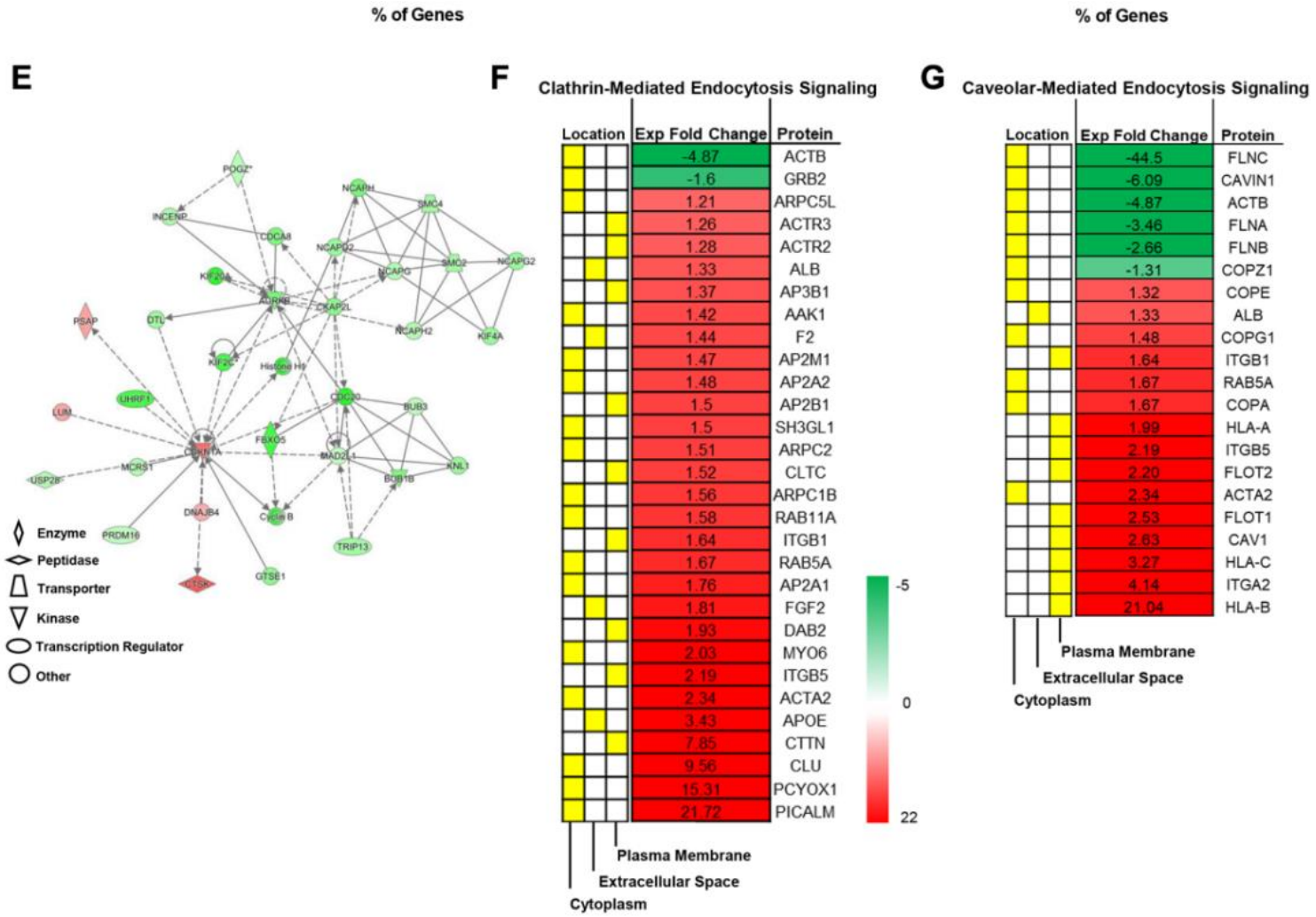
Transcriptome Expression Data

+

Proteomic Expression Data



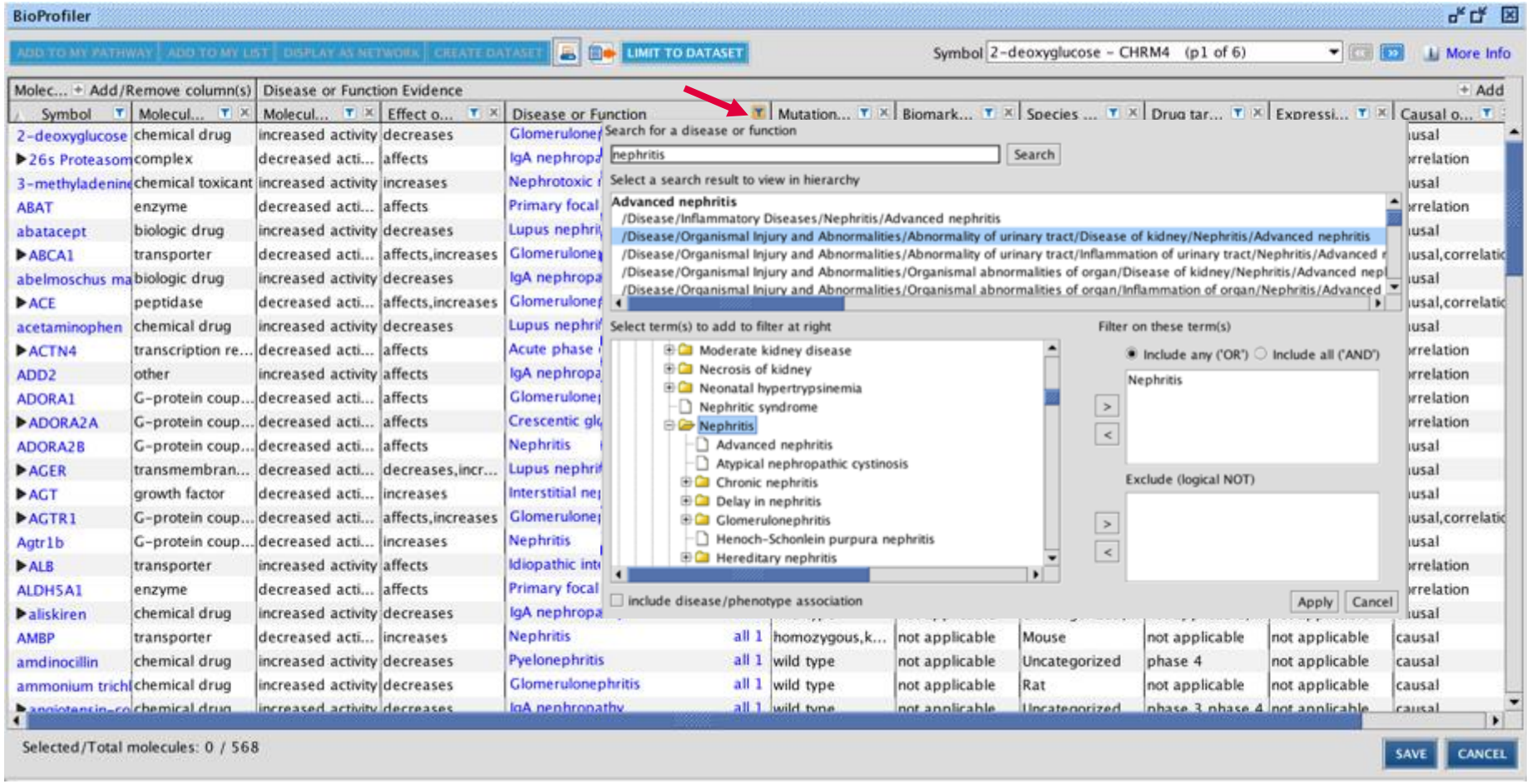
- 蛋白質體與轉錄體的分析結果有高度重疊，基因表現與Cell Division、DNA damage、Adhesion等功能高度相關



- 以endocytic processes為例，包含clathrin以及caveolin，分別有不同程度的蛋白質會在細胞質、細胞膜以及細胞外互相作用。

BioProfiler can be used to explore hypotheses

All molecules (genes, drugs, etc.) known to connect to nephritis



Note how the Ingenuity Ontology is used to gather all nephritis subtypes

BioProfiler: Examples

Targets of toxicity:

- Which genes when [decreased] in activity [increase] [liver cholestasis]? What types of [genetic] evidence support this?

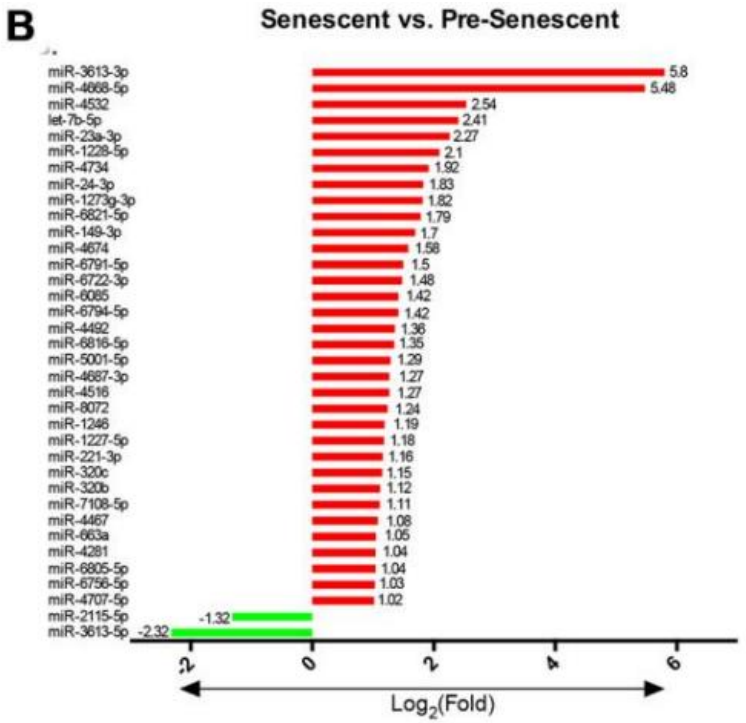
Target discovery:

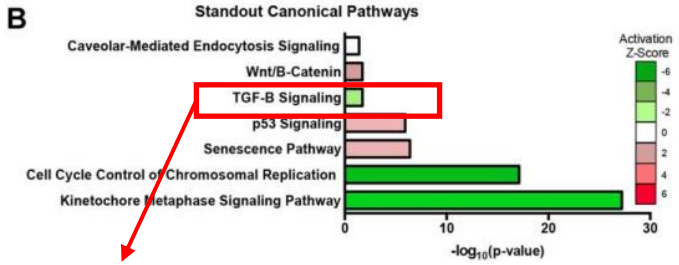
- What [heterozygous knockouts] in [mouse] can [decrease] [asthma]?
- Which drugs or which targets have been in late stage clinical trials or approved to decrease [diabetes]?

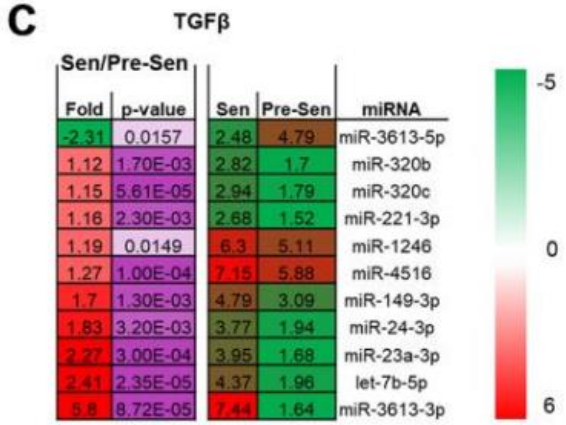
Biomarker research:

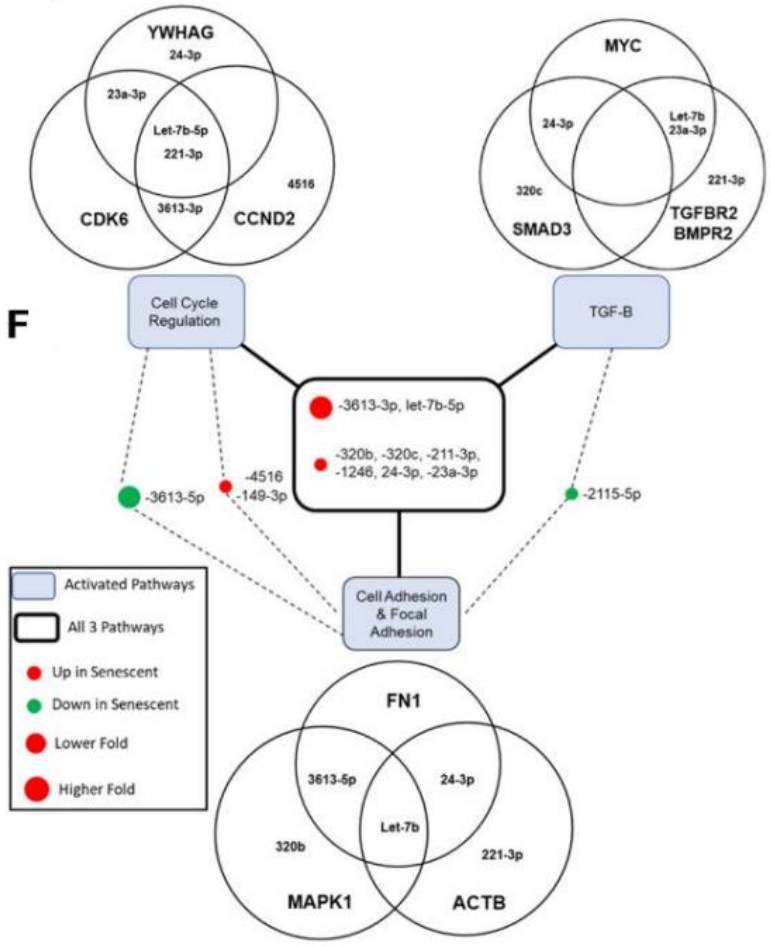
- Which genes are potential [diagnosis OR prognosis] biomarkers of [breast cancer] and are [upregulated] in breast cancer?

研究衰老的間質幹細胞如何透過外泌體中的miRNA影響周圍的細胞

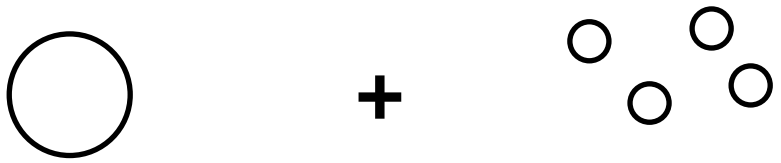






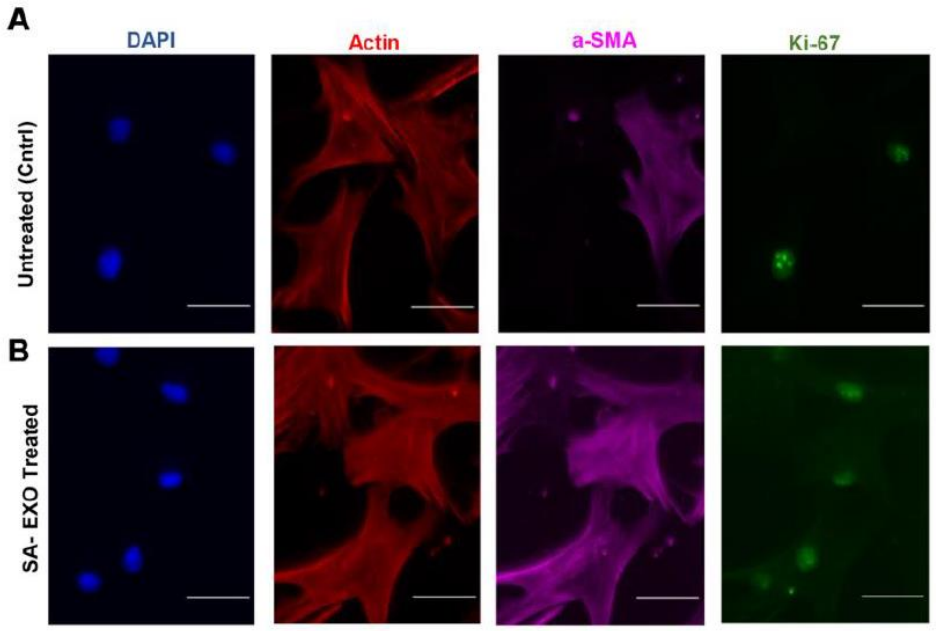


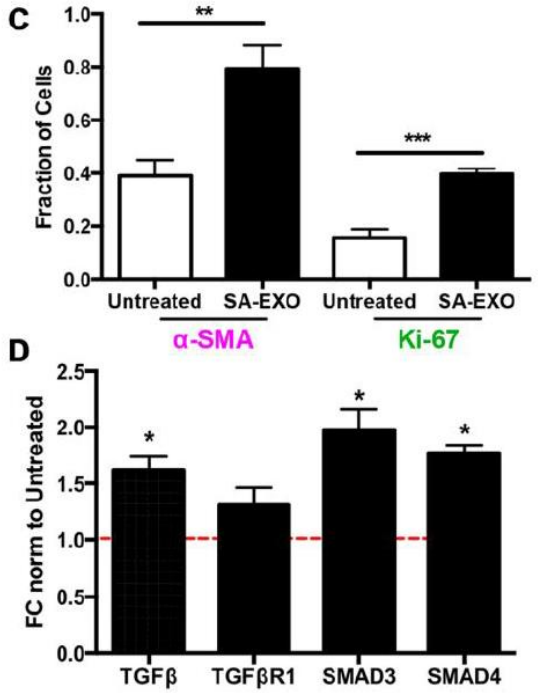
- 多個外泌體中的miRNA會影響TGF-β、Cell Cycle Regulation、Cell Adhesion中的關鍵基因表現



Pre-senescent MSCs

Senescent EXO



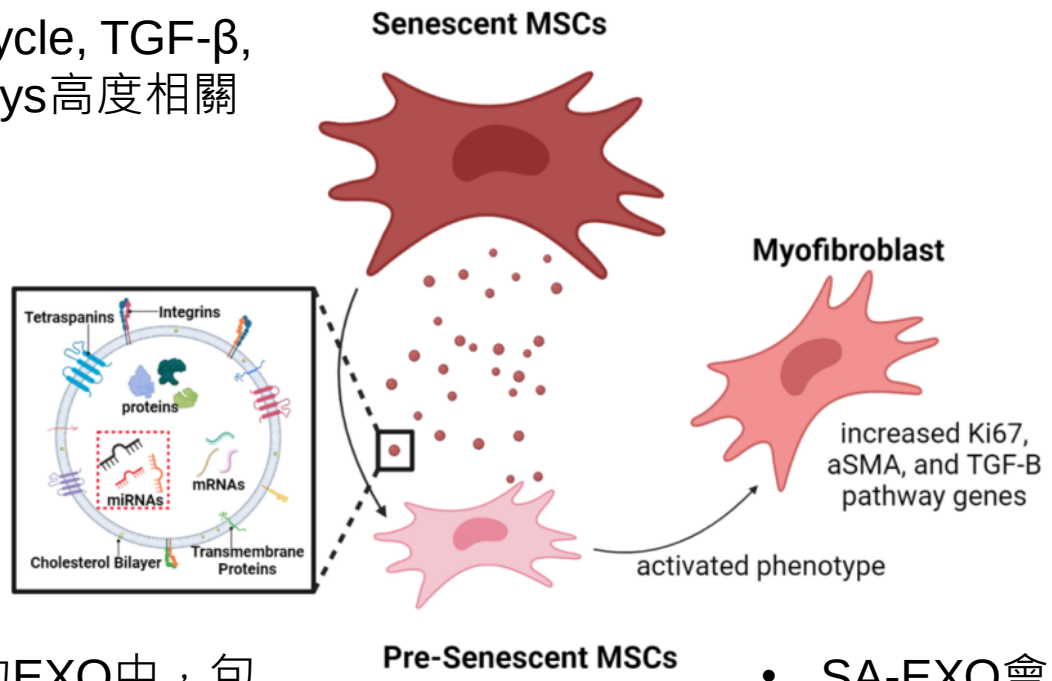


- EXO提升了a-SMA、Ki-67、TGF-β、SMAD3等基因表現

- 從轉錄體與蛋白質體分析發現，Senescent MSC本身的基因表現與Cell cycle, TGF-β, and vesicle-mediated pathways高度相關

◆ 針對Sen MSC進行抑制(例如TGF-β 抑制劑SB505)，阻斷相關Pathway傳遞，進而影響分泌出的EXO成分。

◆ 利用特定載體細胞表達EXO，包覆可拮抗原有miRNA的成分比例，進而阻斷對於Pre-Sen MSCs的影響能力。



- 在Senescent MSC分泌出來的EXO中，包含了多種會影響TGF-β、Cell Cycle Regulation、Cell Adhesion的miRNA

- SA-EXO會影響Pre-Sen MSCs多個基因表現，導致細胞分化成Myofibroblast

	IPA	Metacore	KEGG	Note
資料檢索				
基因、蛋白質	O	O	O	
藥物、毒物、代謝物	O	O	O	
疾病與生物功能	O	O	O	
Pathway	O	O	O	
miRNA	O	O	O	
調控作用關係	O	O	O	
Isoform	O	X	X	
Single Cell DB	O	X	X	
Patient Metadata	O	X	X	
Clinical data	O	X	X	
繪製Pathway功能				
互動式Pathway繪製工具	O	O	X(僅提供Mapping)	
Pattern Mapping	O	X	X	根據產生出來的Network以及實驗表現結果，搜尋資料庫疾病、Pathway是否有類似的表現趨勢以及路徑。
Path Tracer	O	X	X	在龐大的訊息路徑中，特別標示感興趣的訊息因子。
表現預測功能	O	O	X	根據實驗結果，預測上下游調控因子表現。

	IPA	Metacore	KEGG	Note
Enrichment Analysis				
基因體、蛋白質體表現分析	O	O	O	
代謝體	O	O	O	
毒物分析	O	O	O	
Enrichment Analysis結果視覺化表現	O	X	X	將各項Enrichment結果以不同的視覺化分析圖表呈現。
Enrichment Analysis Expression Pattern比較	O	X	X	將本次Enrichment結果與其他疾病、實驗的Dataset進行相似性比較。
因果網路分析	O	X	X	將Enrichment結果與感興趣的生物分子或者疾病、生物功能產生關連。
疾病熱圖	O	X	X	以Ontology分類，依據Enrichment分析p-value進行熱圖繪製，可找出較相關的生物功能以及疾病。
網絡關聯圖	O	X	X	將各項Enrichment結果依照重疊的訊息傳遞因子數量進行關聯統計。
泡泡圖分析	O	X	X	以泡泡圖進行三維分析數據結果解讀。可依照生物功能、疾病或者訊息路徑比對關聯性。
比較結果熱圖	O	X	X	以熱圖表示不同Enrichment結果差異，可用做Time or dosage – dependent的實驗比較。

IPA與市售系統生物學分析工具比較

	IPA	Metacore	KEGG	Note
其他功能				
生物特性篩選	O	X	X	Bioprofiler，可篩選出具有相同生物特性的訊息傳遞因子。
Isoform篩選	O	X	X	Isoprofiler，可鑑別出同基因不同Isoform的生物表現結果。
基因於組織差異表現分析	O	X	X	GTEx Expression Pattern，用作於比較相同基因在不同組織的差異分析。
miRNA調控目標預測分析	O	X	X	miRNA Target filter，可進行miRNA與mRNA配對，進而比較出miRNA的作用方式。
磷酸化蛋白質體分析	O	X	X	用於確認不同位點的磷酸化蛋白質功能。
AI預測訊息路徑	O	O (僅有Drug)	X	透過機器學習方式，搜尋相似表現路徑的訊息傳遞因子，連結其相關影響疾病和生物功能。



Better Care with Better Knowledge

Questions?
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