



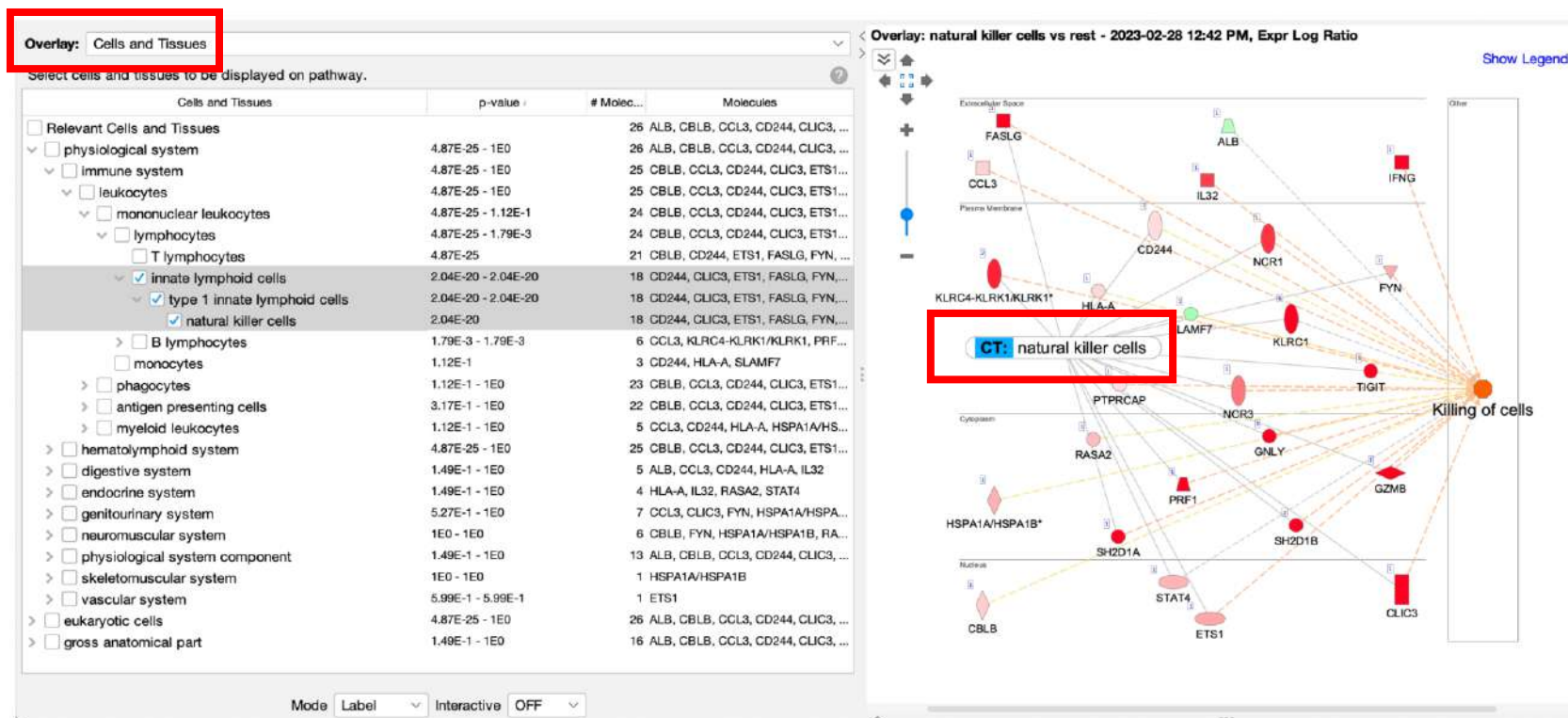
IPA 2023 Spring/Summer Release and Case Study

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Senior Manager, IPA certificated analyst

- 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

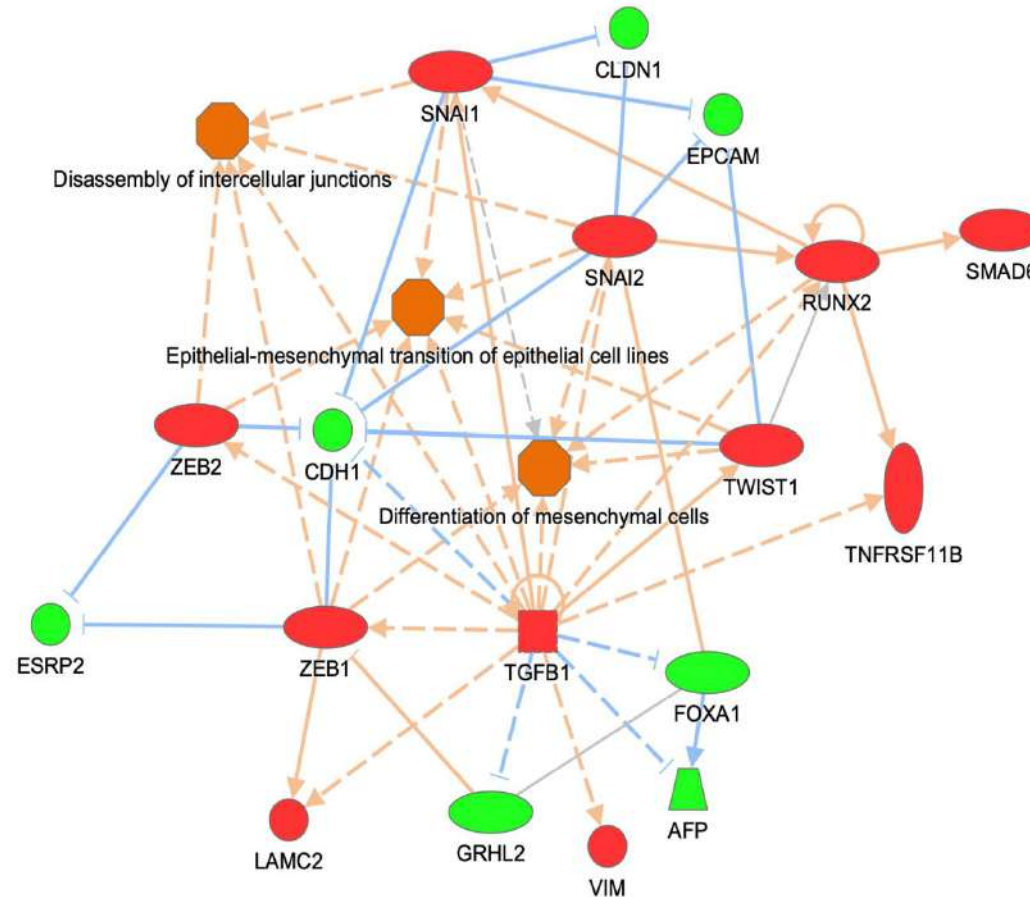
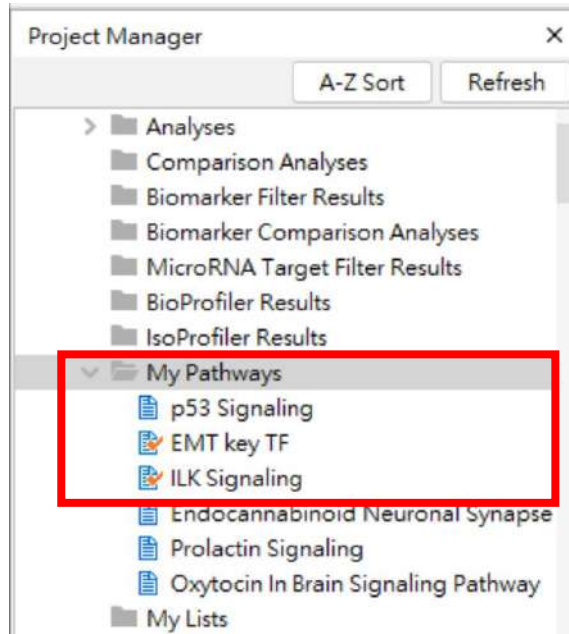
Identify potential cell types based on the set of genes on networks and pathways

Overlay :Cell and Tissues **THE HUMAN PROTEIN ATLAS**



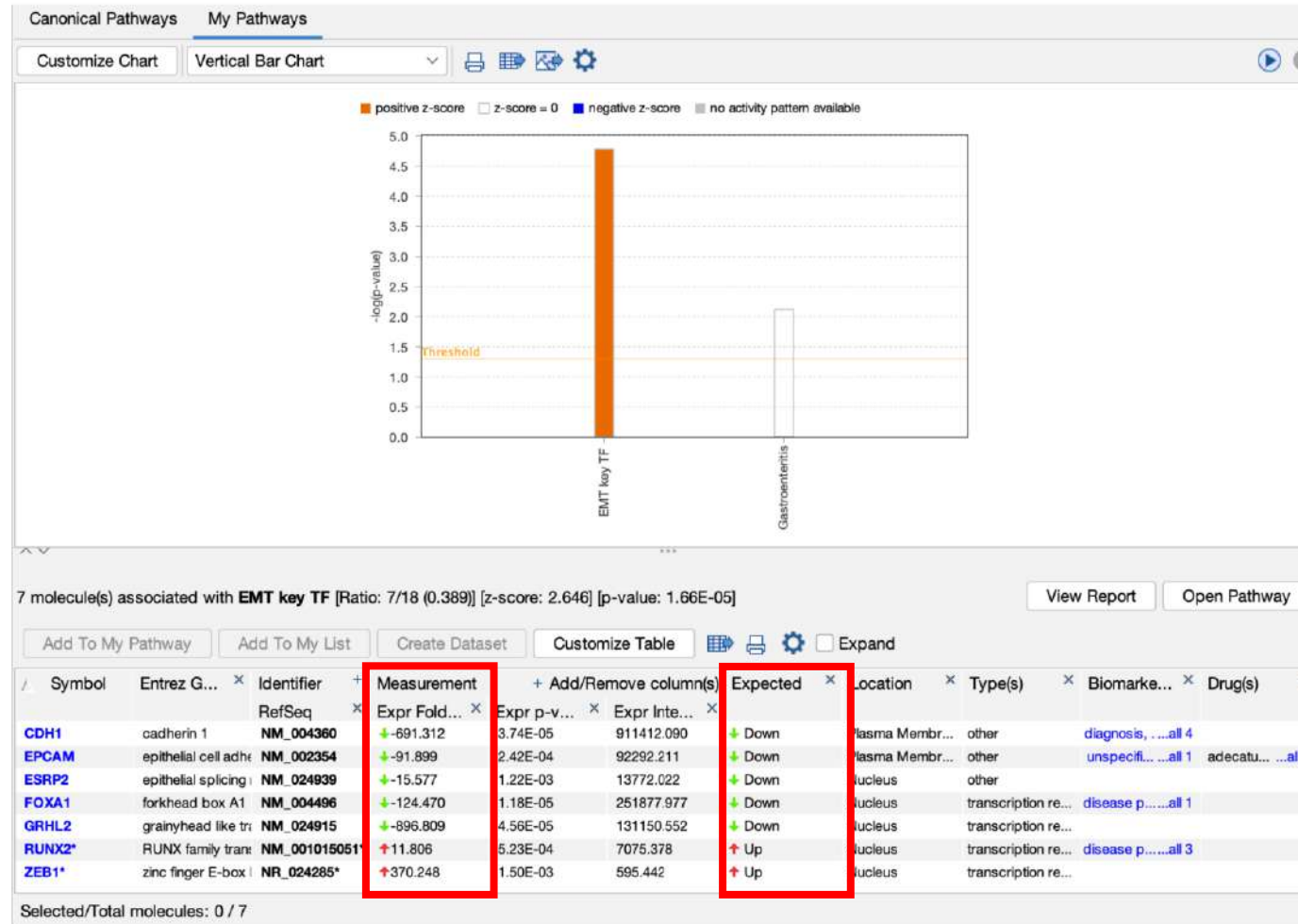
Enrichment of natural killer enriched genes on a network.

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



Causally scoring a My Pathway.

Set the “User Dataset” as the reference set when uploading a dataset

1. Select File Format: Flexible Format

2. Contains Column Header: ☒ Yes ☐ No

3. Select Identifier Type: Please assign at least one column below as “ID”, and assign additional columns as ID to improve mapping coverage.

4. Array platform used for experiments: Not specified/applicable Select relevant array

5. Use the dropdown menus to specify the reference set for each column.

Raw Data (18589) Dataset Summary

Edit Observation Names Infer C

ID/Observation Name	ID	Measurement/Annotation	Ensembl	P-value	Bonferroni	FDR p-value
1	ID					
2	ENSMUSG000000051...			0.8708015979022331	1.0	0.9077575903
3	ENSMUSG000000025...			4.504633100231221...	8.57456910629013E...	4.4210170566
4	ENSMUSG000000033...			6.221800613621819...	1.184319746802913...	7.3009378079
5	ENSMUSG000000025...			1.682341354813838...	3.202336768888141...	1.4496821829

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

Discover more precise matches in Analysis Match

Summary Graphical Summary Pathways Upstream Analysis Diseases & Functions Regulator Effects Networks Lists Analysis Match Molecules									
Evaluate Metadata View As Heatmap View Comparison Customize Table				z-sc... 54.42 - 33.52 (1/539)					
Analysis ...	Pro...	case...	case.t...	compar...	comparisoncontrast				
86- NA [heart] NA	MouseDise...	NA	heart	CellType1 vs. Ce...	CellDescription => heart epithelial cell vs cecum epithelial cell	67.94	50.99	45.83	52.92
828- normal contr	MouseDise...	normal control	fetal heart	Other Compariso...	ExperimentGroup => fetal heart E11.5 vs fetal brain E11.5	62.02	56.57	46.90	50.99
11- normal contro	HumanDise...	normal control	skin	CellType1 vs. Ce...	CellType => iPSC-derived cardiomyocyte vs induced pluripotent stem cell (iPSC)	55.47	61.64	44.72	44.72
4- psoriasis [skin]	HumanDise...	psoriasis	skin	Tissue1 vs. Tissu...	TissueRegion => back vs arm	55.47	52.92	33.17	56.57
150- normal contr	RatDisease	normal control	heart	Tissue1 vs. Tissu...	Tissue:Age[weeks] => 21 -> heart vs testis	55.47	45.83	50.00	45.83
30- normal contro	Human Tiss...	normal control	heart atria	Other Compariso...	TissueDetail_GTEx => Heart - Atrial Appendage vs Others	62.02	46.90	37.42	50.00
1856- normal con	MouseDise...	normal control	pancreas	Other Compariso...	Tissue:Age[months] => pancreas -> 27 vs 24	62.02	44.72	42.43	46.90
132- normal contro	RatDisease	normal control	heart	Tissue1 vs. Tissu...	Tissue:Age[weeks] => 104 -> heart vs testis	55.47	41.23	50.00	47.96
13- fibromyxoid s	OncoHuman	fibromyxoid sa...	soft tissue	Disease1 vs. Dis...	ExperimentGroup => fibromyxoid sarcoma vs Castleman disease follicular dend...	73.38	50.99	25.30	40.00
31- normal contro	Human Tiss...	normal control	heart left ventricle	Other Compariso...	TissueDetail_GTEx => Heart - Left Ventricle vs Others	55.47	45.83	37.42	48.99

Summary Graphical Summary Pathways Upstream Analysis Diseases & Functions Regulator Effects Networks Lists Analysis Match Molecules									
Evaluate Metadata View As Heatmap View Comparison Customize Table				DM (... 52.1226215454257... (1/539)					
Analysis ...	Pro...	case...	case.t...	compar...	comparisoncontrast				
3- normal control	MouseDise...	normal control	hindlimb muscle	CellType1 vs. Ce...	SampleDescription => primary myotubes differentiated for 1 day vs embryonic ...	46.90	33.17	30.00	27.52
2- normal control	MouseDise...	normal control	hindlimb muscle	CellType1 vs. Ce...	SampleDescription => primary myoblasts passage zero vs embryonic stem cell	43.59	41.23	40.00	31.21
5- normal control	MouseDise...	normal control	hindlimb muscle	CellType1 vs. Ce...	SampleDescription => primary myotubes differentiated for 4 days vs embryonic...	44.26		30.51	18.69
1- normal control	MouseDise...	normal control	hindlimb muscle	CellType1 vs. Ce...	SampleDescription => primary myoblasts in proliferation passage 8-10 vs embr...	43.59	31.62	38.73	28.49
828- normal contr	MouseDise...	normal control	fetal heart	Other Compariso...	ExperimentGroup => fetal heart E11.5 vs fetal brain E11.5	62.02	56.57	46.90	50.99
6- normal control	MouseDise...	normal control	quadriceps fem...	Other Compariso...	SampleDescription => quadriceps muscle vs embryonic stem cell	28.40		32.07	15.12
4- normal control	MouseDise...	normal control	hindlimb muscle	CellType1 vs. Ce...	SampleDescription => primary myotubes differentiated for 2 days vs embryonic...	55.47	39.62	28.87	30.99
11- normal contro	MouseDise...	normal control	embryo	CellType1 vs. Ce...	CellType => ESC-derived NPC vs embryonic stem cell (ESC)	37.42	31.62	31.62	25.17
843- normal contr	MouseDise...	normal control	fetal heart	Other Compariso...	ExperimentGroup => fetal heart E12.5 vs fetal brain E12.5	55.68	45.83	23.24	31.19
988- normal contr	RatDisease	normal control	fetal heart	Other Compariso...	ExperimentGroup => fetal heart E11 vs fetal brain E11	55.68	38.73	33.00	31.85

Sorted by original overall z-score match

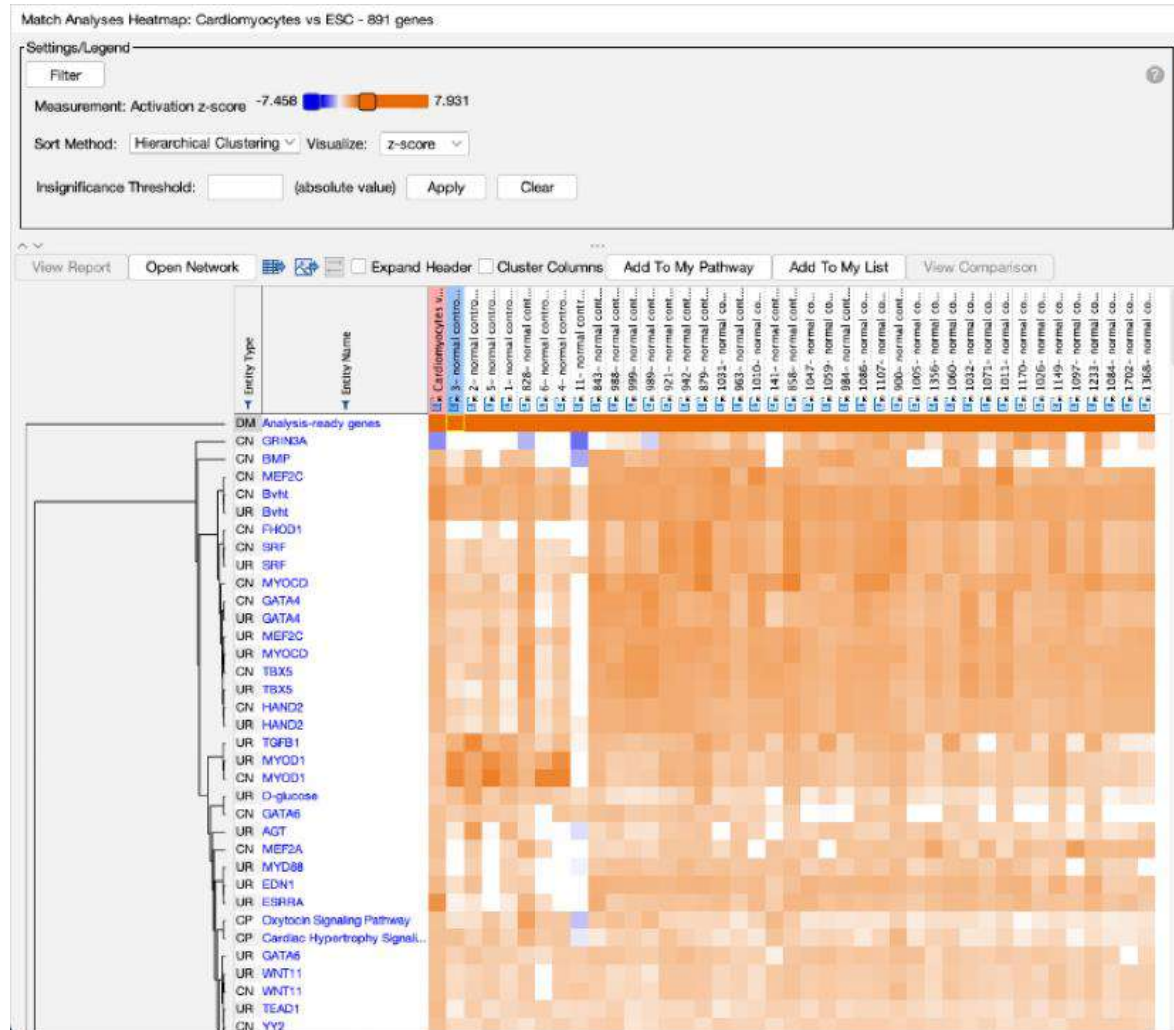
Matches to analyses from many tissue types, such as skin and pancreas

Sorted by new DM "dataset match" column

Results are more strictly heart or muscle cells vs embryonic cells

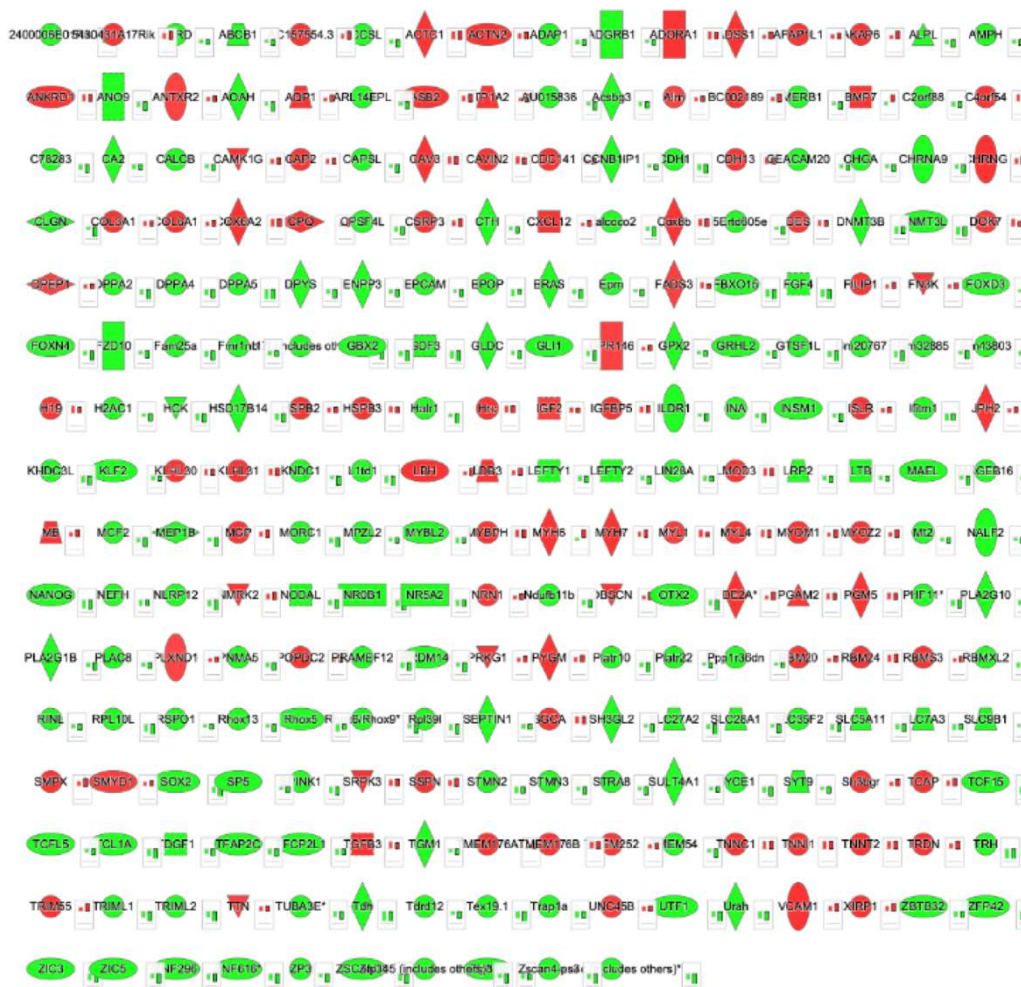
Analysis Match results sorted by the original score (top) and new score (bottom).

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.

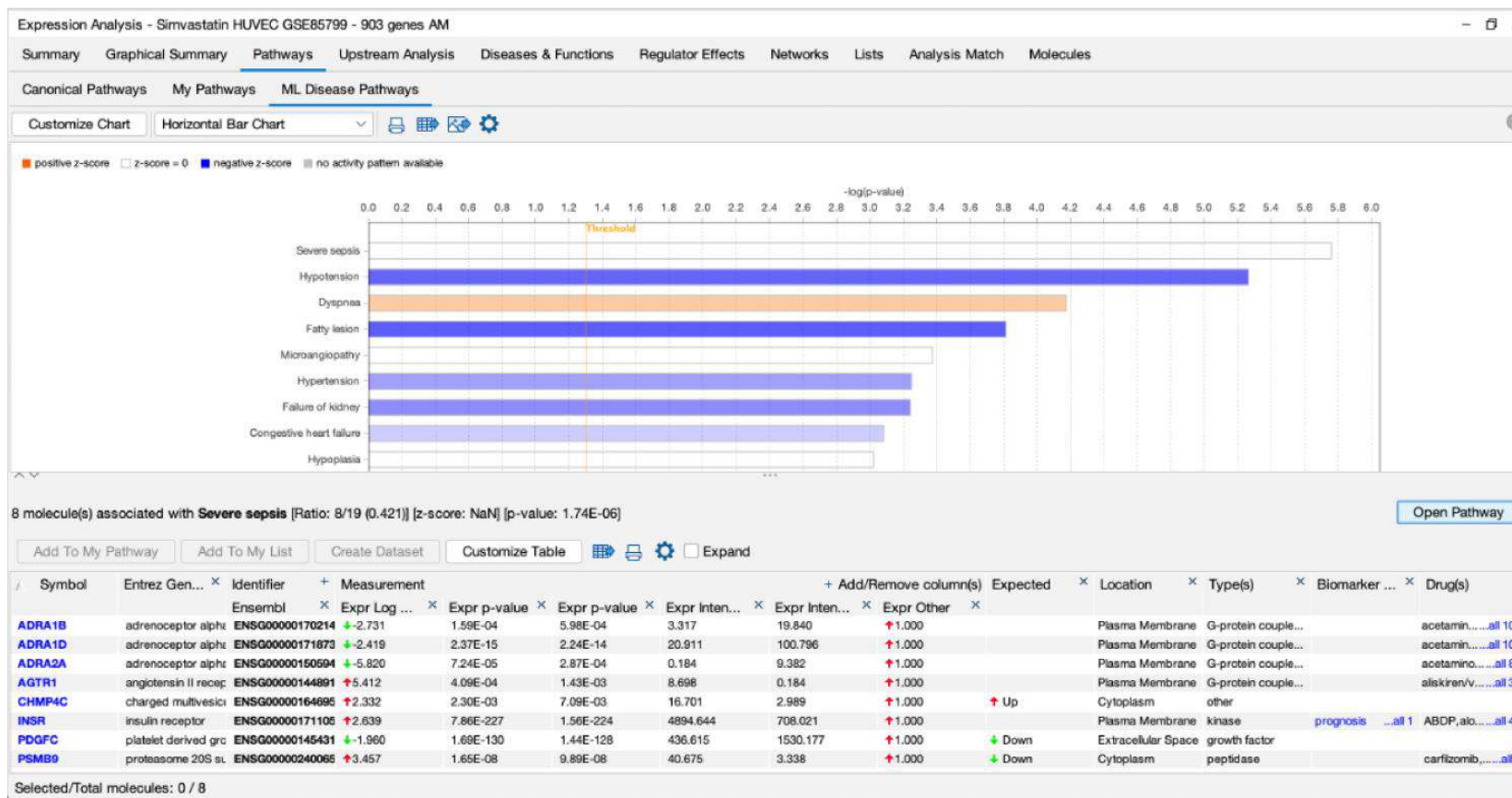
The new scoring method using a small dataset.

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.

Summary Graphical Summary Pathways Upstream Analysis Diseases & Functions Regulator Effects Networks Lists Analysis Match Molecules										
Evaluate Metadata		View As Heatmap		View Comparison		Customize Table		DM (... 89.4427190999915... (1/25) < > >> ?		
Analysis Name	Project	case.dise...	case.tissue	comparis...	comparisoncontrast	C...	U...	C...	D...	z...
5- normal control [hindlimb m...	MouseDisease	normal control	hindlimb muscle	CellType1 vs. CellT...	SampleDescription => primary myotubes differentiated for 4 days vs embr...					89.44
3- normal control [hindlimb m...	MouseDisease	normal control	hindlimb muscle	CellType1 vs. CellT...	SampleDescription => primary myotubes differentiated for 1 day vs embry...					83.67
4- normal control [hindlimb m...	MouseDisease	normal control	hindlimb muscle	CellType1 vs. CellT...	SampleDescription => primary myotubes differentiated for 2 days vs embr...					83.67
2- normal control [hindlimb m...	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 m...	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

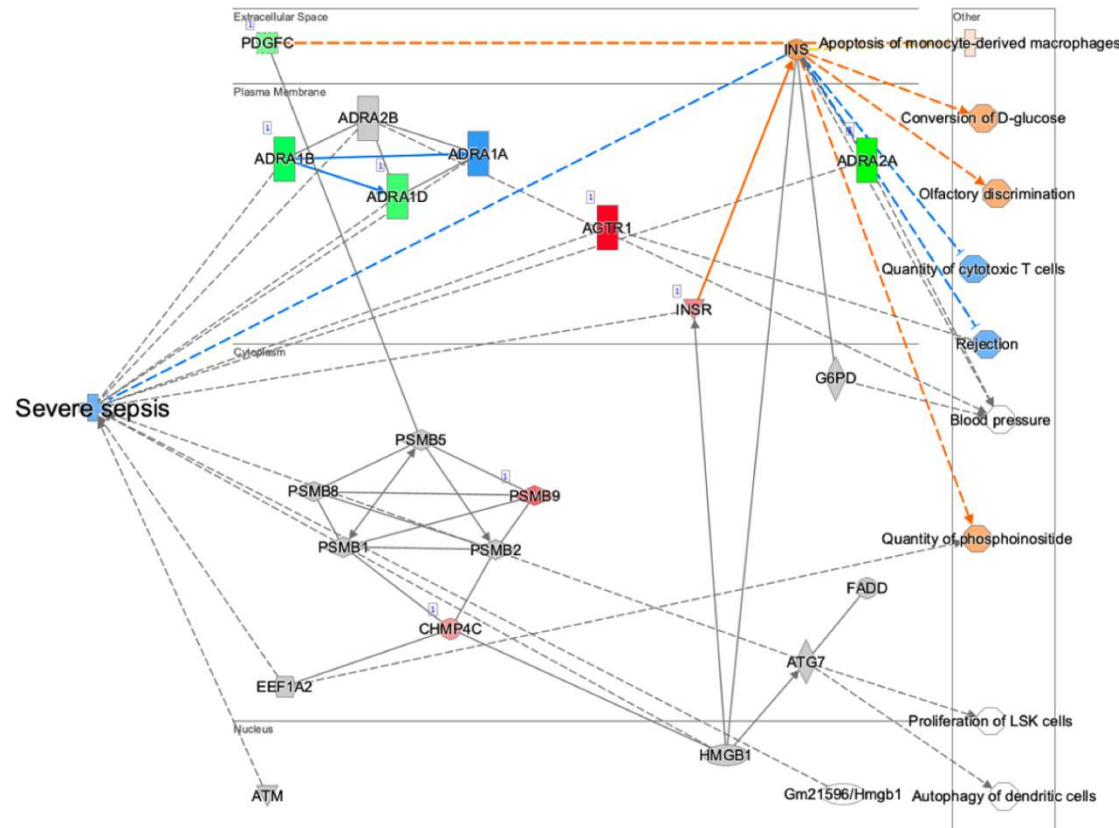
The analysis of a 10-gene dataset from the cardiomyocytes versus embryonic stem cells matches the expected types of analyses.

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.

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

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

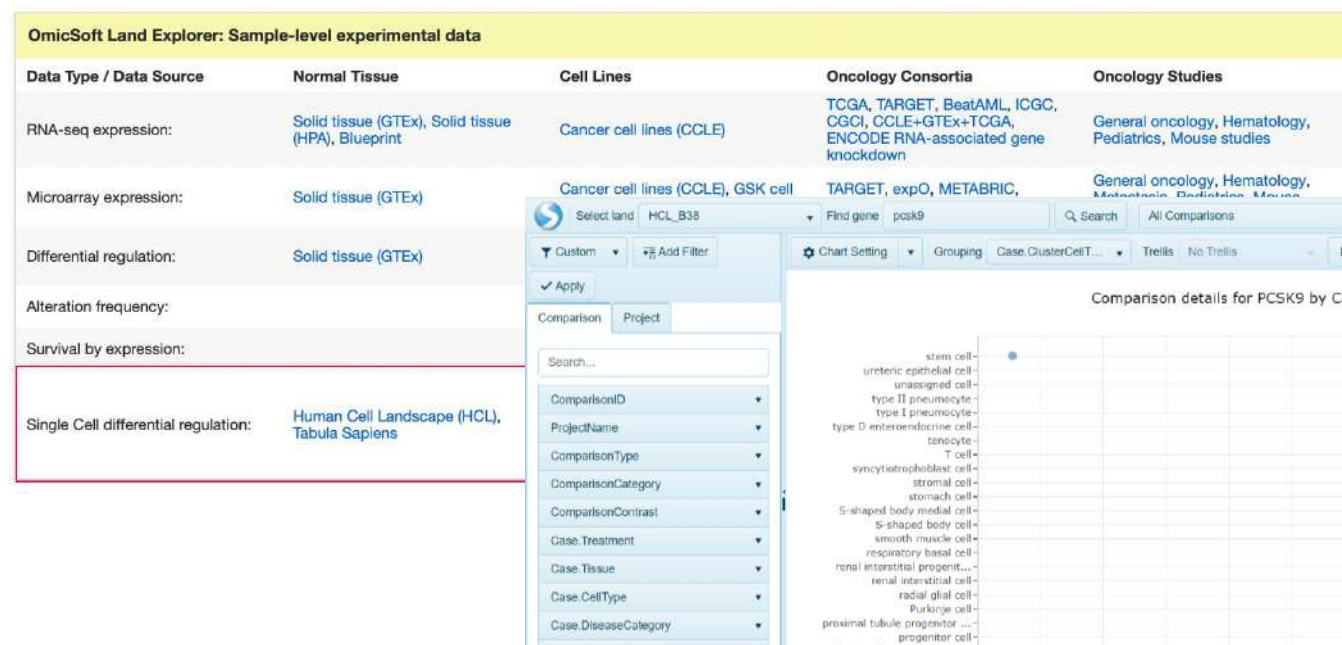
141,323 expression datasets (5,689 added)

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	
	MetastaticCancer	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	

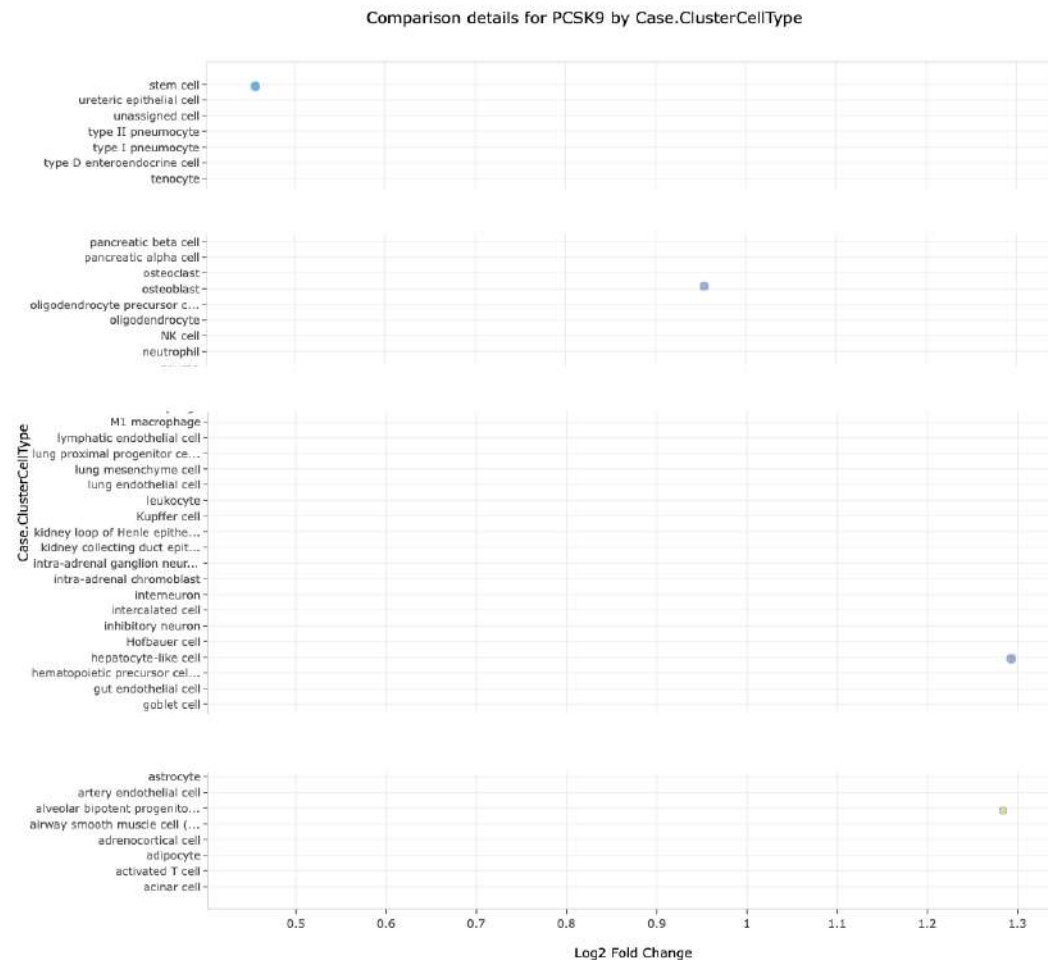
- What's new 2023 IPA Spring/Summer Release介紹
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*Land Explorer for IPA license is required to view the linked pages

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

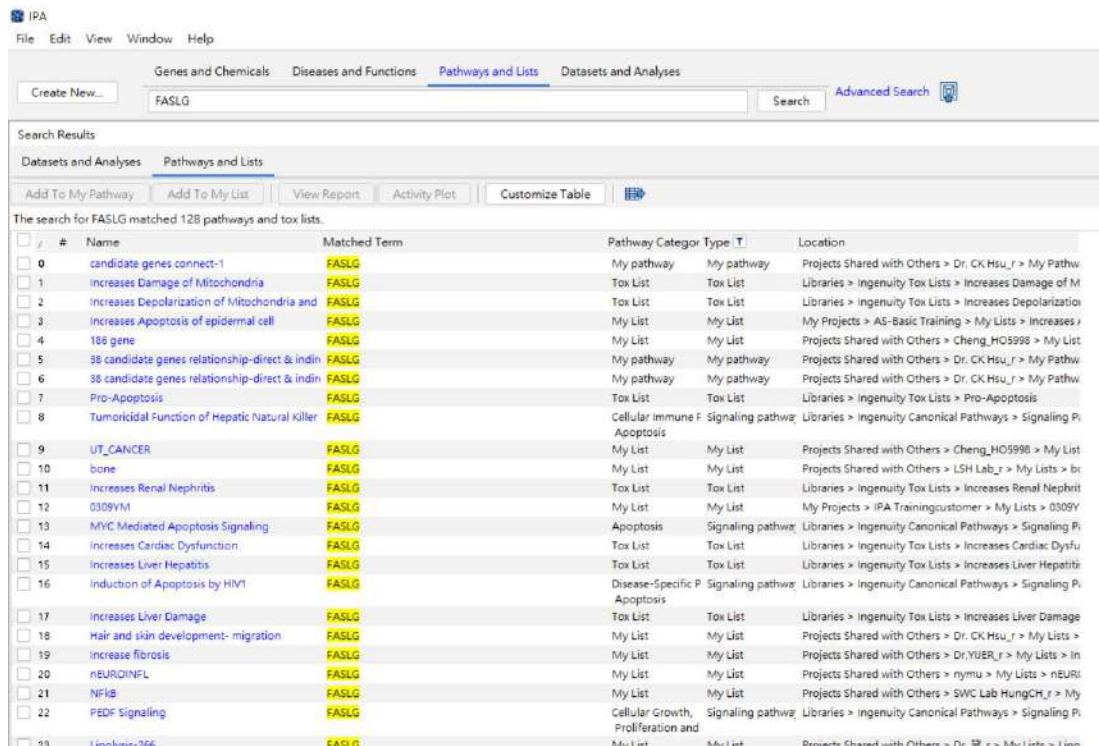


The figure shows how PCSK9 is overexpressed in hepatocyte-like cells, and less so in stem cells and osteoblasts



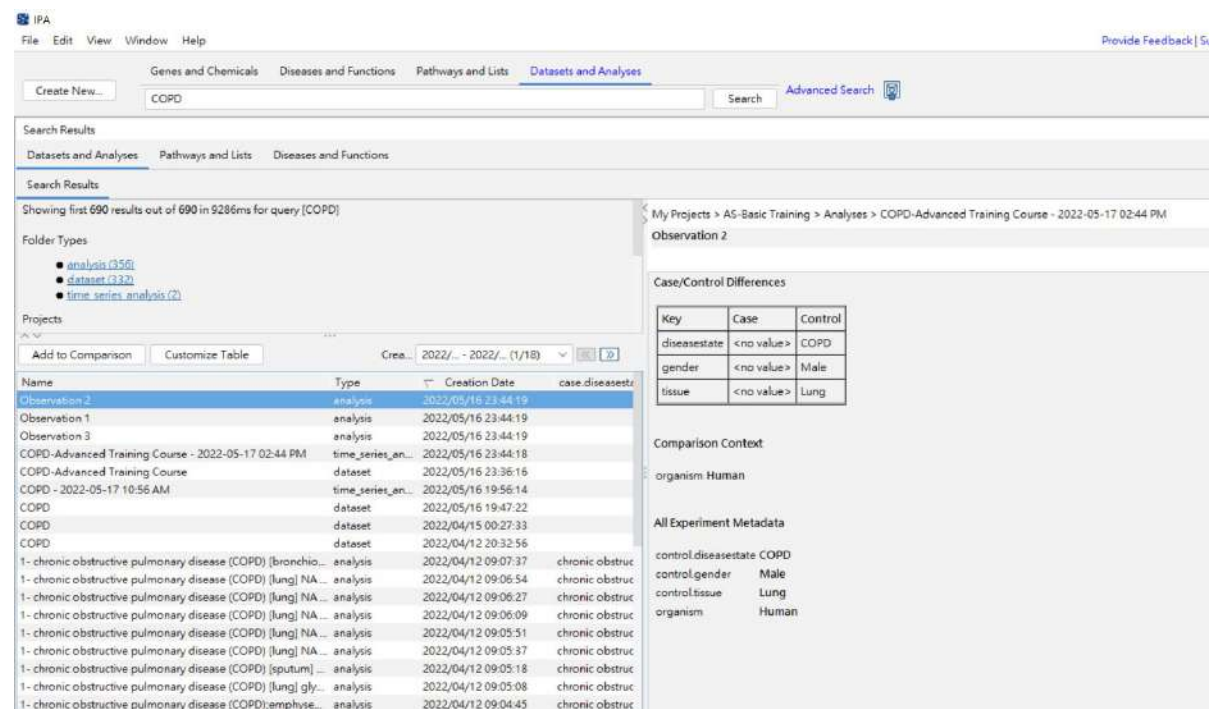
Improved ease of use and increased capabilities of search

- 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.



IPA Search Results for FASLG. The search returned 128 pathways and tox lists. The results are displayed in a table with columns: #, Name, Matched Term, Pathway Category, Type, and Location.

#	Name	Matched Term	Pathway Category	Type	Location
0	candidate genes connect-1	FASLG	My pathway	My pathway	Projects Shared with Others > Dr. CK Hsu, r > My Pathw...
1	Increases Damage of Mitochondria	FASLG	Tox List	Tox List	Libraries > Ingenuity Tox Lists > Increases Damage of M...
2	Increases Depolarization of Mitochondria and	FASLG	Tox List	Tox List	Libraries > Ingenuity Tox Lists > Increases Depolarization
3	Increases Apoptosis of epidermal cell	FASLG	My List	My List	My Projects > AS-Basic Training > My Lists > Increases /
4	186 gene	FASLG	My List	My List	Projects Shared with Others > Cheng_HO5998 > My List
5	38 candidate genes relationship-direct & indire	FASLG	My pathway	My pathway	Projects Shared with Others > Dr. CK Hsu, r > My Pathw...
6	38 candidate genes relationship-direct & indire	FASLG	My pathway	My pathway	Projects Shared with Others > Dr. CK Hsu, r > My Pathw...
7	Pro-Apoptosis	FASLG	Tox List	Tox List	Libraries > Ingenuity Tox Lists > Pro-Apoptosis
8	Tumoricidal Function of Hepatic Natural Killer	FASLG	Cellular Immune F	Signaling pathwa	Libraries > Ingenuity Canonical Pathways > Signaling P...
9	UT_CANCER	FASLG	My List	My List	Projects Shared with Others > Cheng_HO5998 > My List
10	bone	FASLG	My List	My List	Projects Shared with Others > LSH Lab, r > My Lists > b...
11	Increases Renal Nephritis	FASLG	Tox List	Tox List	Libraries > Ingenuity Tox Lists > Increases Renal Nephrit
12	0309YM	FASLG	My List	My List	My Projects > IPA Trainingcustomer > My Lists > 0309Y
13	MYC Mediated Apoptosis Signaling	FASLG	Apoptosis	Signaling pathwa	Libraries > Ingenuity Canonical Pathways > Signaling P...
14	Increases Cardiac Dysfunction	FASLG	Tox List	Tox List	Libraries > Ingenuity Tox Lists > Increases Cardiac Dysfu
15	Increases Liver Hepatitis	FASLG	Tox List	Tox List	Libraries > Ingenuity Tox Lists > Increases Liver Hepatit
16	Induction of Apoptosis by HIV1	FASLG	Disease-Specific P	Signaling pathwa	Libraries > Ingenuity Canonical Pathways > Signaling P...
17	Increases Liver Damage	FASLG	Tox List	Tox List	Libraries > Ingenuity Tox Lists > Increases Liver Damage
18	Hair and skin development- migration	FASLG	My List	My List	Projects Shared with Others > Dr. CK Hsu, r > My Lists > b...
19	Increase fibrosis	FASLG	My List	My List	Projects Shared with Others > Dr.YUER, r > My Lists > in
20	nEUROINFL	FASLG	My List	My List	Projects Shared with Others > nymu > My Lists > nEURi
21	NFkB	FASLG	My List	My List	Projects Shared with Others > SWC Lab HungCH, r > My
22	PDGF Signaling	FASLG	Cellular Growth, Proliferation and	Signaling pathwa	Libraries > Ingenuity Canonical Pathways > Signaling P...



IPA Search Results for COPD. The search returned 9286ms for query [COPD]. The results are displayed in a table with columns: Name, Type, Creation Date, and case.diseasestr.

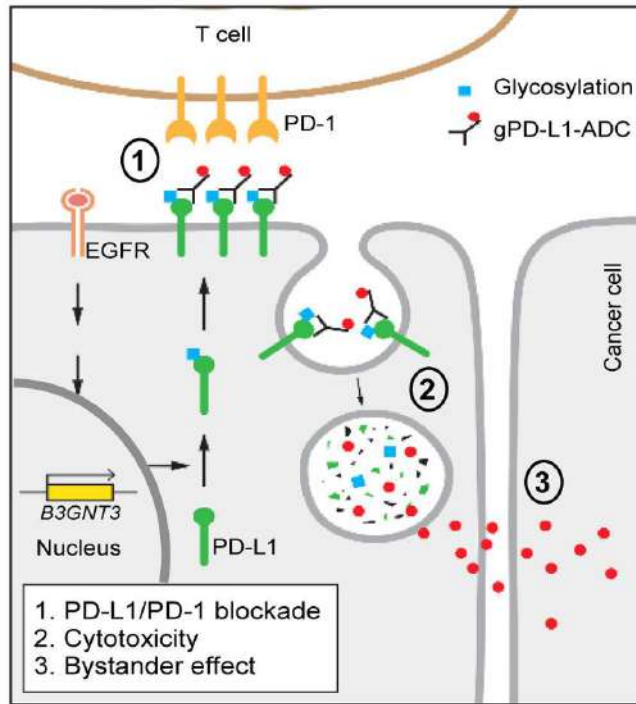
Name	Type	Creation Date	case.diseasestr
Observation 2	analysis	2022/05/16 23:44:19	
Observation 1	analysis	2022/05/16 23:44:19	
Observation 3	analysis	2022/05/16 23:44:19	
COPD-Advanced Training Course - 2022-05-17 02:44 PM	time_series_an...	2022/05/16 23:44:18	
COPD-Advanced Training Course	dataset	2022/05/16 23:36:16	
COPD - 2022-05-17 10:56 AM	time_series_an...	2022/05/16 19:56:14	
COPD	dataset	2022/05/16 19:47:22	
COPD	dataset	2022/04/15 00:27:33	
COPD	dataset	2022/04/12 20:32:56	
1- chronic obstructive pulmonary disease (COPD) [bronchio...	analysis	2022/04/12 09:07:37	chronic obstruct
1- chronic obstructive pulmonary disease (COPD) [lung] NA...	analysis	2022/04/12 09:06:54	chronic obstruct
1- chronic obstructive pulmonary disease (COPD) [lung] NA...	analysis	2022/04/12 09:06:27	chronic obstruct
1- chronic obstructive pulmonary disease (COPD) [lung] NA...	analysis	2022/04/12 09:06:09	chronic obstruct
1- chronic obstructive pulmonary disease (COPD) [lung] NA...	analysis	2022/04/12 09:05:51	chronic obstruct
1- chronic obstructive pulmonary disease (COPD) [lung] NA...	analysis	2022/04/12 09:05:37	chronic obstruct
1- chronic obstructive pulmonary disease (COPD) [lung] NA...	analysis	2022/04/12 09:05:18	chronic obstruct
1- chronic obstructive pulmonary disease (COPD) [lung] gly...	analysis	2022/04/12 09:05:08	chronic obstruct
1- chronic obstructive pulmonary disease (COPD);emphyse...	analysis	2022/04/12 09:04:45	chronic obstruct

Comparison Context:

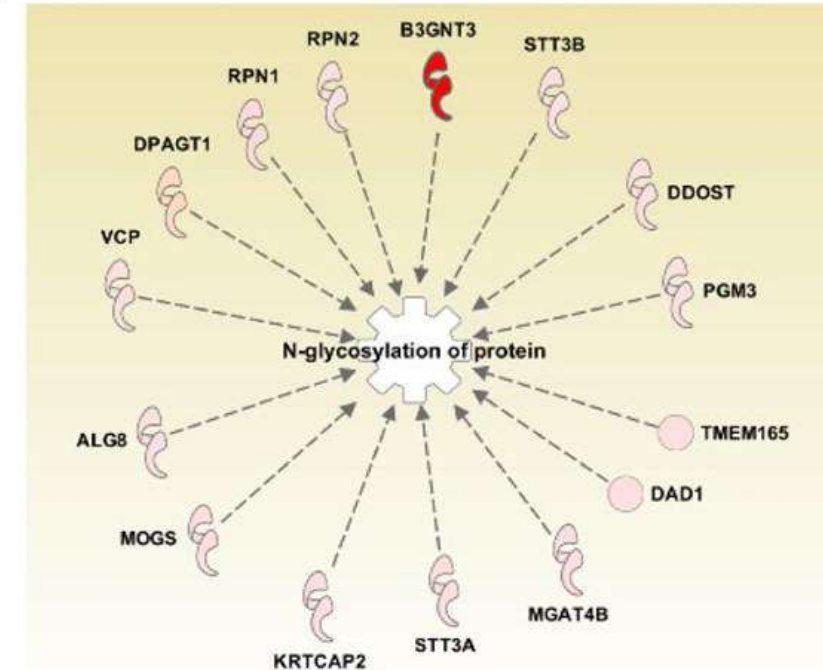
Key	Case	Control
diseasestate	<no value>	COPD
gender	<no value>	Male
tissue	<no value>	Lung

All Experiment Metadata:

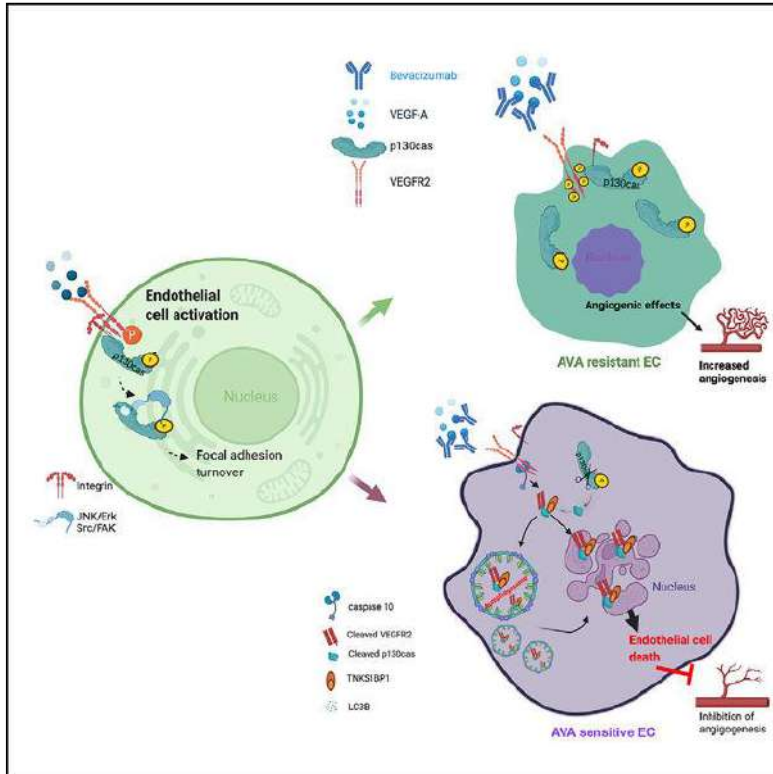
control.diseasestate	control.gender	control.tissue	organism
COPD	Male	Lung	Human



F

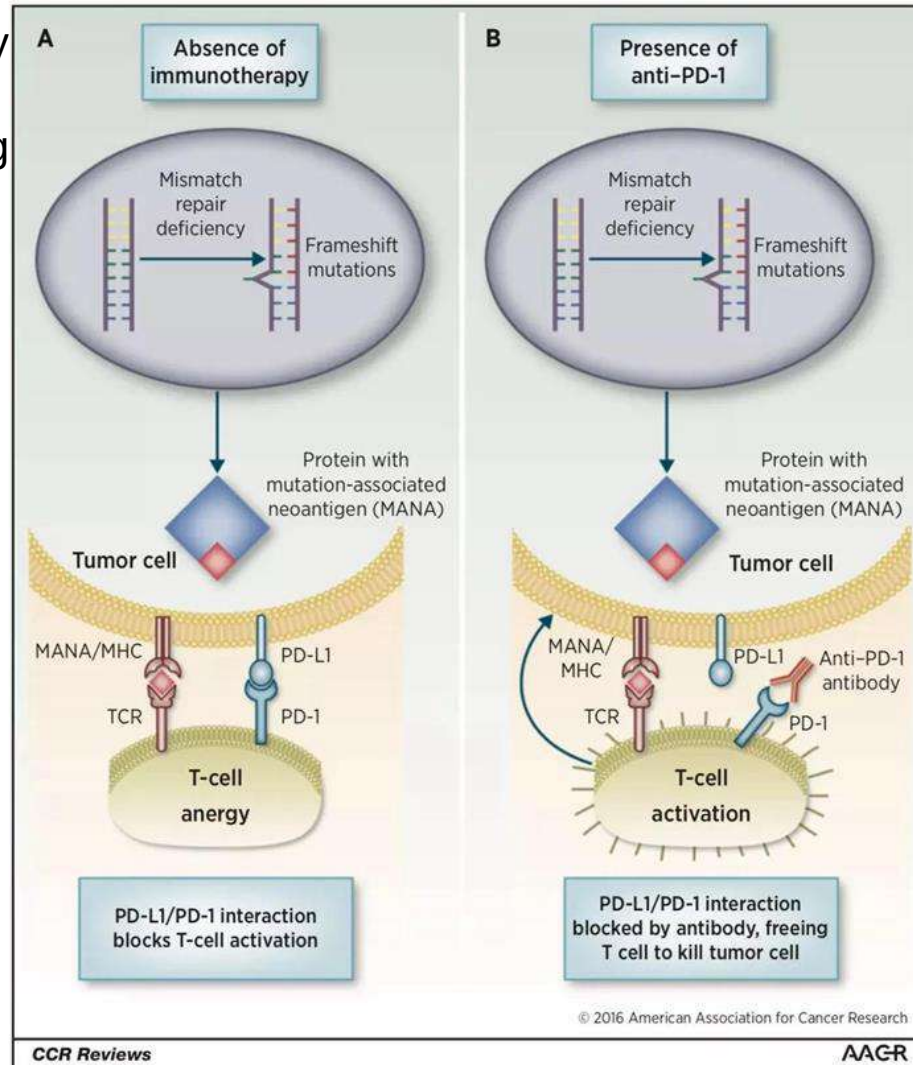


PD-L1 bound N-linked glycosylation-associated proteins shown by Ingenuity Pathway Analysis (IPA). PD-L1 bound proteins were identified from Flag-PD-L1 co-immunoprecipitated protein complex using MS/MS analysis followed by IPA



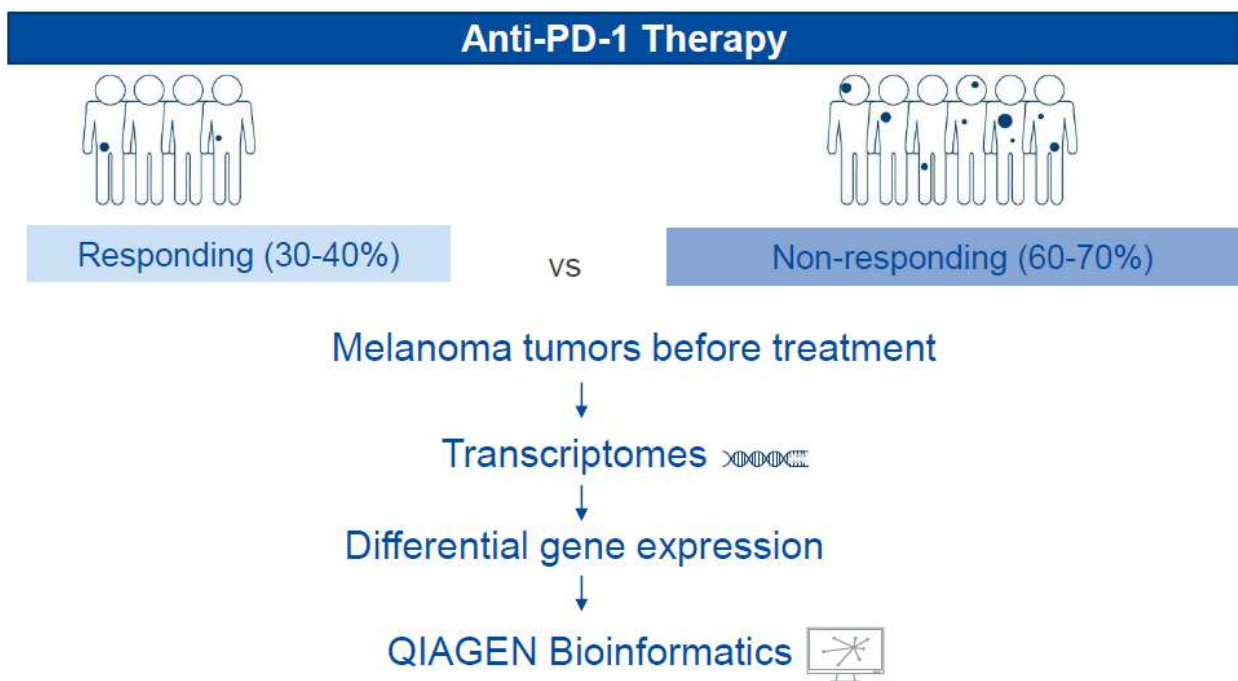
- Schematic representing Ingenuity Pathway Analysis of a cDNA microarray of ECs isolated from anti-VEGF-A antibody (B20)-sensitive ID8 tumors and B20-resistant ID8 tumors.

- Immunoassay
- Anti-PD1 drug



and inhibiting receptors located on effector T cells

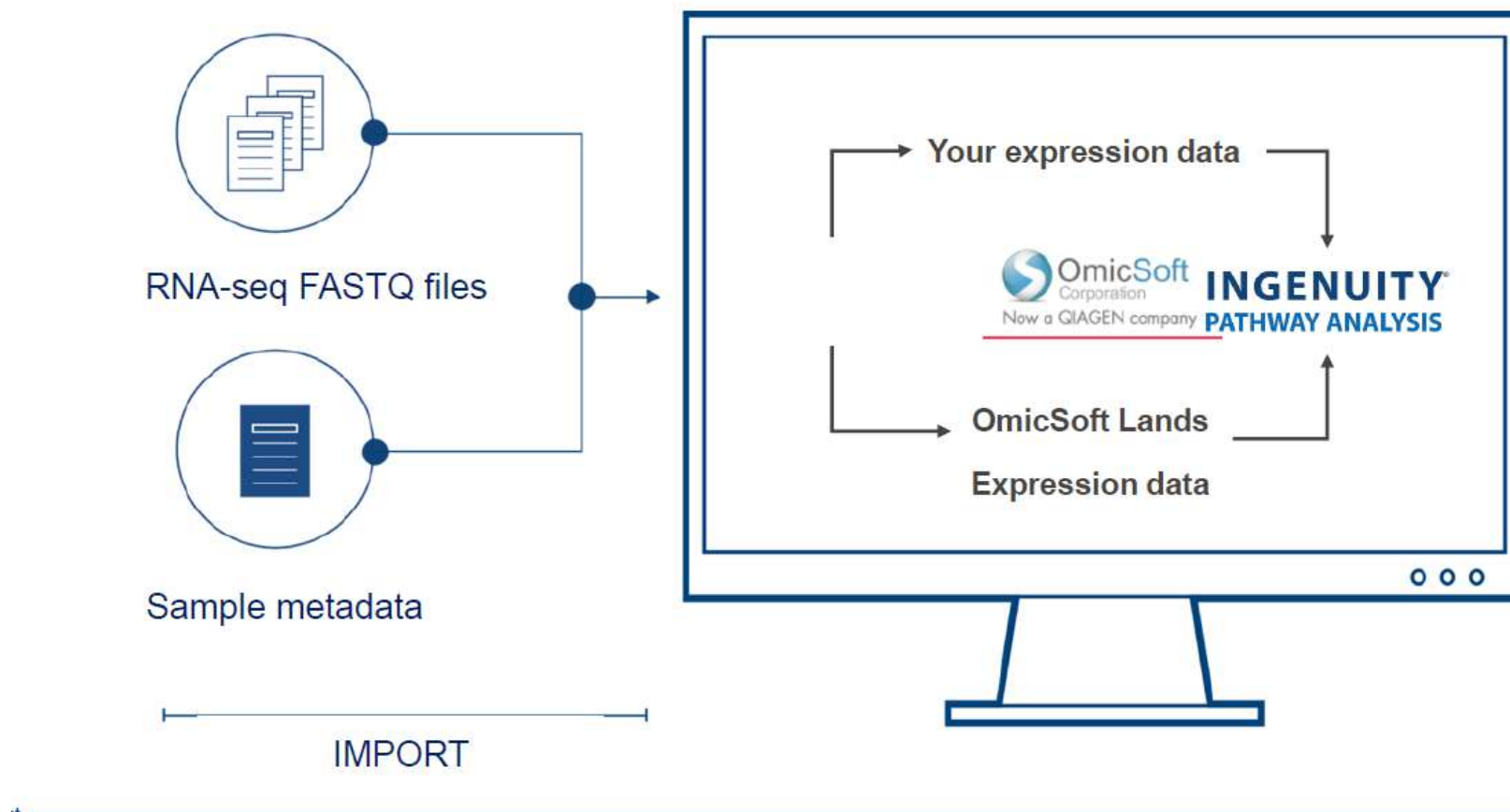
cells, killing cancer cells



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



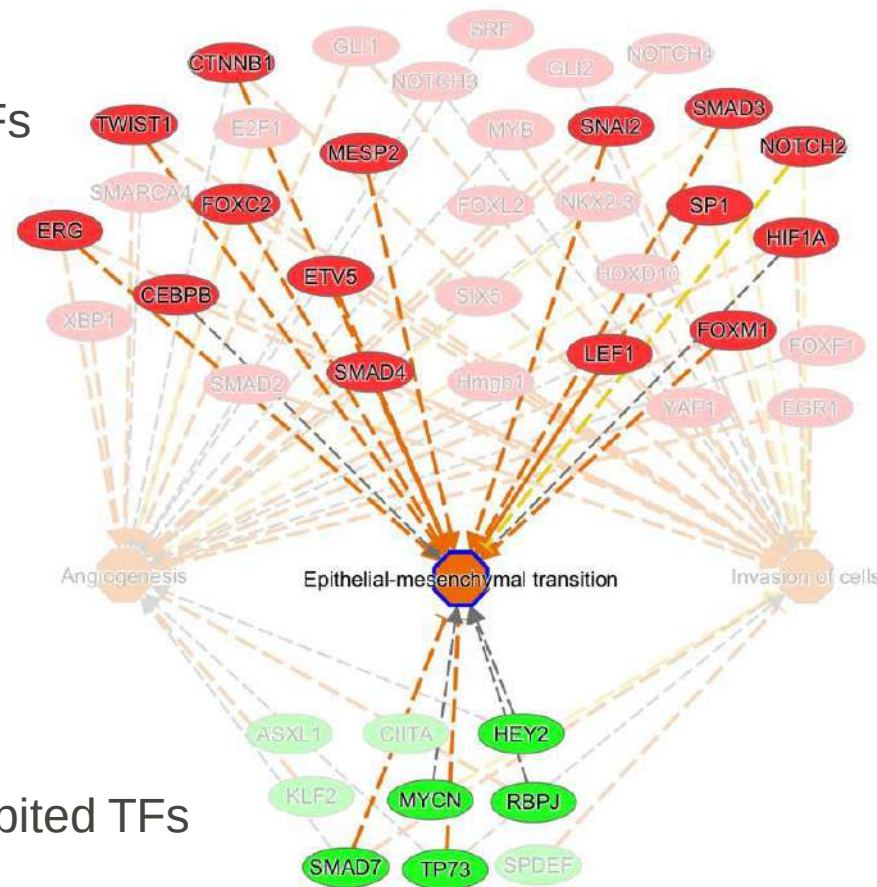
Upstream Regulator Analysis: Transcriptional Regulators

Upstream Regulators		Causal Networks					
ADD TO MY PATHWAY		ADD TO MY LIST		DISPLAY AS NETWORK		CUSTOMIZE TABLE	
Upstream Reg...		DISPLAY AS NETWORK		Molecule Type		Predicted Activati...	
						Activation z-s...	
						p-value of overlap	
						Target molecu...	
						Mechanistic N...	
SMAD2	↑3.505	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

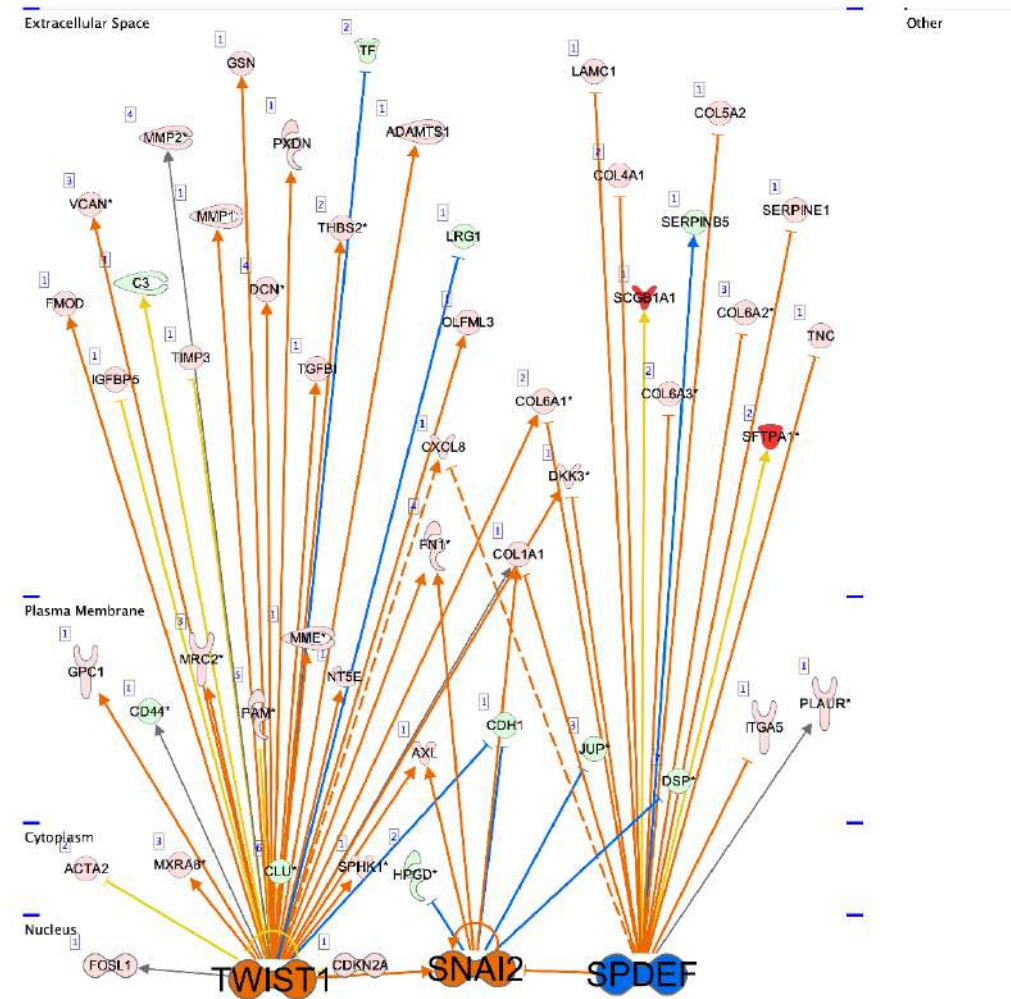
Angiogenesis
p-value 3.72E-25

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.

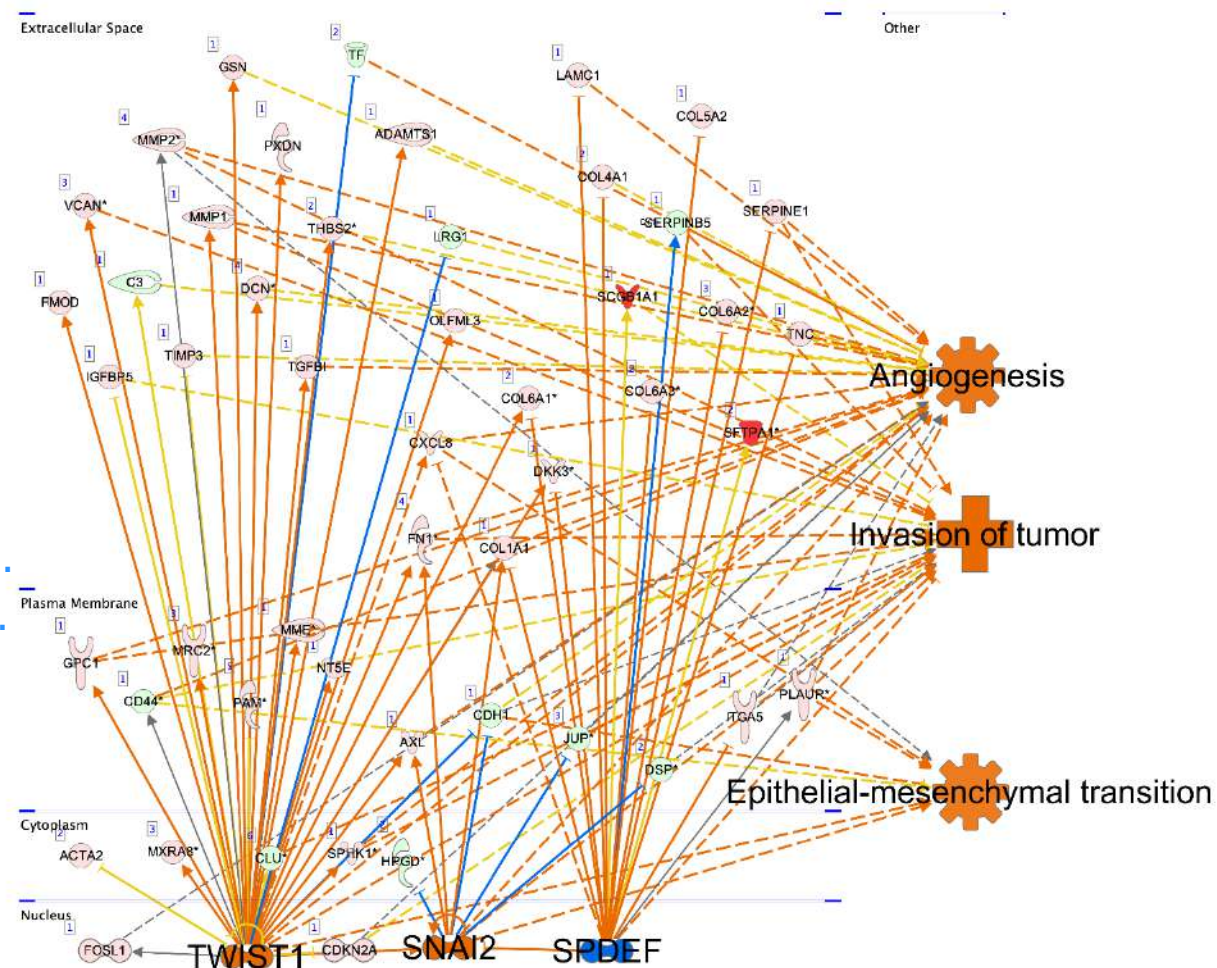


EMT is regulated by at least two transcription factors: SNAI2 and TWIST1

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

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

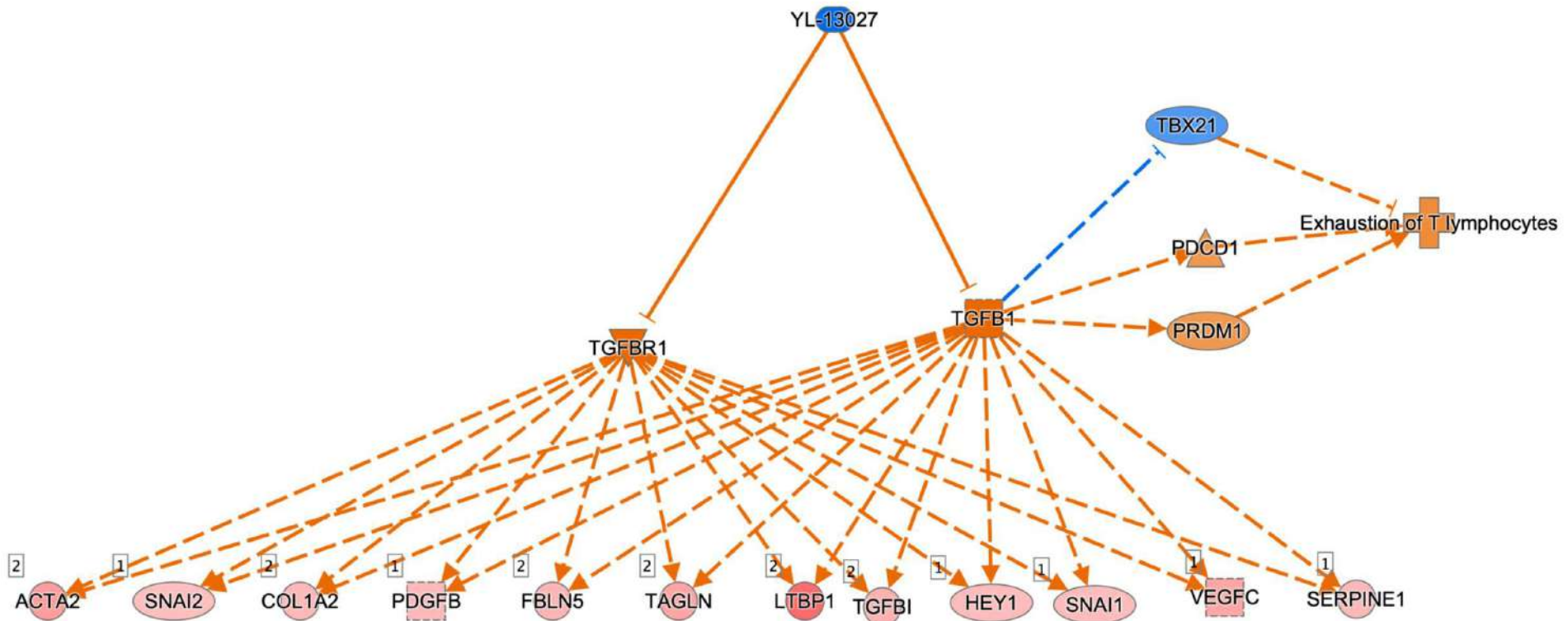
They drive increases in EMT, angiogenesis, and invasion.



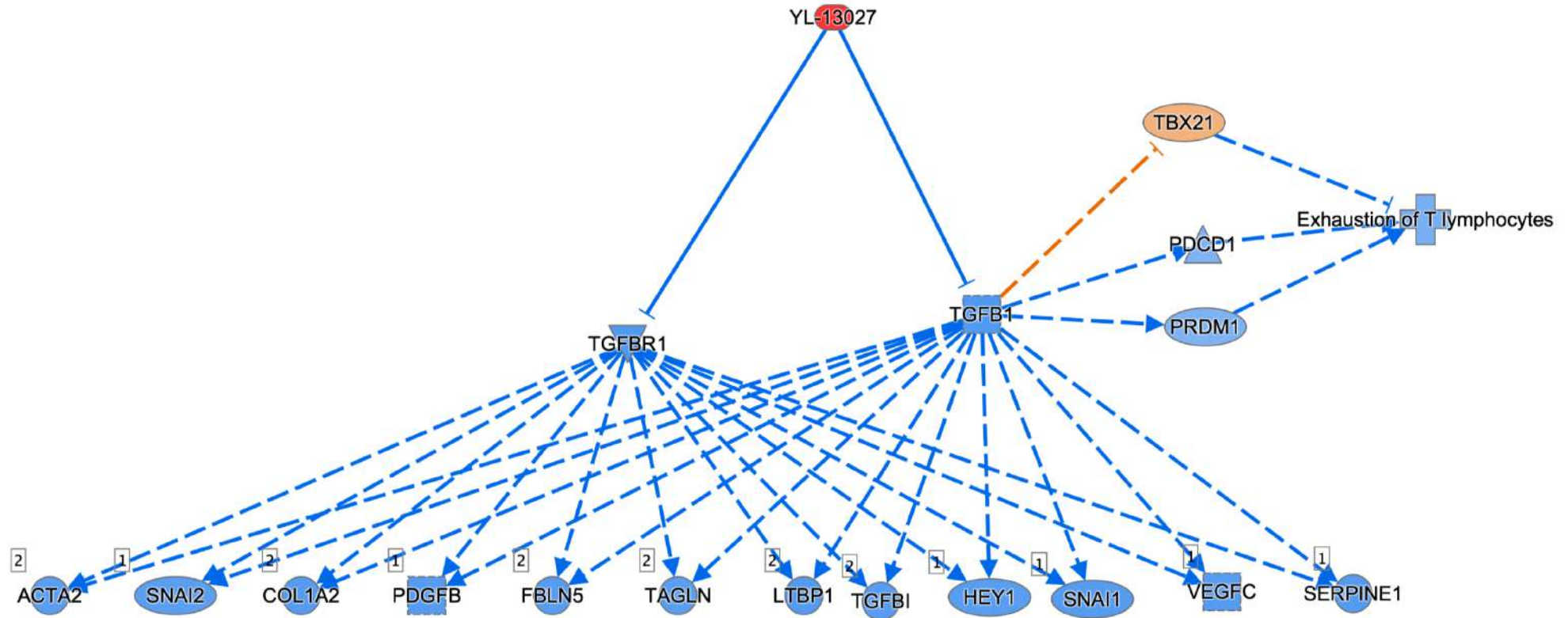
Causal Network Analysis to find chemicals to augment treatment (hypotheses)

Upstream Regulators Causal Networks														
ADD TO MY PATHWAY ADD TO MY LIST   More														
Master Regulator	Molecule Type	De...	Pre...	...	p-...	Net...	Tar...	Ca...	Len...	Path Types	Len...	Path Types	Len...	P...
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	IL
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	IL
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	IL
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	IL
galunisertib	chemical drug	2	Inhibited	-4.950	2.35E-08	2.00E-04	↑.....all 32	32 (3)			3 1	DU(1)	2 2	IL
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	IL
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	IL
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	IL
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	IL
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	IL
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	IL
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	IL
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

IsoProfilers filters

Filters

Biotype

☐ Select all
 ☒ protein-coding
 ☐ 3prime overlapping ncRNA
 ☐ antisense
 ☐ bidirectional promoter lncRNA
 ☐ IG C pseudogene
 ☐ IG D pseudogene
 ☐ IG J pseudogene

GTEx Tissue Expression (Enrichment)

Keep genes with at least one isoform that is in your dataset that is enriched in Any selected tissue(s)

CLEAR

SELECT ALL

Start typing to find certain tissues

☐ Pancreas
 ☐ Pituitary
 ☐ Prostate
 ☒ Skin - Not Sun Exposed (Suprapubic)
 ☒ Skin - Sun Exposed (Lower leg)
 ☐ Small Intestine - Terminal Ileum

Gene-level Disease or Function

CLEAR

SELECT ALL

melanoma

☒ Acral lentiginous melanoma
 ☒ Activation of melanoma cells
 ☒ Adhesion of melanoma cell lines
 ☒ Adhesion of melanoma cells
 ☒ Advanced BRAF V600 positive melanoma
 ☒ Advanced cutaneous melanoma
 ☒ Advanced melanoma
 ☒ Advanced stage sinonasal mucosal melanoma

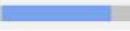
IsoProfiler: 46 genes have isoforms that meet all criteria

IsoProfiler; Universe = Human isoforms from Ensembl with Expr Fold Change and Expr Intensity/RPKM/FPKM/Counts

ADD TO MY PATHWAY ADD TO MY LIST ISOPROFILER FINDINGS CREATE DATASET CUSTOMIZE TABLE Symbol ADAM15 - LIPH (p1 of 2) More Info

Symbol	Molecule ...	Gene-level Disease or Function	Expression Patterns	Max ...
ALDH3B2	enzyme	Cutaneous melano... Liver carcino... Metabol... all 7	11 GTEX 8 7 ---- 3-	↓-3.549 1
ANO1	ion channel	Abnormal morphology of cartilage tiss... Abn.....all 38	62 GTEX 4 1 3 14 ---- 1-	↑2.720 1
CELSR2	G-protein cou...	Abnormal morphology of lateral cerebral ven.....all 32	49 GTEX 5 -- 6	↓-2.464 1
COMP	other	Aggregation of blood platele...Angiogenes..... all 64	174 GTEX 16 3 5 8	↑4.539 1
CTSG	peptidase	Accumulation of neutrophil... Activation of blo... all 84	134 GTEX 7 -	↑2.763 1
CYP39A1	enzyme	Alzheimer disea... Catabolism of cholester...H... all 8	13 GTEX 2 1 - 2-	↓-3.755 1
DACT2	other	Adhesion of cel... Cutaneous melano... Devel.....all 14	17 GTEX 7 -	↓-3.044 1
DNK2	other	Abnormal morphology of corn... Abnormal m.....all 17	25	↑3.385 1

Selected rows 1 / 46

Isoform Tracks										Add/Remove column(s)		GTEX CHARTS	TranscriptLevel
Transcript	Protein	Schematic	...	...	APPRIS	Biotype	...	...	...	All ...	Tiss...	ID	
1 DACT2-2...	DACT2 isoform a		774	2942	PRINCIPAL:1	protein-coding	TSL:2			0.460	7 tissues	ENST00000366	
2 DACT2-2...	DACT2 isoform b		604	2088		protein-coding	TSL:1			0.000			
3 DACT2-2...	DACT2-203		366	1620		protein-coding	TSL:1			0.000			
4 DACT2-2...	DACT2 isoform c		280	2028		protein-coding	TSL:1			0.000			

Save Apply

Filters

Start typing to find certain tissues

- ☐ Ovary
- ☐ Pancreas
- ☐ Pituitary
- ☐ Prostate
- ☒ Skin - Not Sun Exposed (Suprapubic)
- ☒ Skin - Sun Exposed (Lower leg)
- ☐ Small Intestine - Terminal Ileum
- ☐ Spleen
- ☐ Stomach
- ☐ Exclude unselected tissue(s)

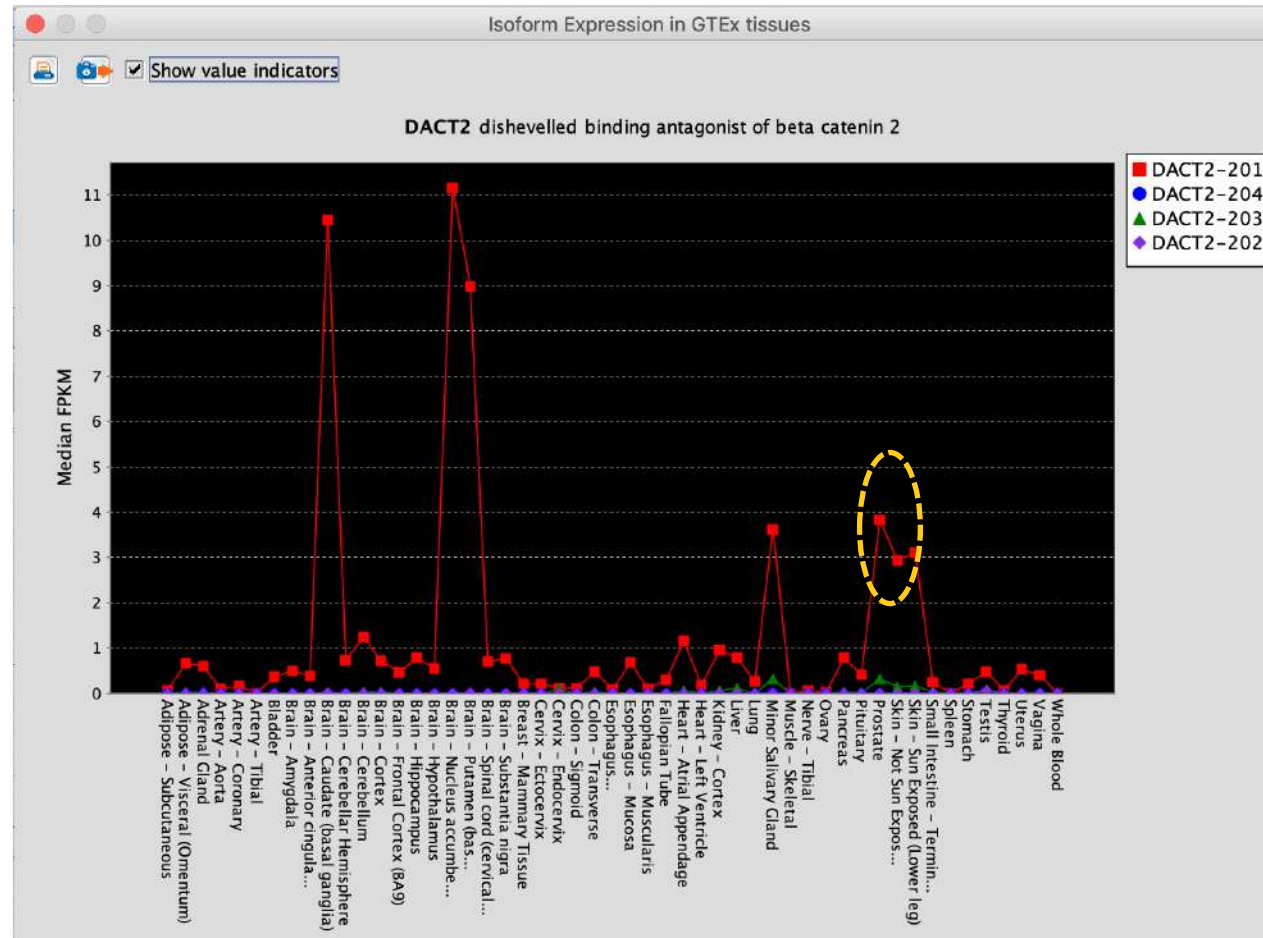
Gene-level Disease or Function

CLEAR SELECT ALL

melanoma

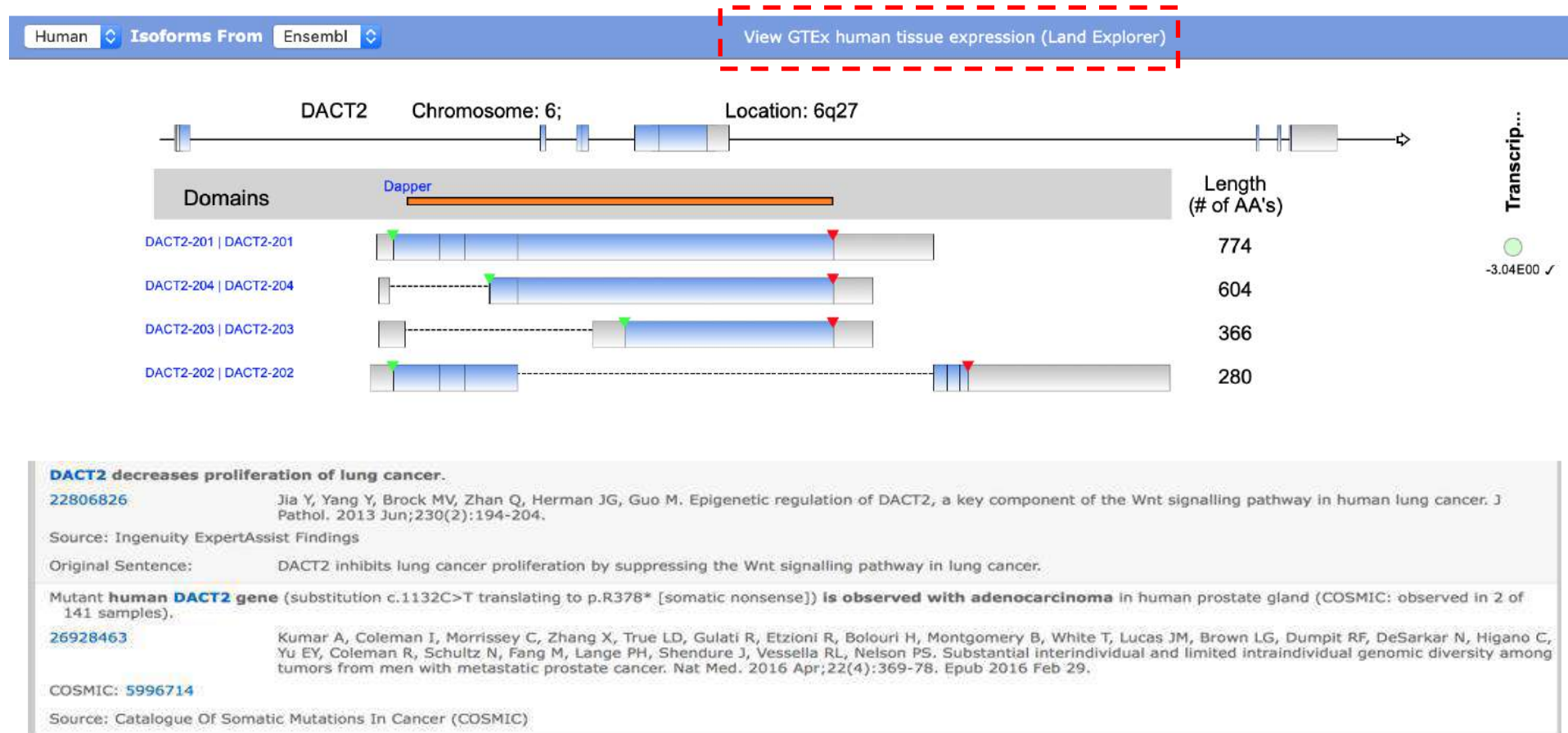
- ☒ Acral lentiginous melanoma
- ☒ Adhesion of melanoma cell lines
- ☒ Adhesion of melanoma cells
- ☒ Adhesion of myeloid cells in melanoma
- ☒ Advanced BRAF V600 positive melanoma
- ☒ Advanced melanoma
- ☒ Aggregation of melanoma cell lines
- ☒ Apoptosis of melanoma cell lines

DACT2 isoform expression across GTEx tissues. Enriched in skin tissue

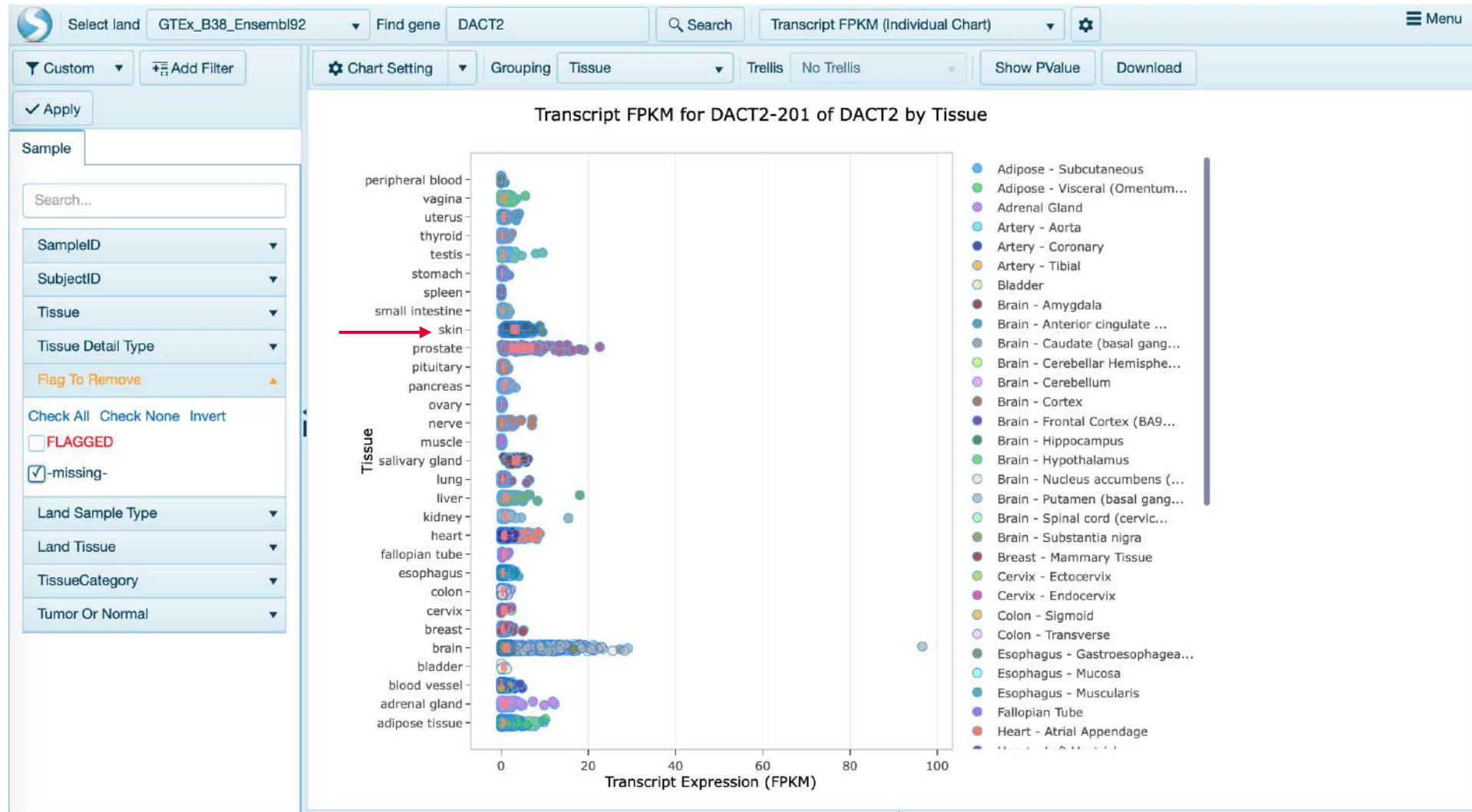


Transcript name: DACT2-201
 ID: ENST00000366795
 Tissue name: Prostate
 All tissue median FPKM: 0.460
 Median FPKM: 3.825
 Ratio: 7.003x (Enriched)

DACT2 is a tumor suppressor enriched in normal skin tissues



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?

Expression Analysis - Mouse expression RNA-seq High Insulin vs untreated FDR0.01

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

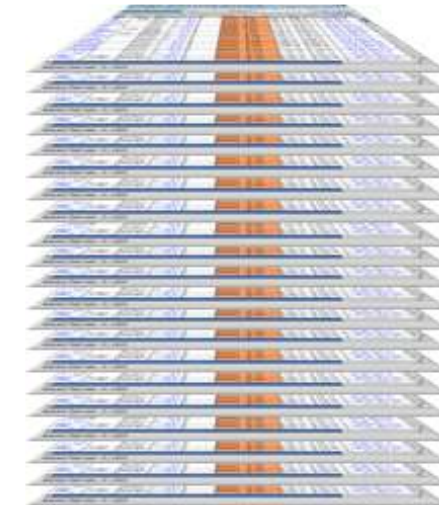
Activation z-score: 6.067 - 3.803 (p1 of 29)

Maste...	Ex...	Mol...	Par...	De...	Predic...	z...	p...	Net...	Tar...	Ca...	T
CEBPD	↑2.253	transcript...	C...all 6	2	Activated	6.067	3.73E-36	1.00E-04	...all 235	235 (6)	6
INSR	↑1.812	kinase	...all 1	1	Activated	5.908	1.39E-17	1.00E-04	...all 66	66 (1)	1
1D-chiro-ir		chemical ...	...all 3	2	Activated	5.889	3.77E-20	1.00E-04	...all 75	75 (3)	2
benzylamin		chemical ...	...all 4	2	Activated	5.889	5.40E-20	1.00E-04	...all 75	75 (4)	3
HPSE		enzyme	...all 8	2	Activated	5.713	2.52E-22	8.90E-03	...all 206	206 (8)	8
UBA1	↑2.339	enzyme	...all 61	3	Activated	5.611	1.74E-43	1.00E-04	...all 545	545 (61)	6
ciglitazone		chemical ...	...all 24	2	Activated	5.590	1.41E-37	1.00E-04	...all 320	320 (24)	2
LPIN1	↑2.062	phosphat...	...all 7	2	Activated	5.575	7.09E-30	1.00E-04	...all 181	181 (7)	7
D-thioctic a		chemical ...	...all 4	2	Activated	5.480	1.04E-22	1.00E-04	...all 112	112 (4)	4
hexarelin		chemical ...	...all 6	2	Activated	5.426	8.10E-32	1.00E-04	...all 181	181 (6)	6
mibolerone		chemical ...	...all 31	3	Activated	5.353	2.98E-41	6.00E-04	...all 554	554 (31)	3
hydroxyflut		chemical ...	...all 35	3	Activated	5.345	1.57E-38	1.70E-03	...all 547	547 (35)	3
testosterone		chemical ...	...all 39	3	Activated	5.250	3.22E-39	1.10E-03	...all 549	549 (39)	3
1,1-bis(3'-		chemical ...	...all 3	2	Activated	5.185	2.05E-29	1.00E-04	...all 162	162 (3)	3
ZMIZ2	↑1.861	transcript...	...all 31	3	Activated	5.184	8.28E-37	2.70E-03	...all 527	527 (31)	3

Selected/Total rows: 0 / 2833

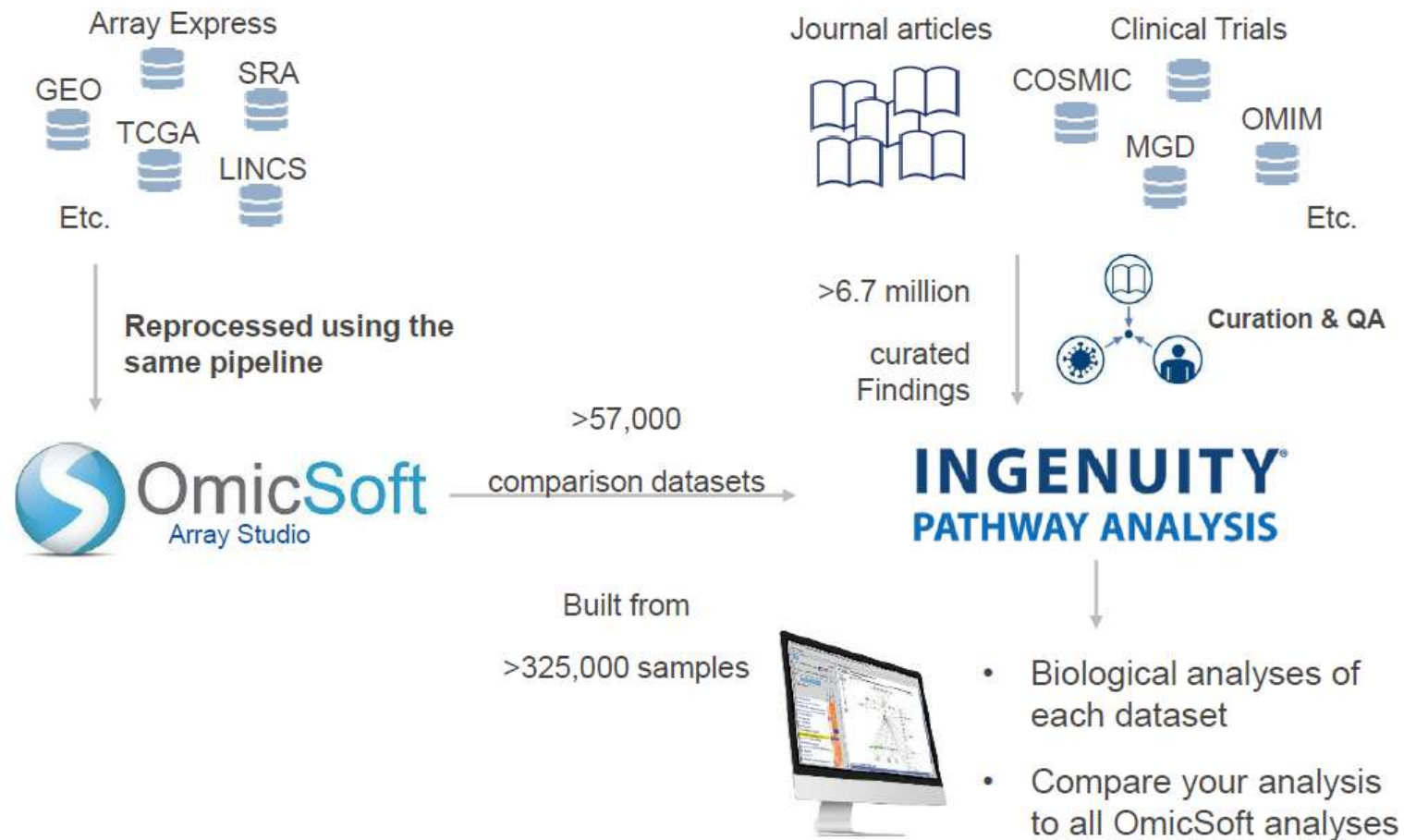
Match against

>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

Expression Analysis – TranscriptLevel2.DEseq.NRvsR. userref fc2 p0.05 max10–2017–08–26

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

VIEW AS HEATMAP | VIEW COMPARISON | CUSTOMIZE TABLE

More Info

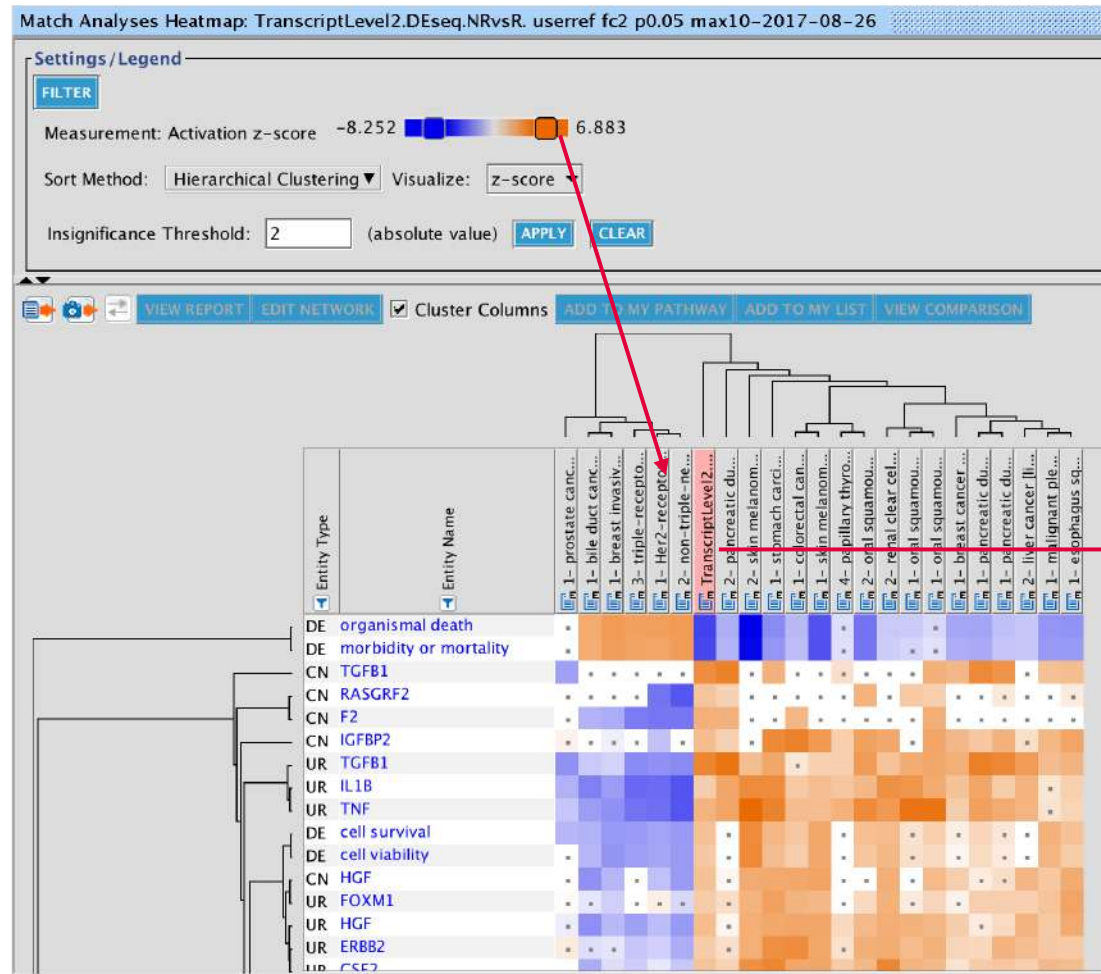
Analysis Name	Project	case.diseasestate	case.tis...	comparisoncat...	comparisoncontrast	UR ...	CN...	DE...	
2– pancreatic ductal adenocarcinoma [pancreas] NA 23	MetastaticCancer	pancreatic ductal adenocarcinoma	pancreas	Disease vs. Normal	TissueDescription => prim...	55.75	34.64	53.62	36.00
1– breast cancer [breast] NA 1023	OncoGEO	breast cancer	breast	Disease vs. Normal	LandSampleType => Prim...	53.27	34.64	47.43	33.84
1– oral squamous cell carcinoma [tongue] NA 1852	OncoGEO	oral squamous cell carcinoma	tongue	Disease vs. Normal	LandSampleType => Prim...	50.67	28.28	46.10	31.26
1– stomach carcinoma [stomach] NA 1716	OncoGEO	stomach carcinoma	stomach	Disease vs. Normal	LandSampleType => Prim...	51.99	22.36	50.00	31.09
1– pancreatic ductal adenocarcinoma [pancreas] NA 820	OncoGEO	pancreatic ductal adenocarcinoma	pancreas	Disease vs. Normal	LandSampleType => Prim...	47.93	24.49	47.43	29.96
1– esophagus squamous cell carcinoma [esophagus] NA 525	OncoGEO	esophagus squamous cell carcin...	esophagus	Disease vs. Normal	LandSampleType => Prim...	49.32	24.49	41.83	28.91
2– renal clear cell carcinoma (KIRC) [kidney] NA 75	MetastaticCancer	renal clear cell carcinoma (KIRC)	kidney	Disease vs. Normal	LandSampleType:Metastasi...	50.67	20.00	40.31	27.75
1– pancreatic ductal adenocarcinoma [pancreas] NA 309	OncoGEO	pancreatic ductal adenocarcinoma	pancreas	Disease vs. Normal	LandSampleType => Prim...	50.67	20.00	50.00	24.83
2– oral squamous cell carcinoma [mouth] NA 1271	OncoGEO	oral squamous cell carcinoma	mouth	Disease vs. Normal	LandSampleType => Prim...	45.02		48.73	23.44
1– oral squamous cell carcinoma [mouth] NA 1069	OncoGEO	oral squamous cell carcinoma	mouth	Disease vs. Normal	LandSampleType => Prim...	43.50		43.30	21.70
2– liver cancer [liver] NA 961	OncoGEO	liver cancer	liver	Disease vs. Normal	LandSampleType => Prim...	47.93		38.73	21.66
1– skin melanoma (SKCM) [skin lymph node] NA 1250	OncoGEO	skin melanoma (SKCM)	skin lymph node	Disease vs. Normal	LandSampleType => Meta...	41.91		40.31	20.56
2– skin melanoma (SKCM) [skin] NA 1251	OncoGEO	skin melanoma (SKCM)	skin	Disease vs. Normal	LandSampleType => Prim...	40.27		41.83	20.53
1– colorectal cancer [colonrectum] NA 662	OncoGEO	colorectal cancer	colonrectum	Disease vs. Normal	LandSampleType => Prim...	38.55		40.31	19.72
1– malignant pleural mesothelioma [lung] NA 1336	OncoGEO	malignant pleural mesothelioma	lung	Disease vs. Normal	LandSampleType => Prim...	39.02		38.73	19.44
4– papillary thyroid carcinoma [thyroid] NA 69	MetastaticCancer	papillary thyroid carcinoma	thyroid	Disease vs. Normal	LandSampleType => Prim...	36.76		40.31	19.27
3– triple-receptor negative breast cancer (TNBC) [breast] NA 1023	OncoGEO	triple-receptor negative breast ...	breast	Disease vs. Normal	DiseaseState => triple-rec...	-40.27		-43.30	-20.89
1– breast invasive carcinoma (BRCA) [breast] NA 85	OncoGEO	breast invasive carcinoma (BRCA)	breast	Disease vs. Normal	CellType:LandSampleType ...	-38.55		-51.23	-22.45
1– bile duct cancer (CHOL) [bile duct] NA 1783	OncoGEO	bile duct cancer (CHOL)	bile duct	Disease vs. Normal	LandSampleType => Prim...	44.72		44.72	-22.81
2– non-triple-negative breast cancer (non-TNBC) [breast] NA 1023	OncoGEO	non-triple-negative breast can...	breast	Disease vs. Normal	DiseaseState => non-triple...	36.76		41.83	-25.77
1– Her2-receptor positive breast cancer [breast] NA 2012	OncoGEO	Her2-receptor positive breast c...	breast	Disease vs. Normal	DiseaseState => Her2-rec...	-38.55	-20.00	-47.43	-26.50
1– prostate cancer [prostate] NA 76	MetastaticCancer	prostate cancer	prostate	Disease vs. Normal	LandSampleType => Prim...	-55.75	-23.33	-44.72	-30.95

Similar pattern in upstream and downstream predictions

Opposite pattern in upstream and downstream predictions

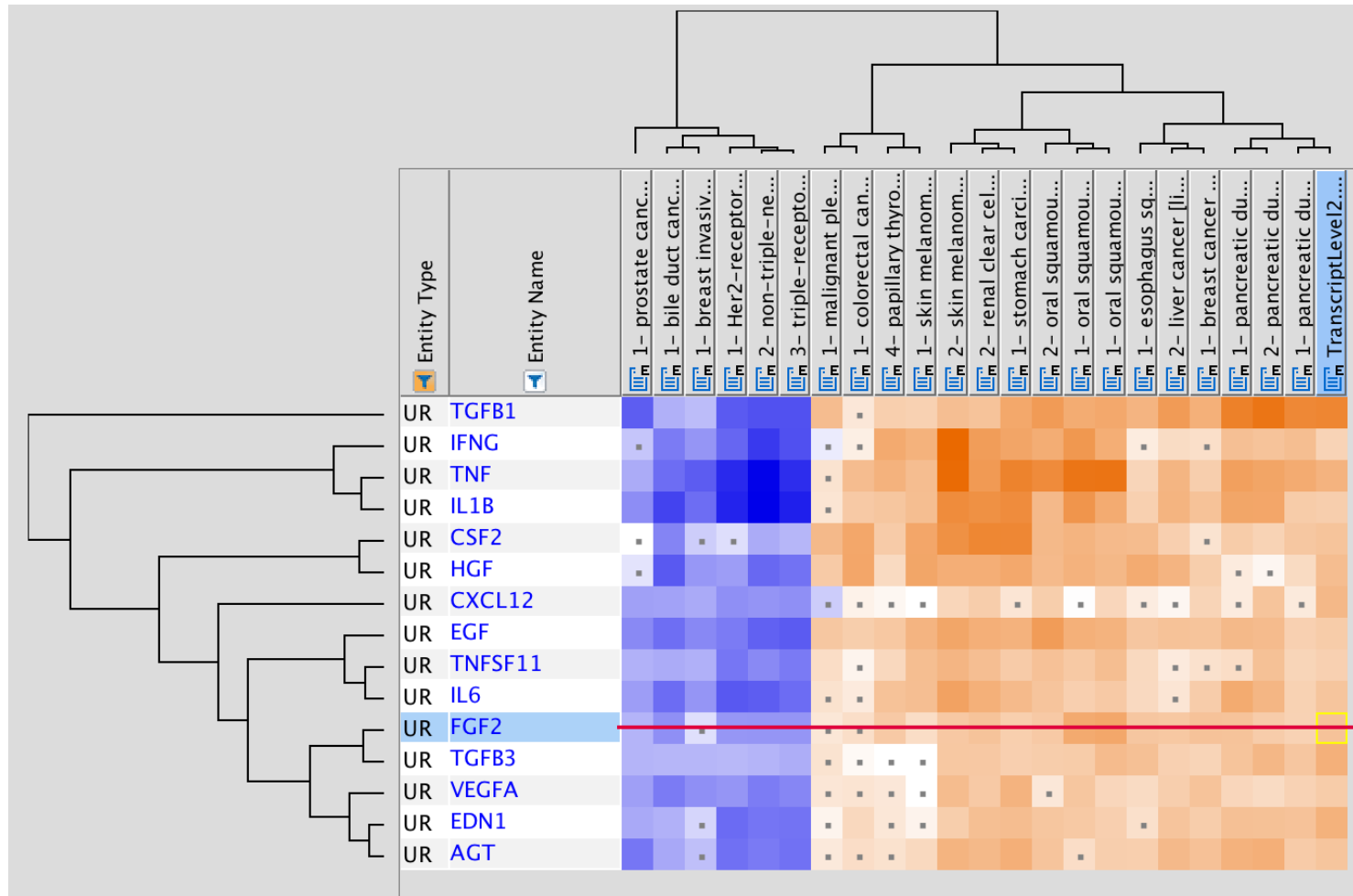
Analysis Match: Melanoma vs. precomputed datasets and your own

Heatmap of the selected analyses



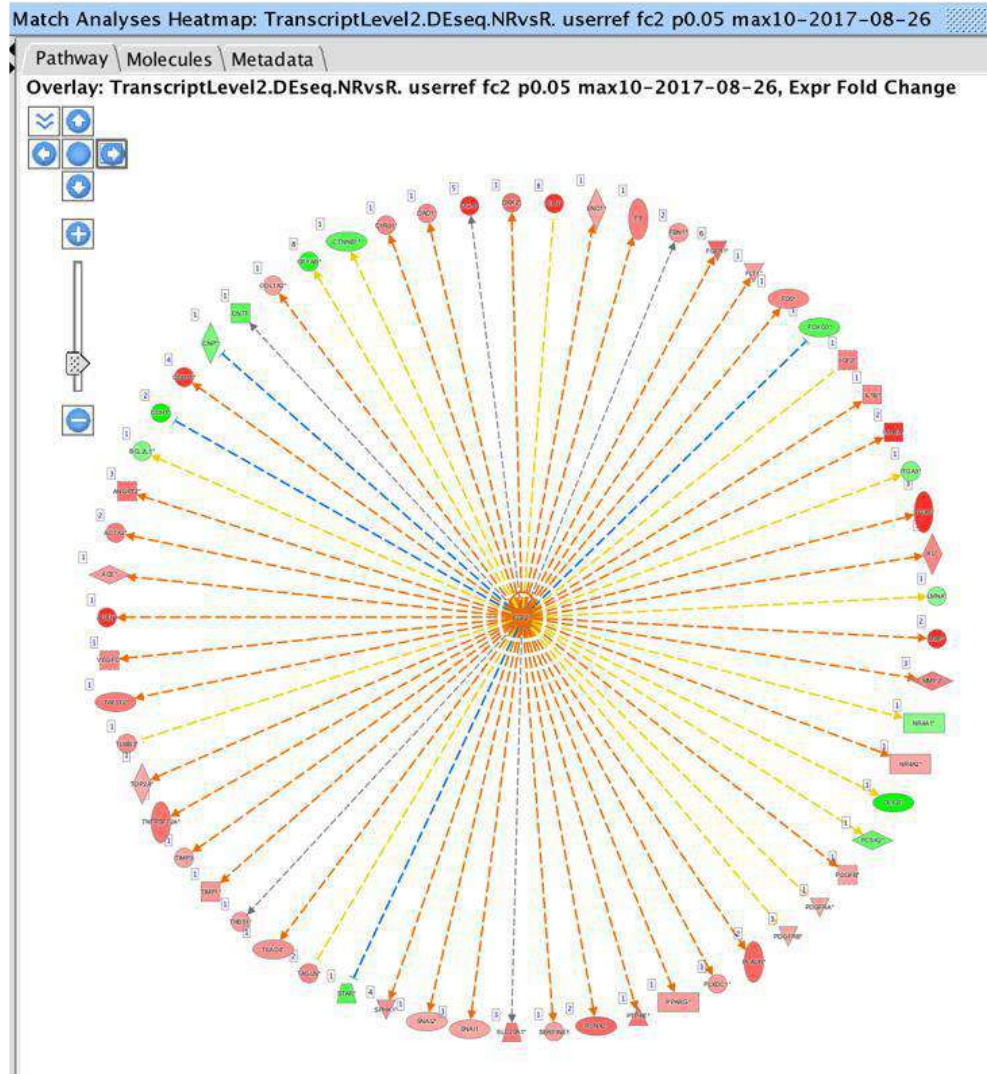
Metadata	
1- colorectal cancer [colonrectum] NA 662	
KEY	VALUE
case.diseasestate	colorectal cancer
case.sampleids	GSM588828;GSM588829;...
case.samplesource	colonrectum
case.tissue	colonrectum
case.treatment	NA
comparisoncategory	Disease vs. Normal
comparisoncontrast	LandSampleType => Prima...
comparisonid	GSE23878.GPL570.test1
comparisonindex	662
comparisonstype	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
sampldatamode	Expression_Intensity_Probes
upregulated log2 cutoff	0.9543
weblink	https://www.ncbi.nlm.nih.g...

Upstream regulator signature related to tumor progression



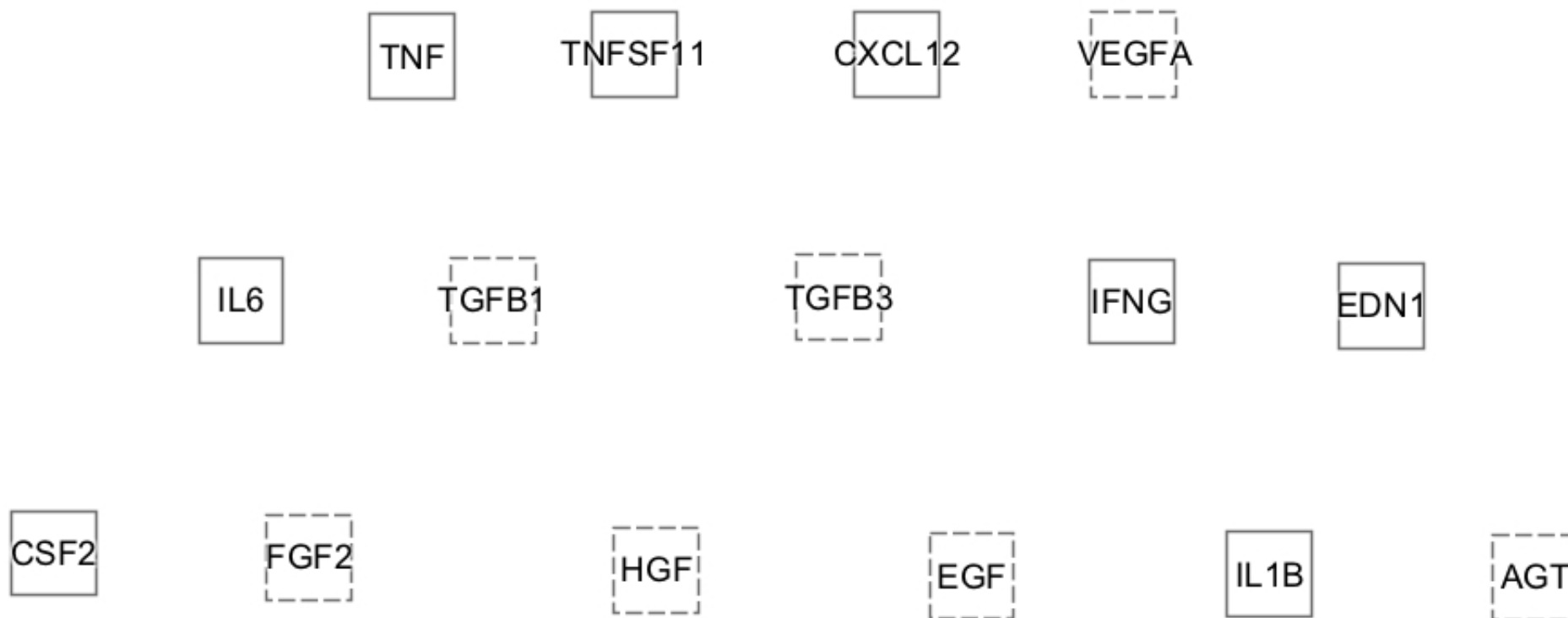
UR filtered by molecule type:
Cytokines and growth factors

Upstream regulator signature related to tumor progression

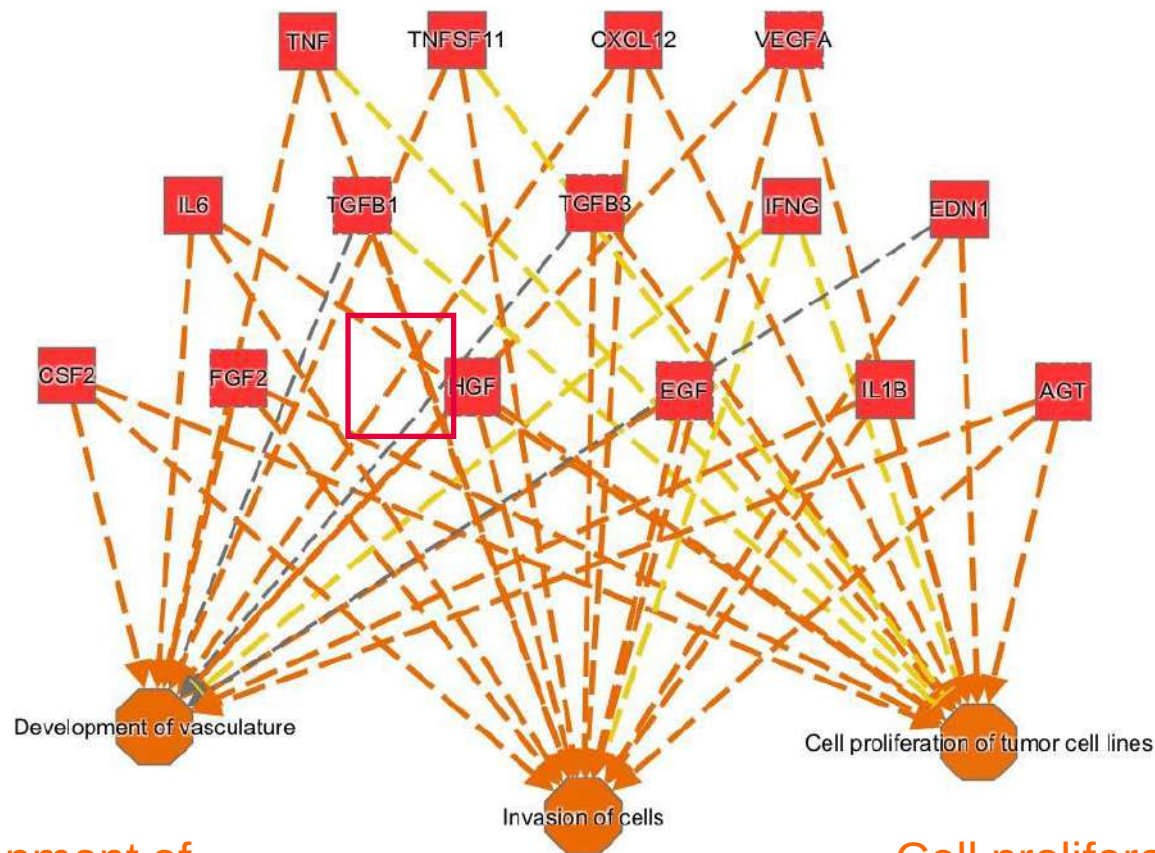


FGF2 is an upstream regulator predicted to be activated in non-responder vs responder

Upstream regulator signature related to tumor progression



Upstream regulator signature related to tumor progression



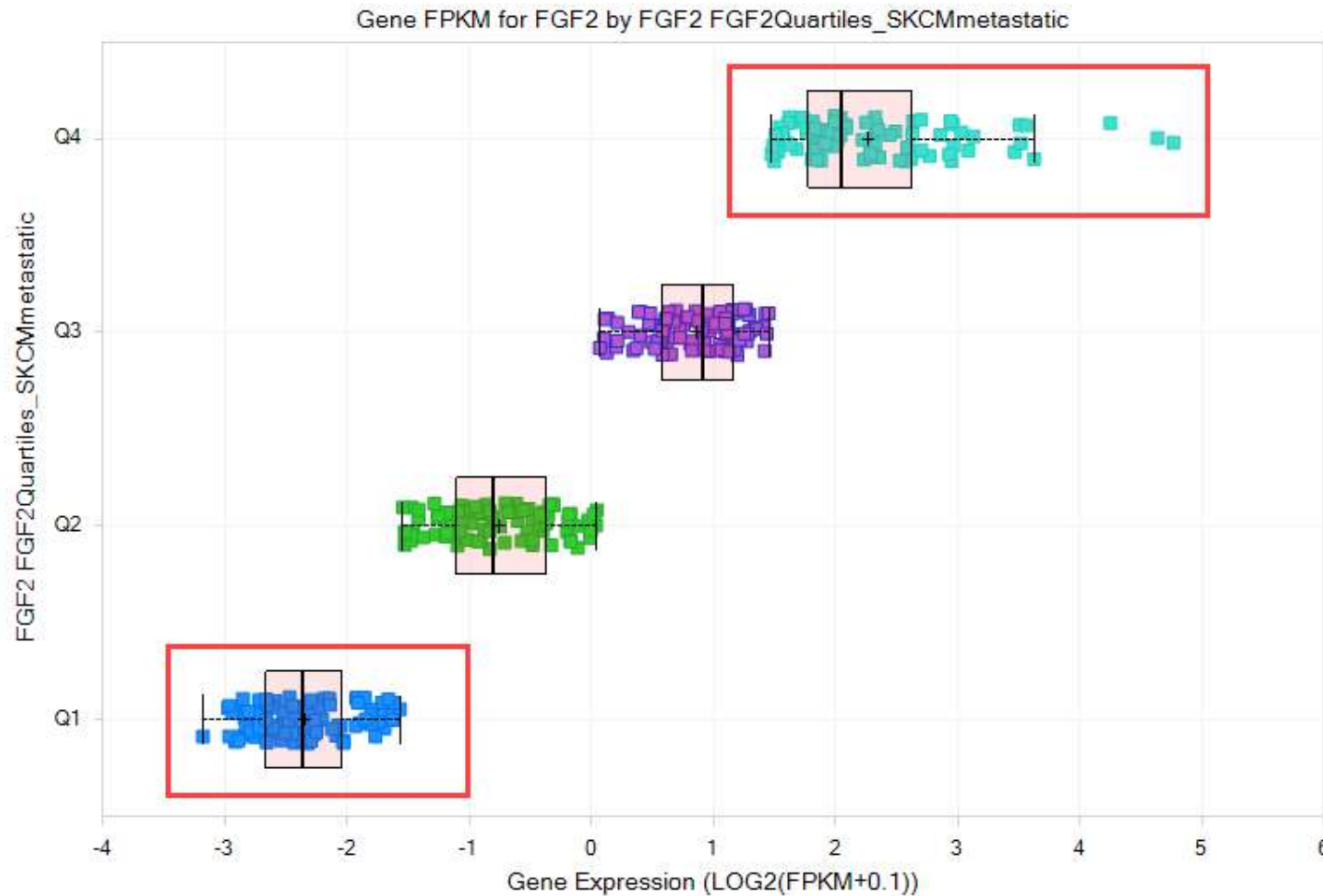
Next: Explore FGF2 in OncoLand

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

SampleGrouping/Mutation Integration

General Mutation Options

Land: TCGA_B38

SampleSet: SKCM metastatic by FGF2 Q1 Q4 [Choose](#) [Reset](#)

GeneSet: (all) [Input](#) [Choose](#) [Reset](#)

Group by: c (all)

Choose a method to derive sample grouping

☐ Choose a column from the meta data

☒ Choose a column from a sample set

Sample set: SKCM metastatic by FGF2 Q1 Q4

Column: F FGF2 FGF2 SKCMmetastatic

☐ Choose a column from local analysis

Data:

Column:

Mutation data: DnaSeq_SomaticMutation

Significance cutoff: 0.05

Use the provided sample grouping to scan the mutation of all genes. Report the correlation of all significant genes

Result set name: Mutated in SKCM metastatic by FGF2 Q1 vs Q4

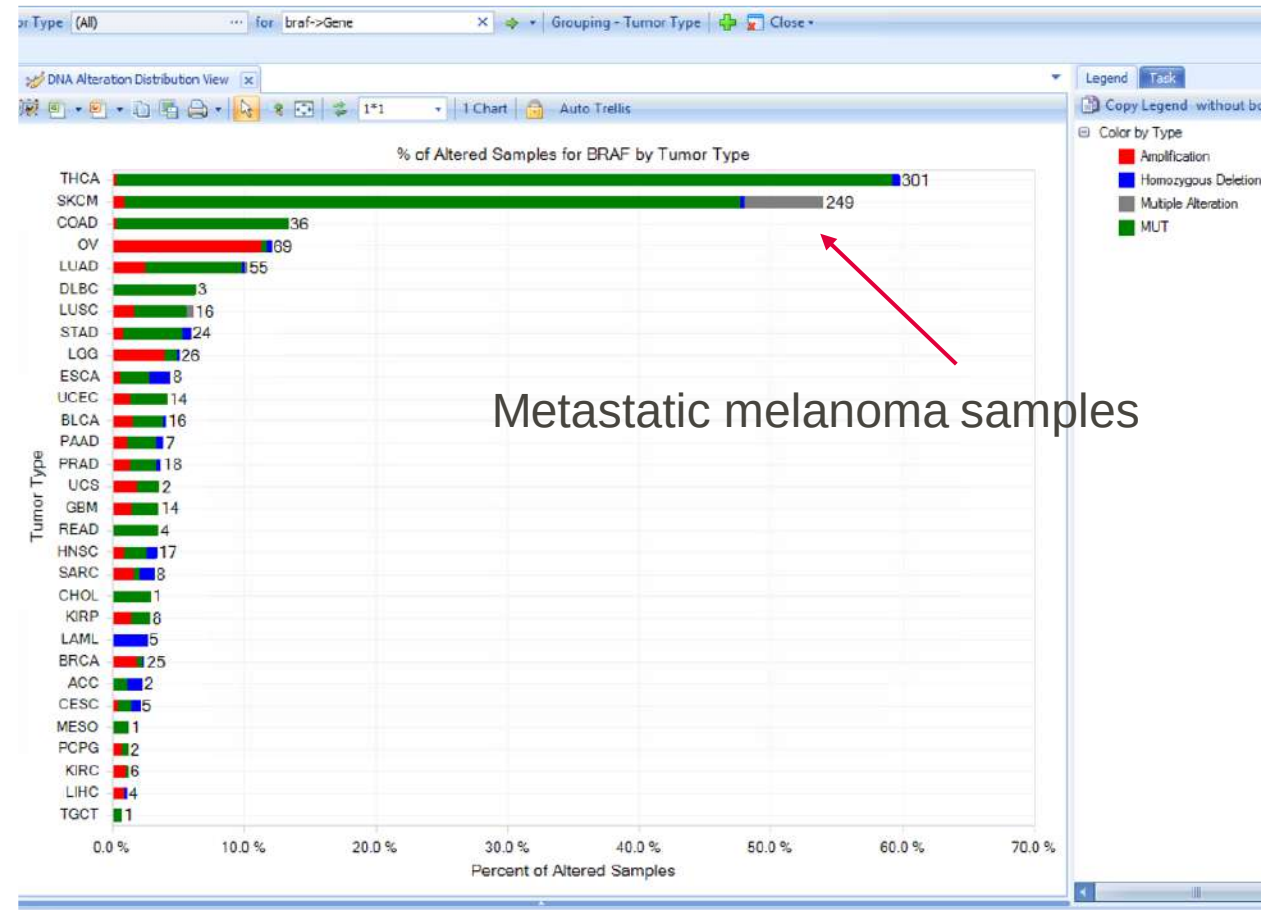
[Help](#) [Show Script](#) [Send To Queue](#) [Cancel](#)

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	<i>SULF1</i>	7194	1.495635474290e-005	0.0071
SVEP1	<i>SVEP1</i>	15269	3.718107130026e-005	0.0071
ENPEP	<i>ENPEP</i>	4995	4.673739698216e-005	0.0071
EPHA7	<i>EPHA7</i>	7489	5.273445707259e-005	0.0071
BRAF	<i>BRAF</i>	2946	5.700041690929e-005	0.0071
TLR4	<i>TLR4</i>	5781	0.0001	0.0107
TSHZ2	<i>TSHZ2</i>	12581	0.0001	0.0120
SMOC1	<i>SMOC1</i>	3698	0.0002	0.0120
ANO2	<i>ANO2</i>	5092	0.0002	0.0129
CGNL1	<i>CGNL1</i>	7339	0.0002	0.0129
MYO18B	<i>MYO18B</i>	8982	0.0002	0.0130
DOCK3	<i>DOCK3</i>	8755	0.0003	0.0130
IGDCC4	<i>IGDCC4</i>	6751	0.0003	0.0130

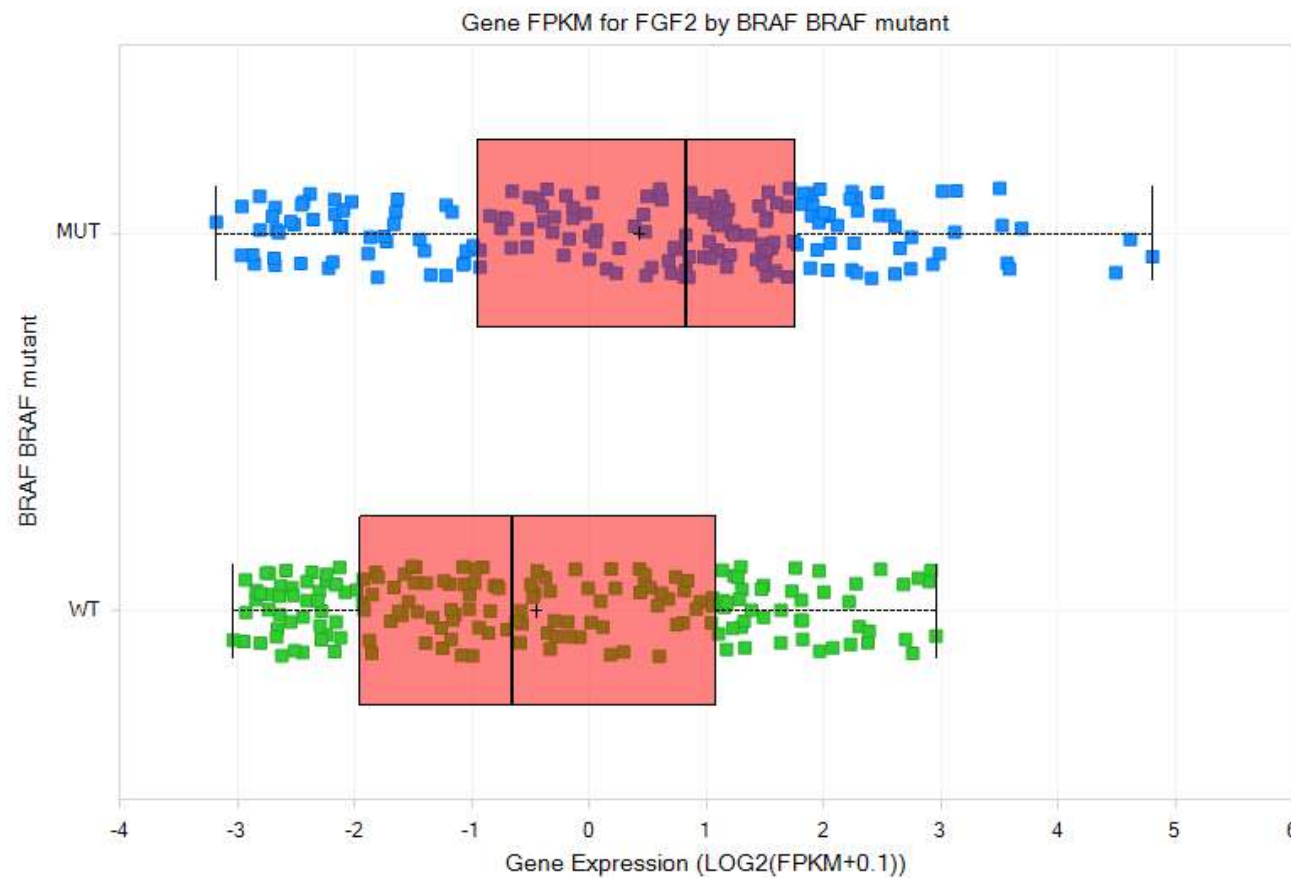
Leveraging vast amounts of public data in OmicSoft's OncoLand

BRAF alteration
frequency by tumor



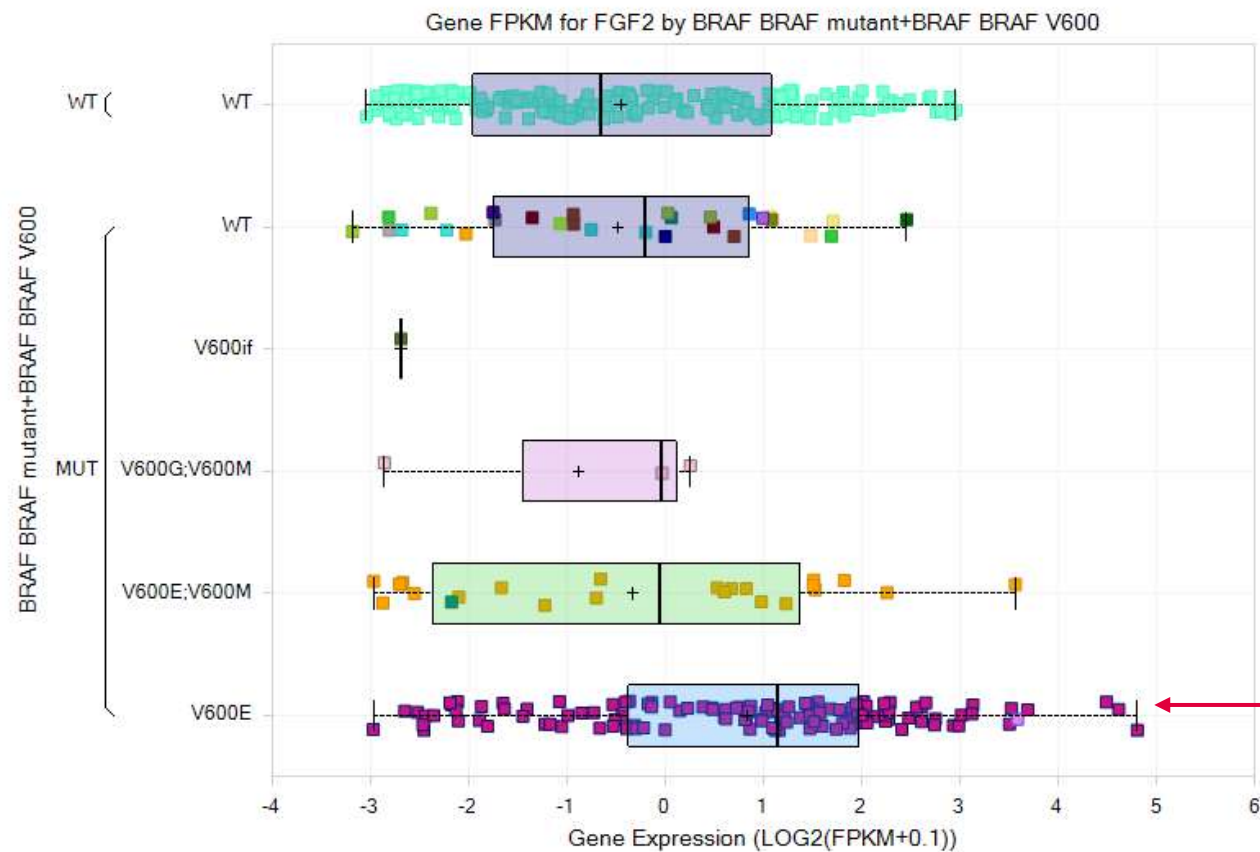
Metastatic melanoma samples

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

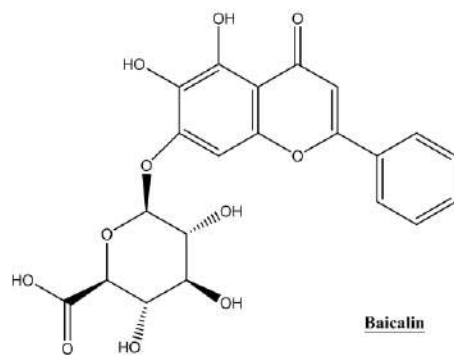
- What's new 2023 IPA Spring/Summer Release介紹
- 疾病與樣本 Metadata 整合分析
- 藥物潛在標的預測 IPA 與第三方軟體整合運用
- 你所不知道的 IPA 製圖技巧 外泌體研究案例分享

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.

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

西藥標靶藥物概念應用於中藥科學成份

西藥



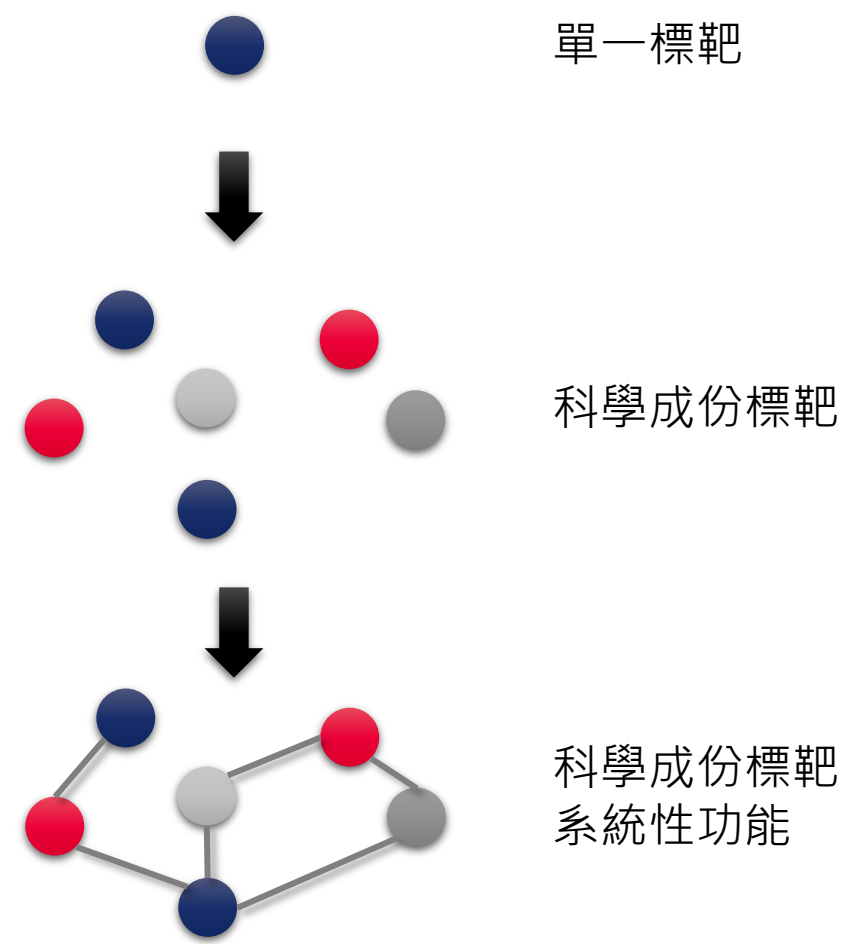
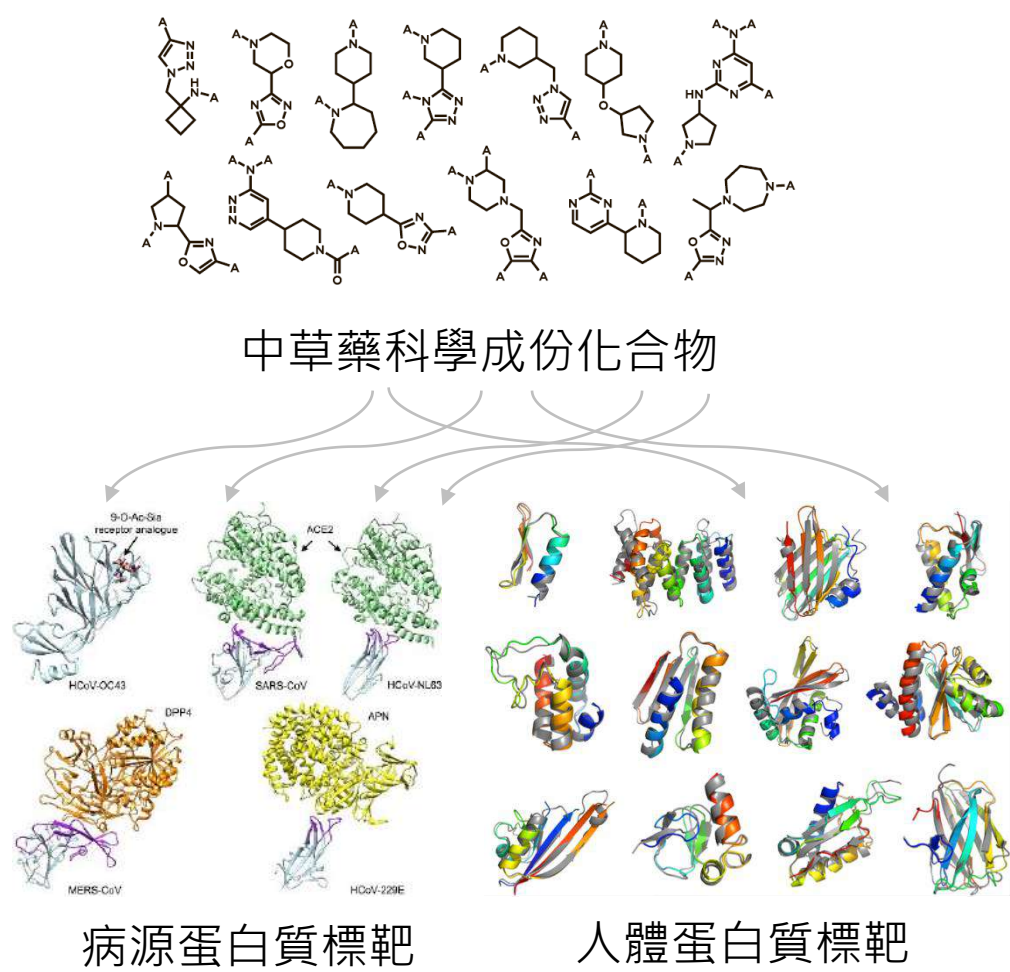
標靶藥物:標靶藥物包含所有可鎖定腫瘤細胞的療法，像是：荷爾蒙療法：鎖定驅動癌細胞生殖的荷爾蒙，阻斷其生成機制、受體、或下游訊息傳遞路徑

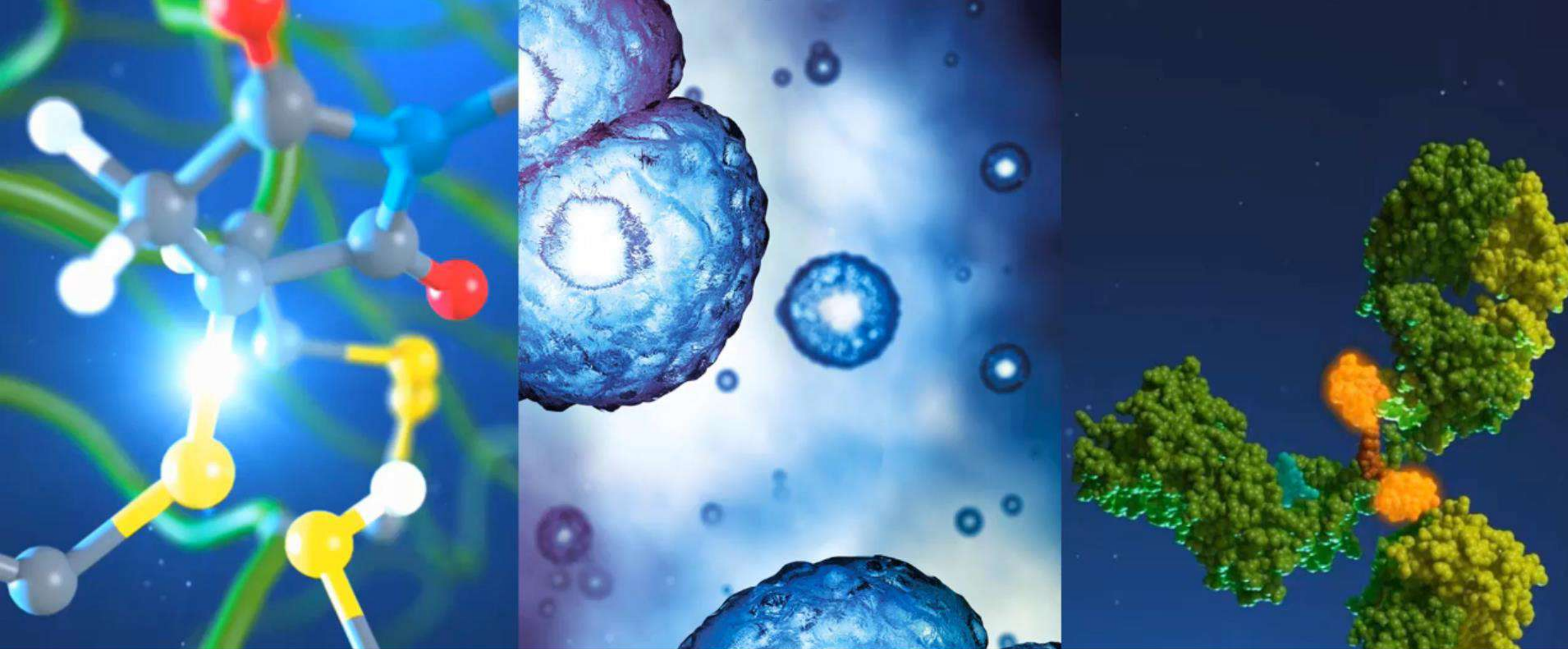
中藥



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

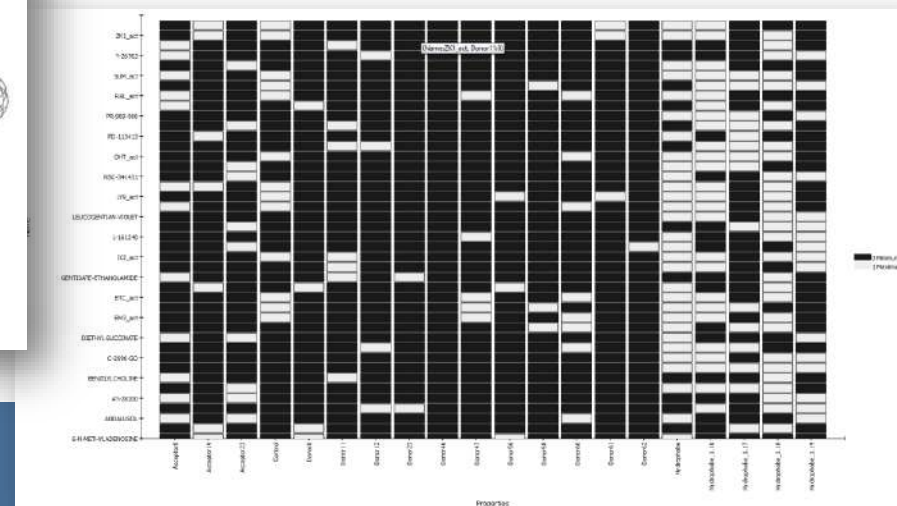
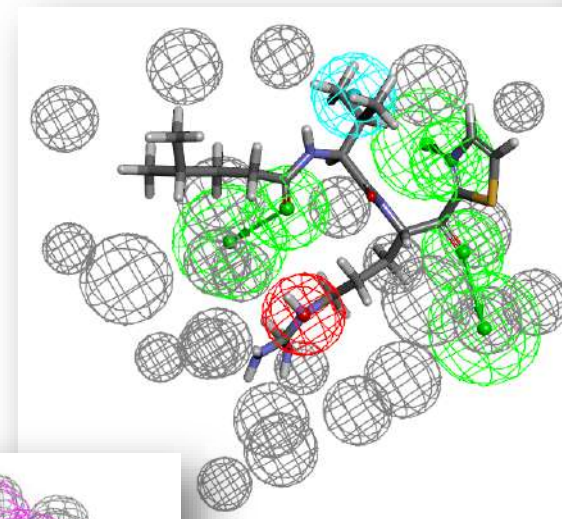
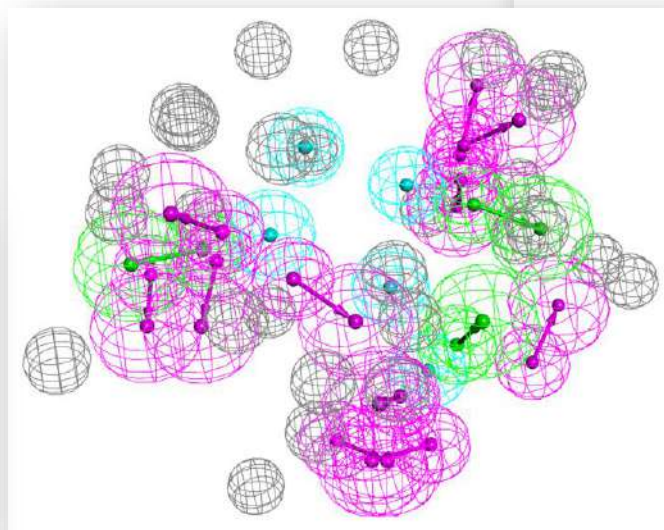




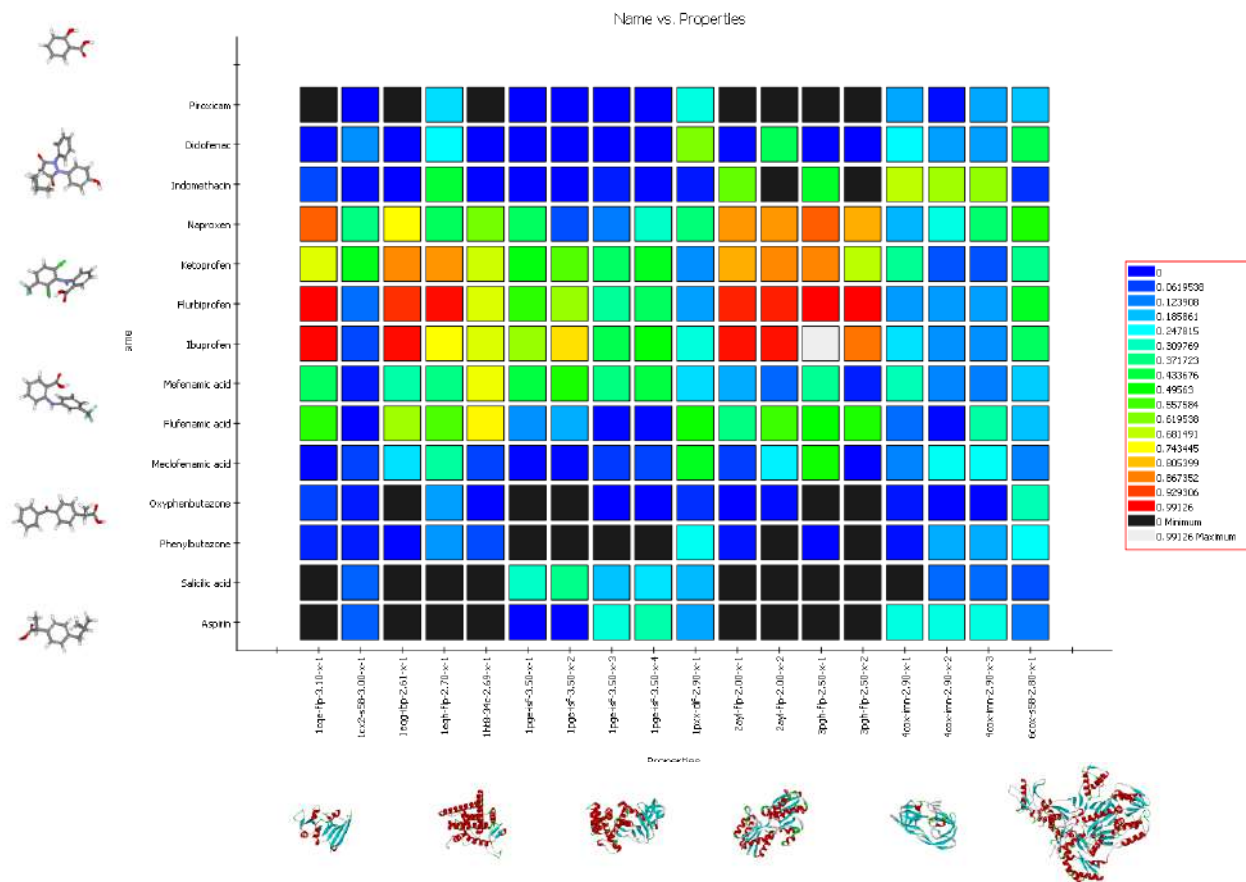
Discovery Studio

Small Molecule and Biologics Lead Identification & Optimization

- Automatic
 - Receptor-Ligand complex
 - Interactions from a binding site
 - Manual
 - Interaction map
 - Fragment-based
- 
- A decorative graphic in the bottom right corner consisting of several overlapping wireframe spheres of different sizes, rendered in a light gray color.



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
3lcn	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
1tm3	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
1w0li	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
2xlii	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



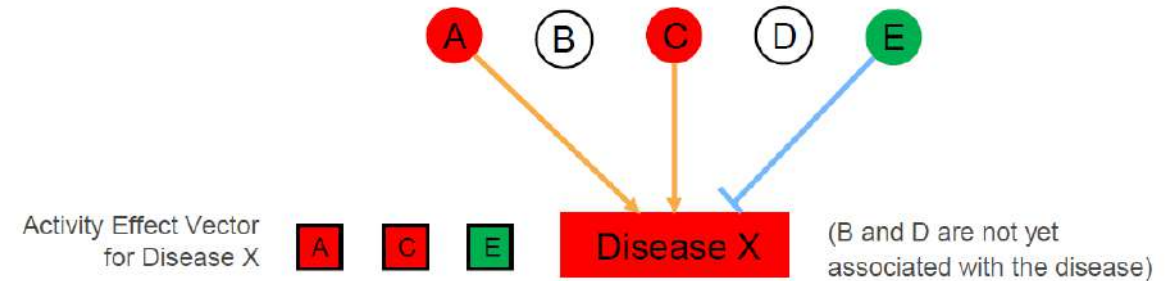
標靶
篩選

- 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

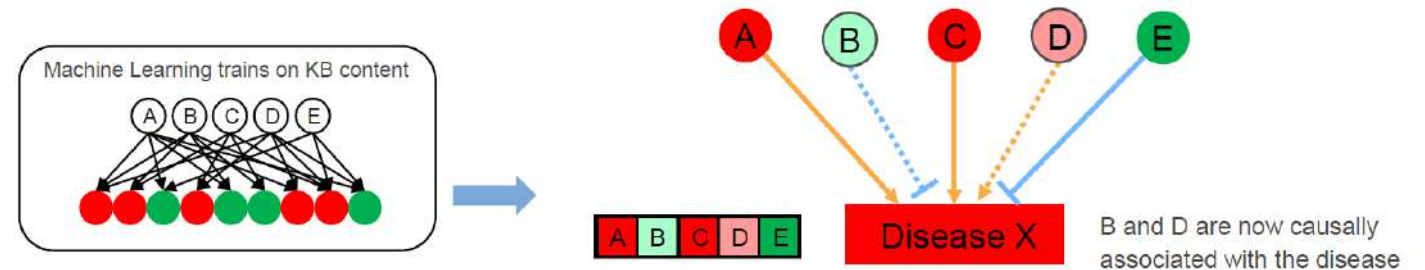
Standard KB

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



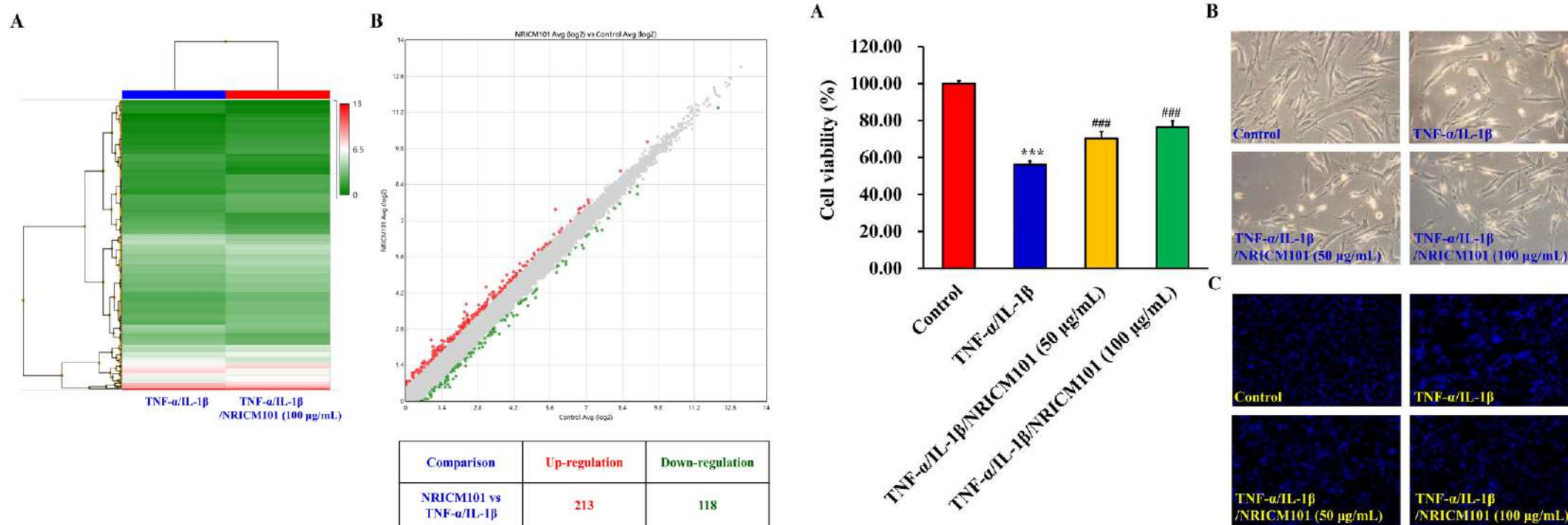
Enhanced KB

- 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.



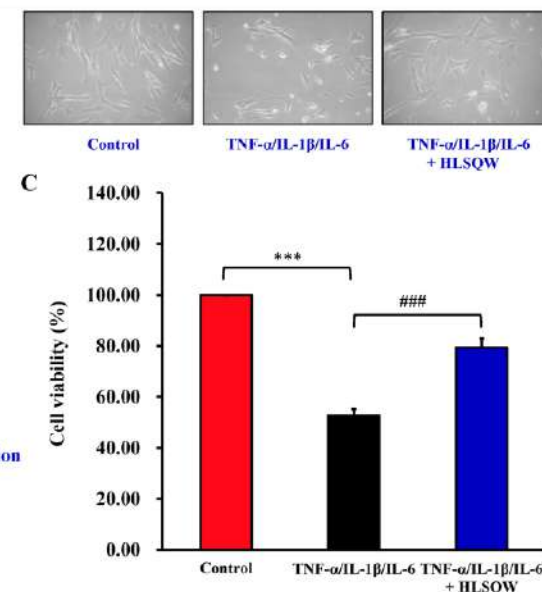
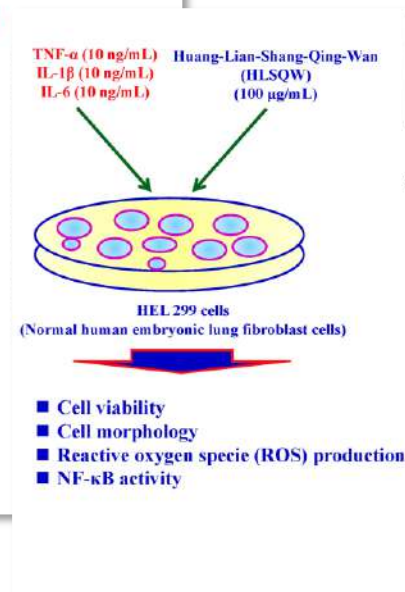
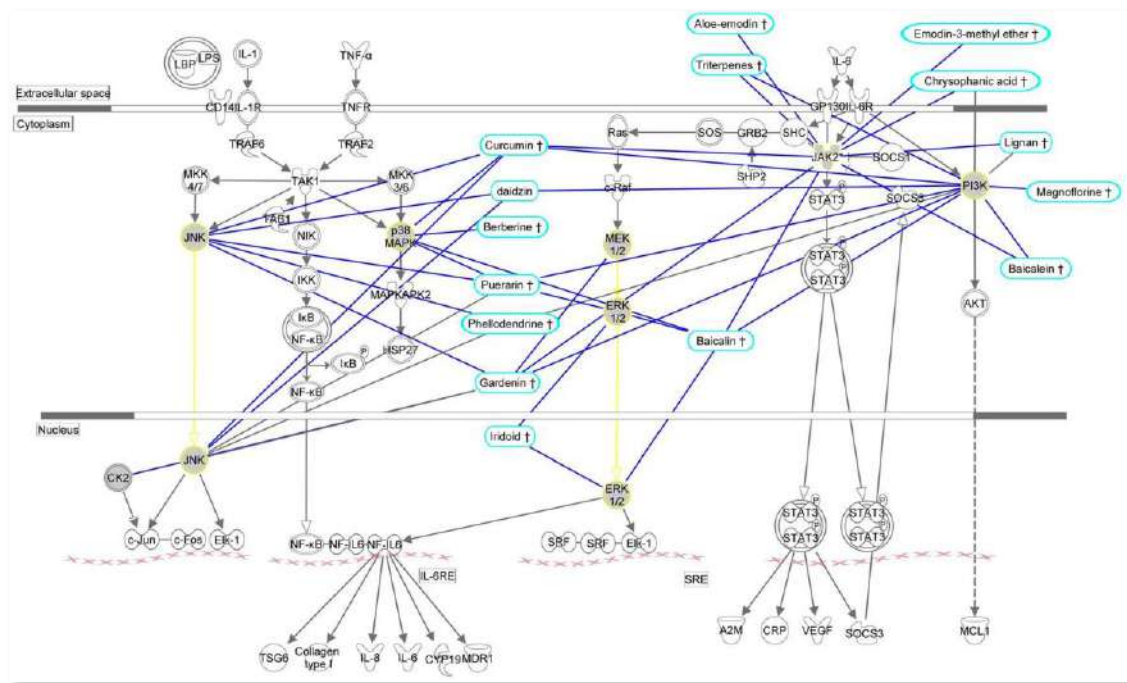
Activity Effect Vectors consist of thousands of molecules in the KB. The approach has been validated by “rediscovering” known, curated findings in the KB.

搭配NGS RNA-Sequencing技術，整合基因體表現資訊



- 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

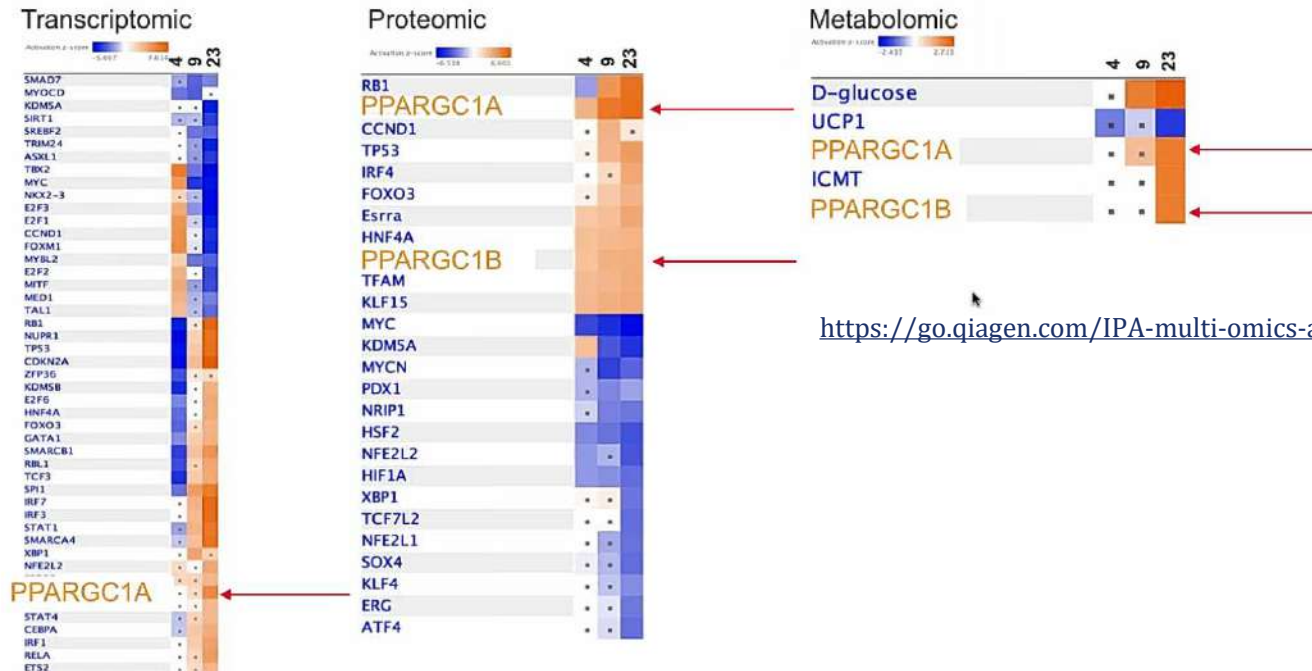
- What's new 2023 IPA Spring/Summer Release介紹
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- 藥物潛在標的預測 IPA 與第三方軟體整合運用
- 你所不知道的 IPA 製圖技巧 外泌體研究案例分享

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

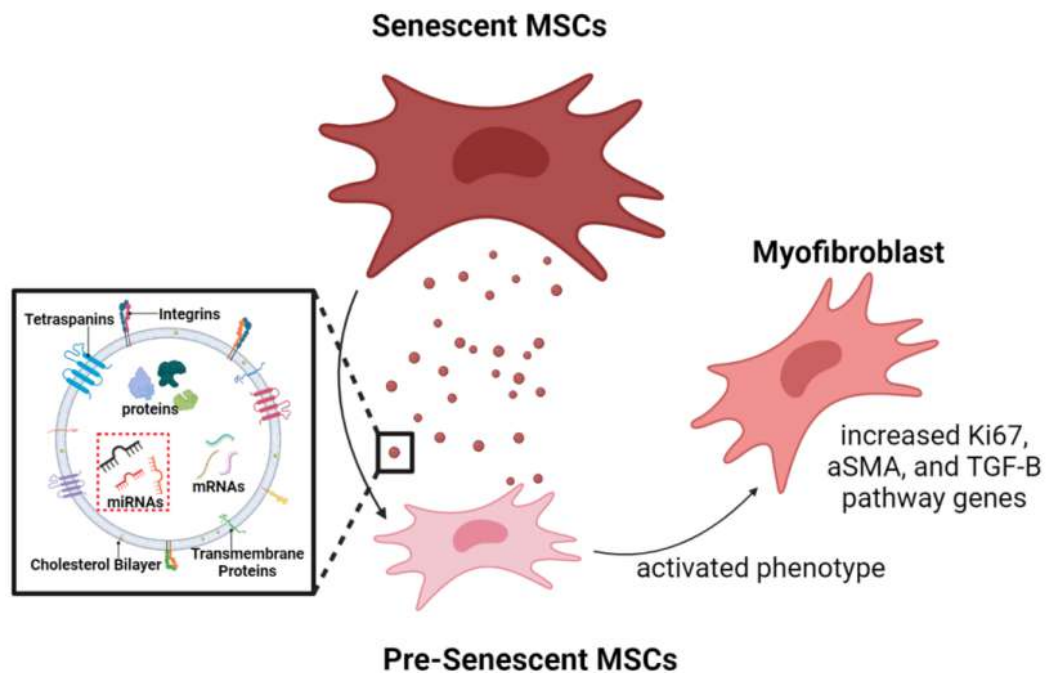
Multi-omics analysis indicate similar transcriptional drivers

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

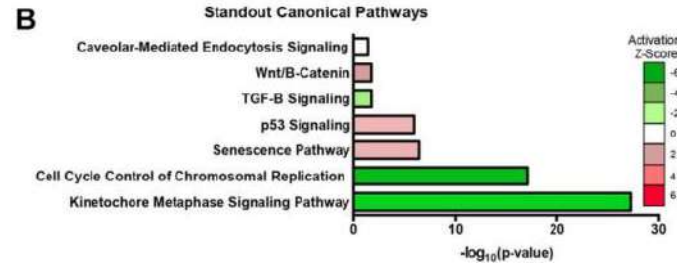
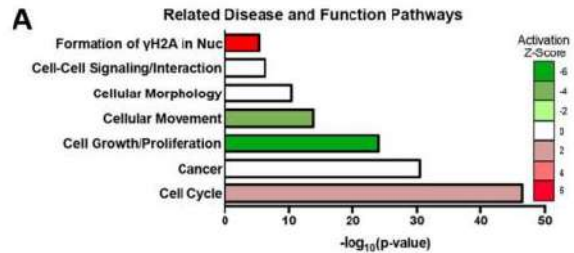


- Senescent MSCs如何影響周遭細胞？
- 主要關鍵成分是什麼？

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	Sen	Pre-Sen		
-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%	17.88	16.51		LAMC1
1.39	2.10E-03	23%	11.85	10.46		NFASC
1.45	2.00E-04	8%	17.85	16.2		CCND1
3.48	4.53E-06	2%	14.95	11.37		LAMC2

E TGFβ

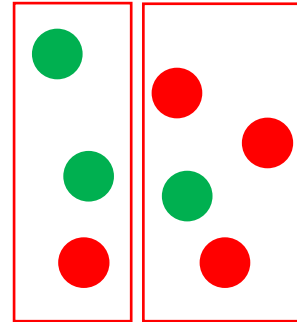
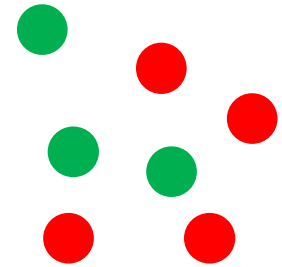
Sen/Pre-Sen			Sen/Pre-Sen			Gene Sym
Fold	p-value	FDR	Sen	Pre-Sen		
-1.8	3.00E-04	9%	7.95	9.78		RBL1
-1.4	1.50E-03	20%	10.2	11.55		E2F4
-1.1	2.40E-03	24%	11.17	12.29		TFDP1
-1	9.00E-04	16%	12.29	13.33		SP1
1.19	2.30E-03	24%	15.8	14.61		SMURF2

Expression data from Transcriptome Analysis

Find related Function/Phenotypes by pathway analysis

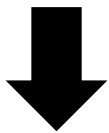
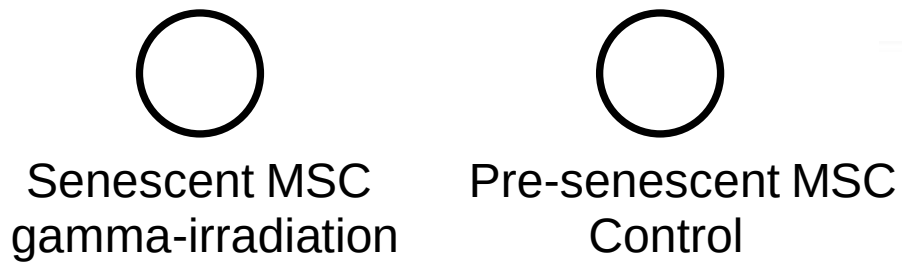
Allocate specific gene in related pathway/function

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



Pathway A Function A

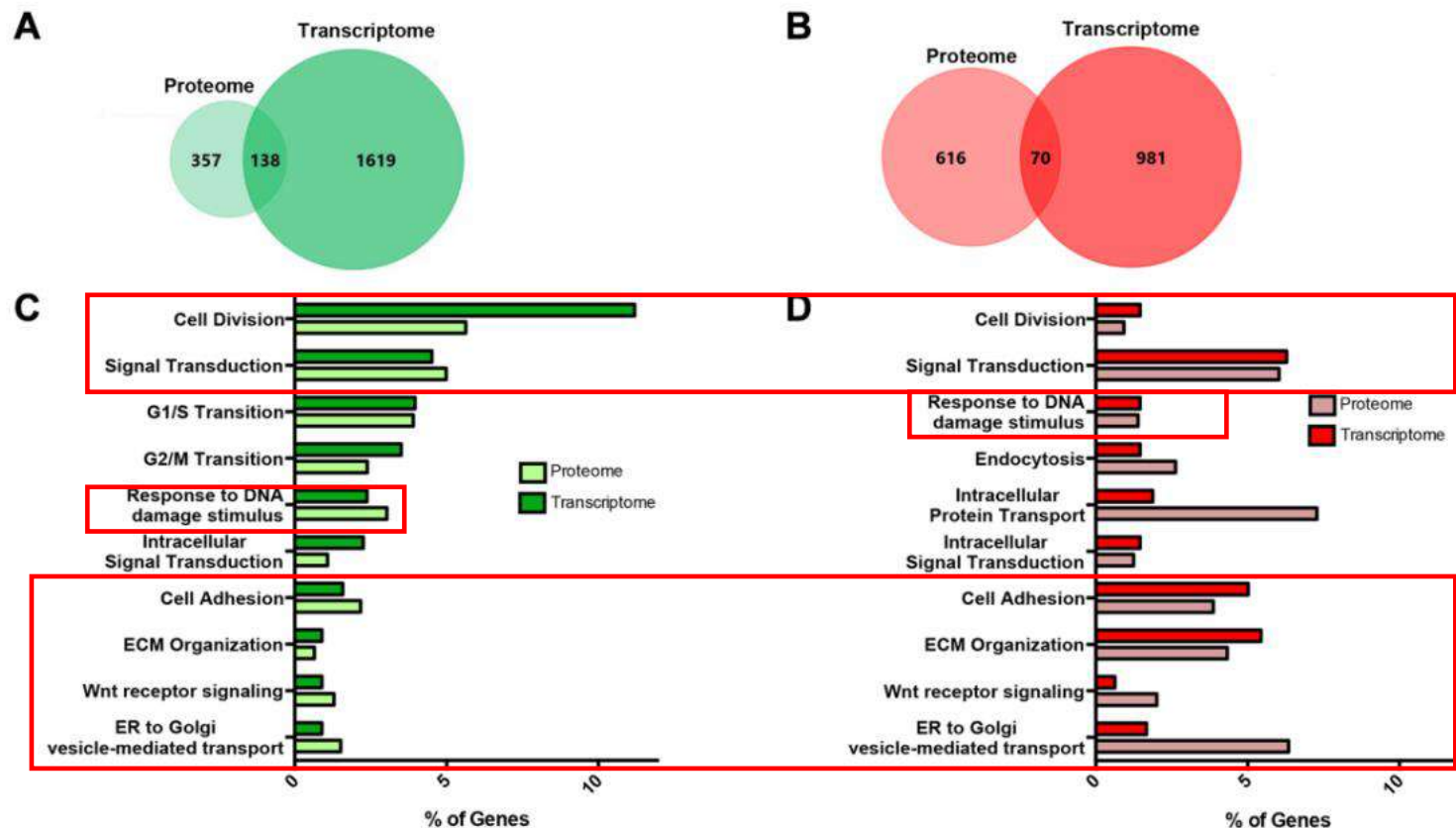




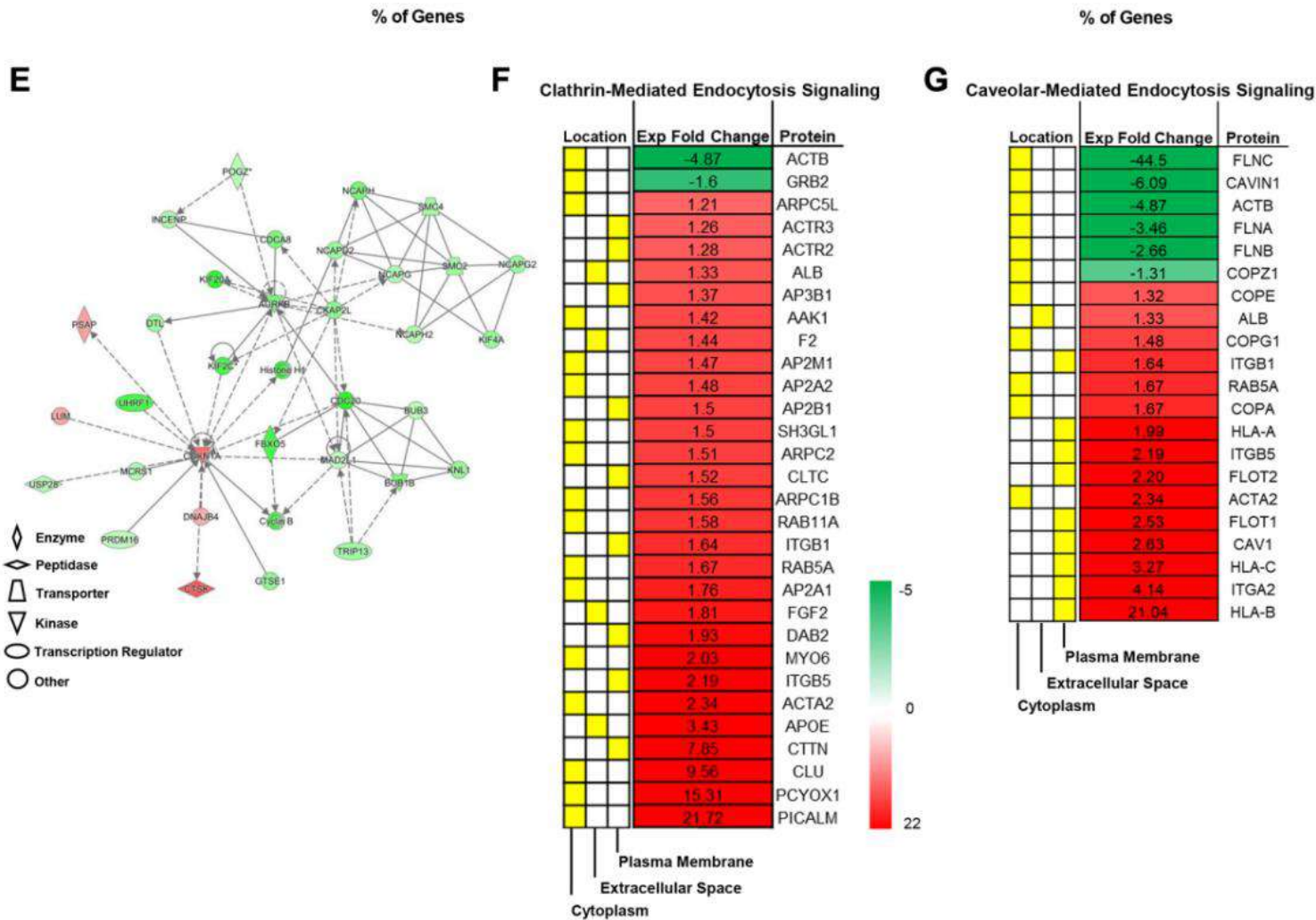
Transcriptome Expression Data

+

Proteomic Expression Data

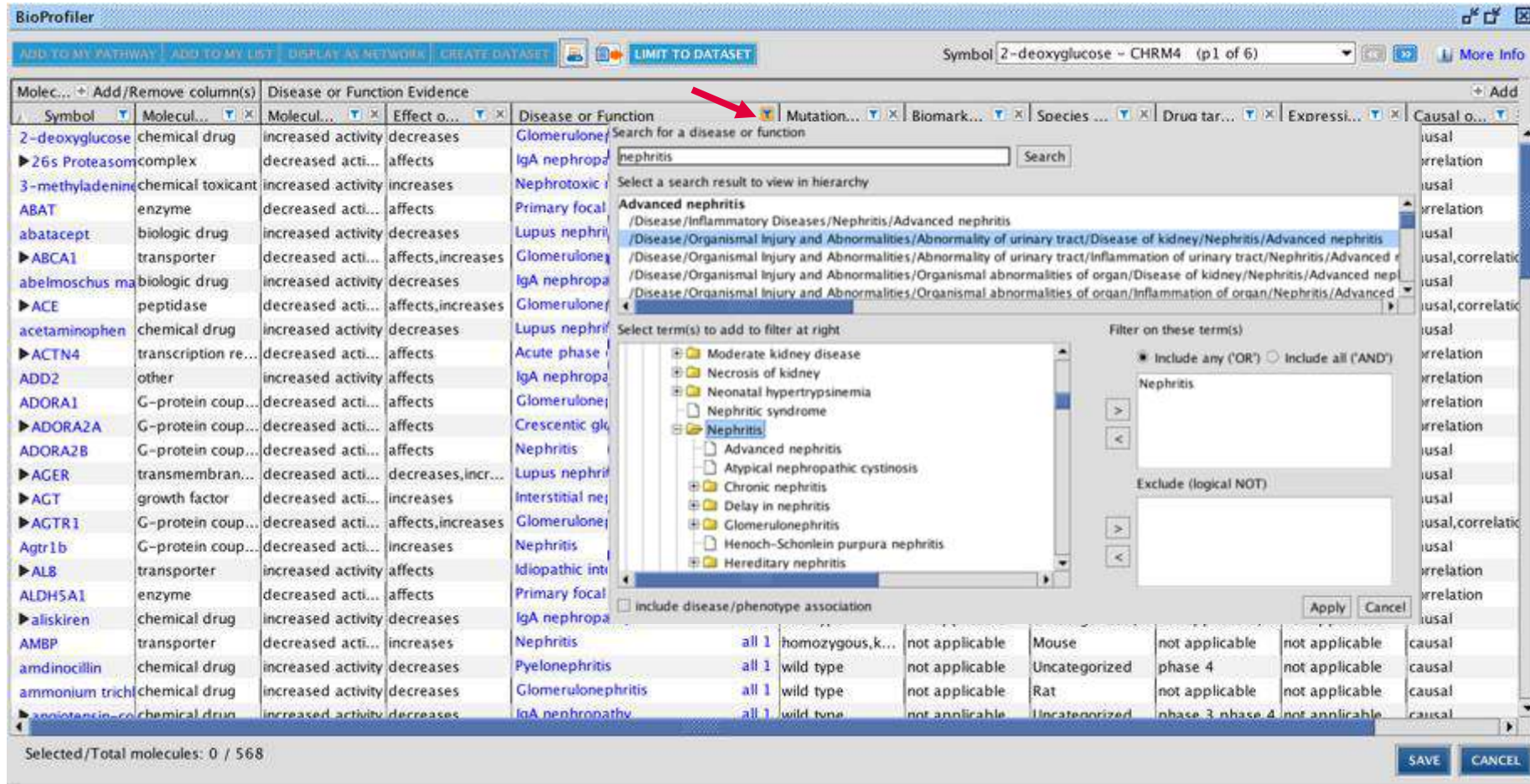


- 蛋白質體與轉錄體的分析結果有高度重疊，基因表現與Cell Division、DNA damage、Adhesion等功能高度相關



- 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。

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



The screenshot shows the BioProfiler web application. The main table lists molecules and their associated diseases/functions. A search for 'nephritis' is active, and a list of nephritis subtypes is displayed on the right. A red arrow points to the 'Disease or Function' column header.

Symbol	Molecule	Effect on	Disease or Function	Mutation	Biomarker	Species	Drug target	Expression	Causal relationship
2-deoxyglucose	chemical drug	increased activity	decreases	Glomerulonephritis					causal
26s Proteasome	complex	decreased activity	affects	IgA nephropathy					causal
3-methyladenine	chemical toxicant	increased activity	increases	Nephrotoxicity					causal
ABAT	enzyme	decreased activity	affects	Primary focal glomerulonephritis					causal
abatacept	biologic drug	increased activity	decreases	Lupus nephritis					causal
ABCA1	transporter	decreased activity	affects, increases	Glomerulonephritis					causal, correlation
abelmoschus mamboc	biologic drug	increased activity	decreases	IgA nephropathy					causal
ACE	peptidase	decreased activity	affects, increases	Glomerulonephritis					causal, correlation
acetaminophen	chemical drug	increased activity	decreases	Lupus nephritis					causal
ACTN4	transcription re...	decreased activity	affects	Acute phase response					causal
ADD2	other	increased activity	affects	IgA nephropathy					causal
ADORA1	G-protein coup...	decreased activity	affects	Glomerulonephritis					causal
ADORA2A	G-protein coup...	decreased activity	affects	Crescentic glomerulonephritis					causal
ADORA2B	G-protein coup...	decreased activity	affects	Nephritis					causal
AGER	transmembran...	decreased activity	decreases, increases	Lupus nephritis					causal
AGT	growth factor	decreased activity	increases	Interstitial nephritis					causal
AGTR1	G-protein coup...	decreased activity	affects, increases	Glomerulonephritis					causal, correlation
Agtr1b	G-protein coup...	decreased activity	increases	Nephritis					causal
ALB	transporter	increased activity	affects	Idiopathic interstitial nephritis					causal
ALDH5A1	enzyme	decreased activity	affects	Primary focal glomerulonephritis					causal
aliskiren	chemical drug	increased activity	decreases	IgA nephropathy					causal
AMBP	transporter	decreased activity	increases	Nephritis					causal
amdinocillin	chemical drug	increased activity	decreases	Pyelonephritis					causal
ammonium trichloroacetate	chemical drug	increased activity	decreases	Glomerulonephritis					causal
amniotin...	chemical drug	increased activity	decreases	IgA nephropathy					causal

Selected/Total molecules: 0 / 568

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



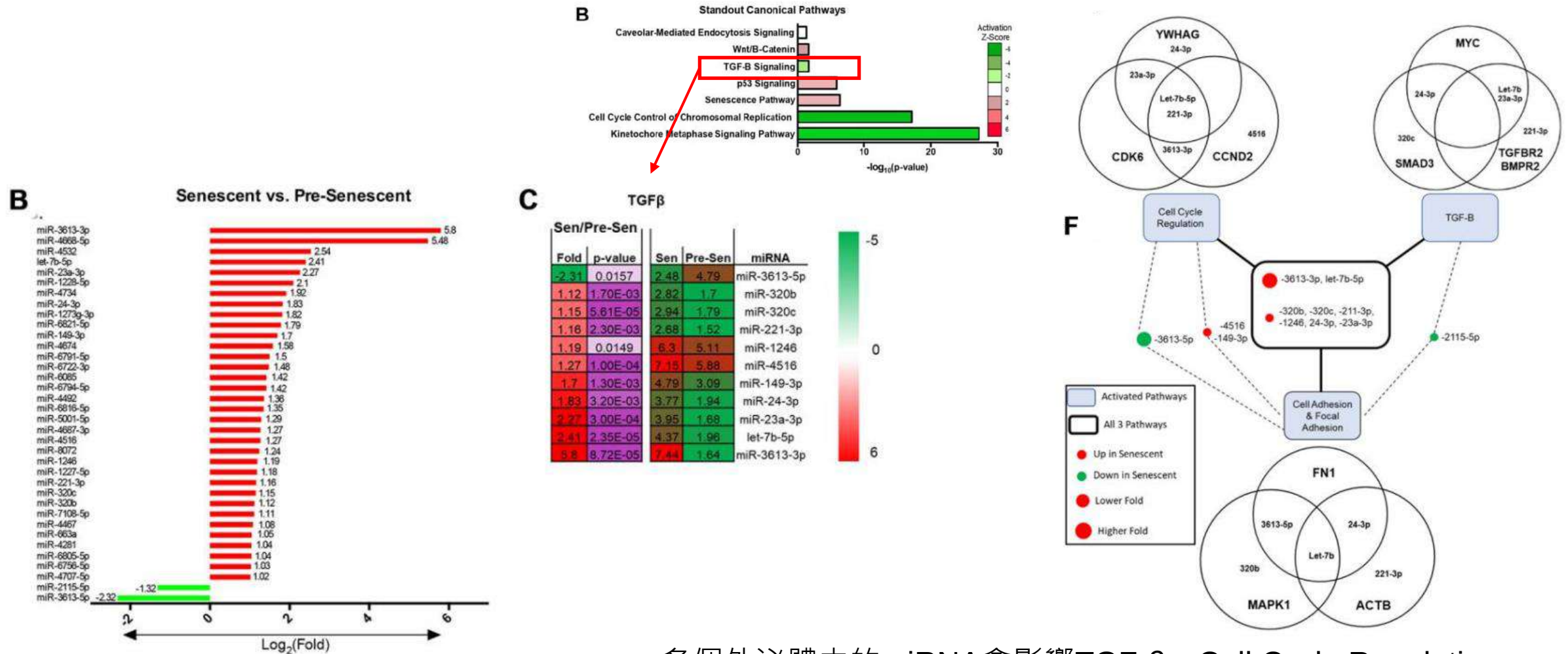
- Which genes when [decreased] in activity [increase] [liver cholestasis]? What types of [genetic] evidence support this?

Target discovery:

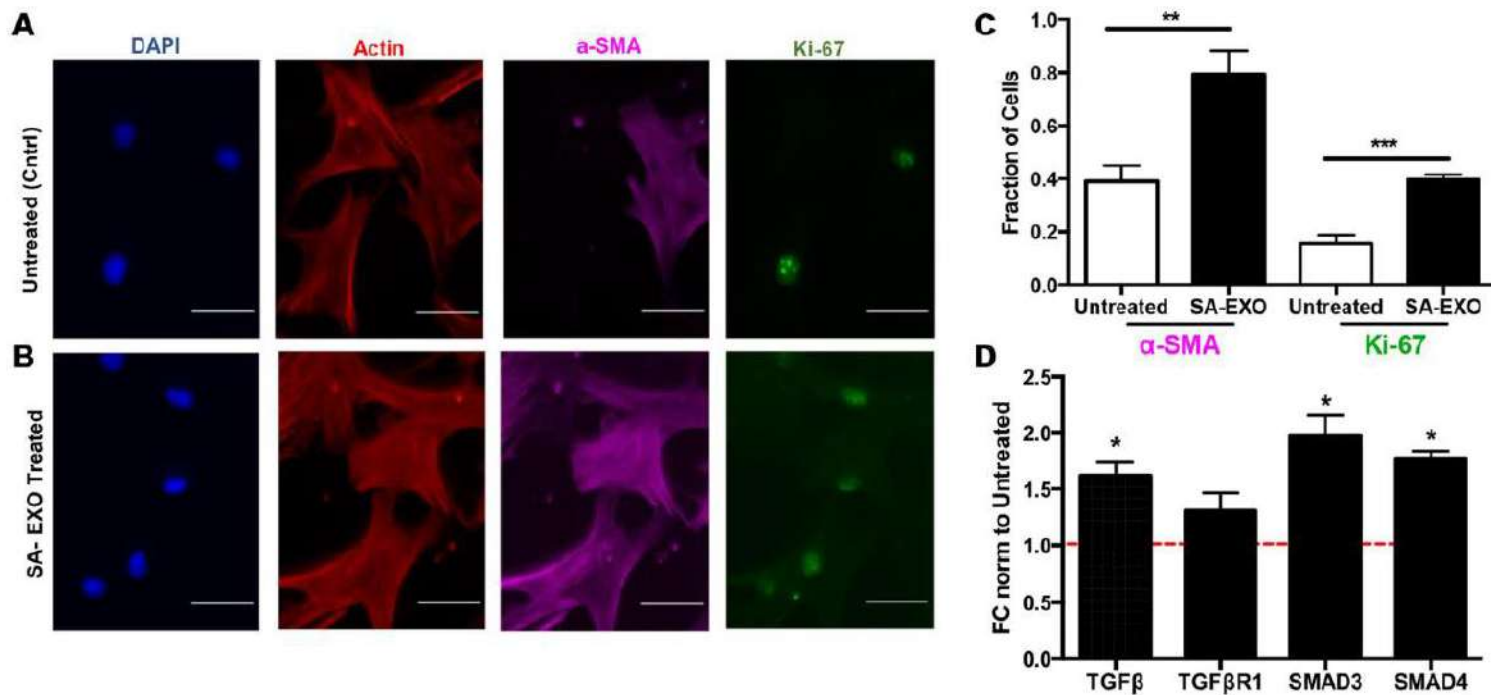
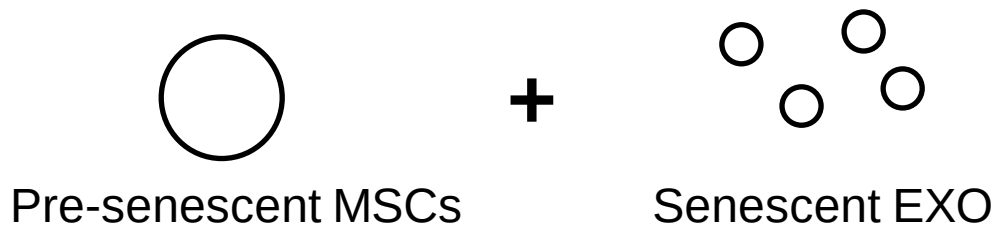
- What [heterozygous knockouts] in [mouse] can [decrease] [asthma]?
- Which drugs or which targets have been in late stage clinical trials or approved to decrease [diabetes]?

Biomarker research:

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



- 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



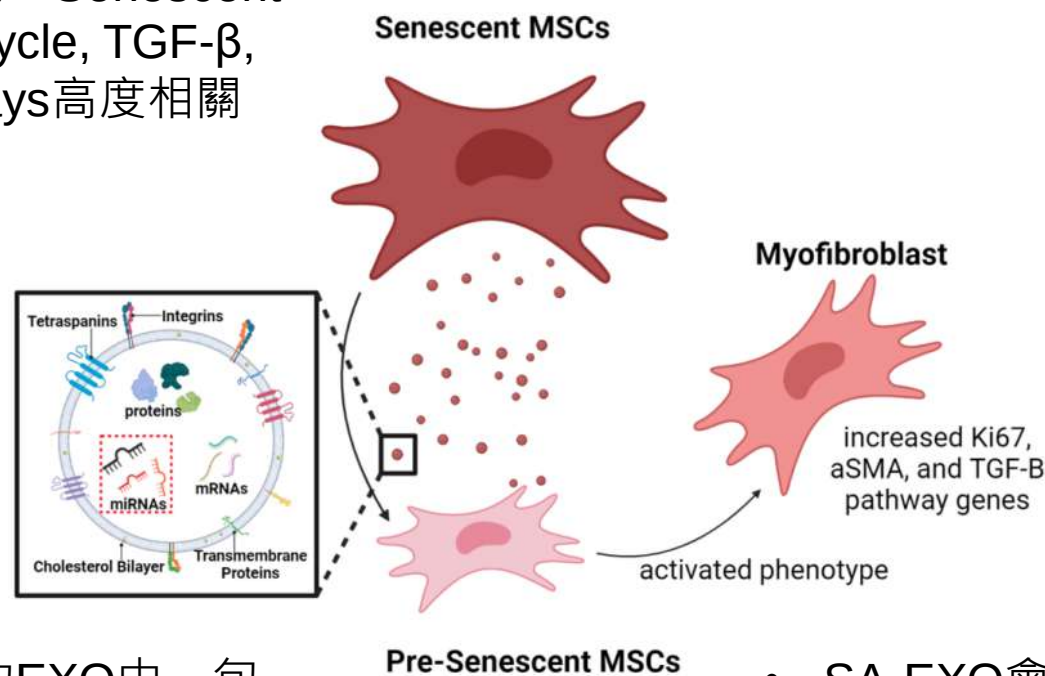
- EXO提升了α-SMA、Ki-67、TGF-β、SMAD3等基因表現

- 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

◆ 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

◆ 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。



- 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	○	○	○	
代謝體	○	○	○	
毒物分析	○	○	○	
Enrichment Analysis結果視覺化表現	○	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	○	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	○	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	○	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	○	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	○	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	○	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	Metacore	KEGG	Note
其他功能				
生物特性篩選	○	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	○	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	○	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	○	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	○	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	○	○ (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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