HACKIN' OMICS

Functional genomics analysis using Pathways, Annotated Gene Lists and Gene Signatures Electronic Repository (PAGER)

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Mentor: Jake Y. Chen, Ph.D.

Institute: UAB Informatics Institute

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Published works

Database

- Zongliang Yue#, Eric Zhang#, Clark Xu, Sunny Khurana, Nishant Batra, Son Dang, and Jake Y. Chen* (2021) PAGER-CoV: A Pathway, Annotated-list and Gene-signature Electronic Repository for Coronavirus Diseases Studies. Nucleic Acids Research, Volume 49, Issue D1, Pages D589–D599, https://doi.org/10.1093/nar/gkaa1094
- Zongliang Yue, Qi Zheng, Michael T Neylon, Minjae Yoo, Jimin Shin, Zhiying Zhao, Aik Choon Tan, Jake Y Chen, (2018) PAGER 2.0: an update to the pathway, annotated-list and gene-signature electronic repository for Human Network Biology, Nucleic Acids Research, Volume 46, Issue D1, Pages D668–D676,https://doi.org/10.1093/nar/gkx1040
- Zongliang Yue, Madhura M. Kshirsagar, Thanh Nguyen, Chayaporn Suphavilai, Michael T. Neylon, Liugen Zhu, Timothy Ratliff, Jake Y. Chen, (2015) PAGER: constructing PAGs and new PAG–PAG relationships for network biology, Bioinformatics, Volume 31, Issue 12,, Pages i250–i257,https://doi.org/10.1093/bioinformatics/btv265

Method & Application

- Zongliang Yue, Radomir Slominski, Samuel Bharti, Jake Y Chen* (2022) PAGER Web APP: An interactive, online gene set and network interpretation tool for functional genomics, Frontiers in Genetics, https://doi.org/10.3389/fgene.2022.820361
- Zongliang Yue, Michael T. Neylon, Thanh Nguyen, Timothy Ratliff, and Jake Y. Chen* (2017) "Super gene set" causal relationship discovery from functional genomics data, IEEE Transactions on Computational Biology and Bioinformatics, DOI: 10.1109/TCBB.2018.2858755
- Jake Y. Chen*, Zongliang Yue, Michael T. Neylon, Thanh Nguyen, Nafisa Bulsara, Itika Arora, and Timothy Ratliff (2016) Towards constructing "Super Gene Sets" regulatory networks. Proceeding of the 2016 international Conference on Bioinformatics, & Biomedicine, Shenzhen, China, doi:10.1109/BIBM.2016.7822534
- Chayaporn Suphavilai, Liugen Zhu, and Jake Y. Chen* (2015) A method for developing regulatory gene set networks to characterize complex biological systems. BMC Genomics, Vol.16, Suppl.11, S4
- Chayaporn Suphavilai, Liugen Zhu, and Jake Y. Chen* (2014) Constructing regulatory gene set networks to reveal novel insights into biological systems. Vol.10, Suppl.11, S5.

Integrative Gene-set, Network, and Pathway Analysis (GNPA)

RNA-SEQ

Exome

Chip-seq

Upstream Analysis

Format Conversation → Data Extraction → Noise Reduction → Statistical Analysis

- **Extension of sequencing pipeline**
- **Automated,**
- **Mature, CPU/Disk intensive**

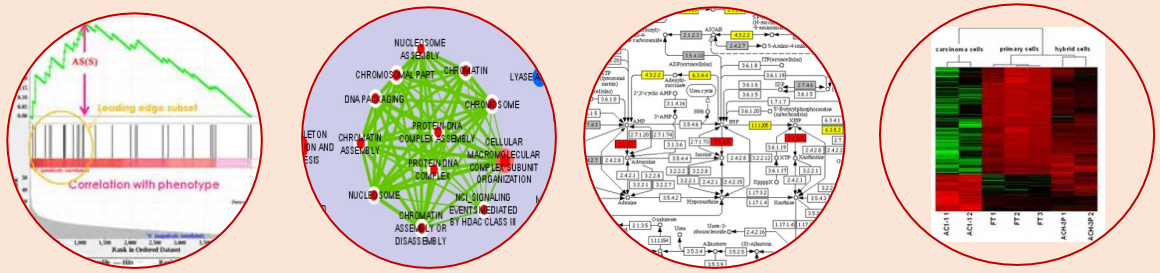
Integrative Omics Analysis

Biological Data Analysis → Ranking & Hypothesis Generation

- **Time-consuming**
- **Many tools**
- **Specialists required**
- **Immature**

Downstream Analysis

Wet Lab Validation → Publication & Sharing



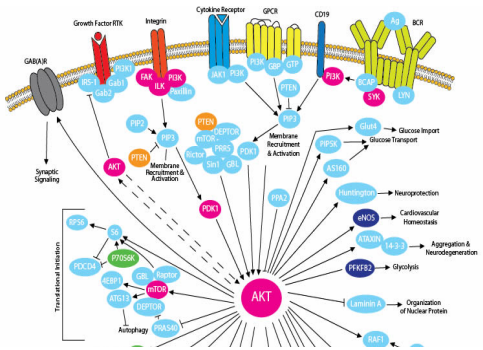
Can we characterize large Omics data sets in their complex biomolecular systems context, while performing integrated **GNPA** to improve biomedical discovery potential?

PAG to represent a “Super Gene Set”

- It is a new data representation concept called **PAG** to support integrative GNPA
  - Each PAG = a set of genes + curation
  - Optional information: weights, structure, data links, …

Pathways

From RNA-seq, microarrays, proteomics, …



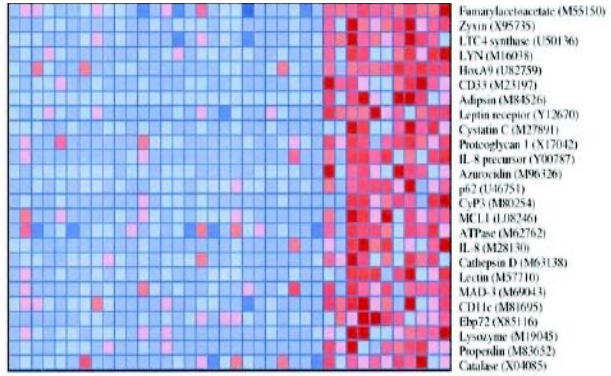
Annotated lists

From RNA-seq, microarrays, proteomics, …

Locus	Gene	Inheritance
PARK1/4	*SNCA*	AD
PARK2	*PARK2*	AR
PARK3	?	AD
PARK5	*UCHL1*	?
PARK6	*PINK1*	AR
PARK7	*DJ-1*	AR
PARK8	*LRRK2*	AD
PARK9	*ATP13A2*	AR

Gene signatures

From RNA-seq, microarrays, proteomics, …



An example PAG: “FAX003040”

Functional genomics

Curated from literature

No interactions

FAX003040 GSEA Hallmark Pancreatic Cancer Tissue Explants (Extracellular Vesicles) -- Epithelial Mesenchymal Transition

PAG Summary

PAG Title	GSEA Hallmark Pancreatic Cancer Tissue Explants (Extracellular Vesicles) -- Epithelial Mesenchymal Transition
PAG ID	FAX003040
Type	A (Annotated-lists)
Source Link	Cell
Publication Reference	Hoshino A, Kim HS, Bojmar L, et al. Extracellular Vesicle and Particle Biomarkers Define Multiple Human Cancers. Cell. 2020;182(4):1044-1061.e18. doi:10.1016/j.cell.2020.07.009
PAG Description	Top 3 pathways enriched in pancreatic cancer tissue extract extracellular vesicle particles compared to matched pancreas adjacent tissue using Hallmark gene sets (GSEA)
Species	Homo sapiens
Curator	PAGER curation team
Curator Contact	PAGER-contact@googlegroups.com
nCoCo Score	709
Base PAG ID	FAX003040
Human Phenotyte Annotation	Bulbous tips of toes; Fragmented epiphyses; Recurrent loss of toenails and fingernails

PAG Members

Total number of genes: 53

Show 15 rows | Download As | Search:

Gene ID	Gene symbol	Gene name	RP_score
2335	FN1	fibronectin 1	21.66
3688	ITGB1	integrin subunit beta 1	16.57
3693	ITGB5	integrin subunit beta 5	16.06
3685	ITGAV	integrin subunit alpha V	14.71
3690	ITGB3	integrin subunit beta 3	13.84
3673	ITGA2	integrin subunit alpha 2	13.21
3678	ITGA5	integrin subunit alpha 5	12.59
7057	THBS1	thrombospondin 1	10.36
960	CD44	CD44 molecule (Indian blood group)	10.21
1311	COMP	cartilage oligomeric matrix protein	8.17
2316	FLNA	filamin A	8.03
3918	LAMC2	laminin subunit gamma 2	7.44

Related PAGs

Top-ranked neighbors

1. Genes in the cancer module 47
2. The diagnosis of Transitional cell carcinoma (stage iii) in Posterior wall of bladder (TCGA-DK-A3IQ FPKM>=100)
3. The diagnosis of Infiltrating duct carcinoma, NOS (stage iia) in Pancreas, NOS (TCGA-IB-7893 FPKM>=100)
4. GO:0030198 biological_process extracellular matrix organization
5. The diagnosis of Metaplastic carcinoma, NOS (stage iia) in Breast, NOS (TCGA-BH-A6R9 FPKM>=100)

more...

Top-ranked upstream regulatory PAGs

1. GO:0009889 biological_process regulation of biosynthetic process
2. GO:0031326 biological_process regulation of cellular biosynthetic process
3. GO:0019219 biological_process regulation of nucleobase-containing compound metabolic process
4. GO:0010556 biological_process regulation of macromolecule biosynthetic process
5. GO:0031325 biological_process positive regulation of cellular metabolic process

more...

Top-ranked downstream regulatory PAGs

1. GO:0051716 biological_process cellular response to stimulus
2. GO:0070887 biological_process cellular response to chemical stimulus
3. Lymphoma Melendez05 4229genes

http://discovery.informatics.uab.edu/PAGER/index.php/geneset/view/FAX003040

PAG naming Standard

PAG ID Standard Naming Convention

A1	A2	A3	d	d	d	d	d	d

Pos #1: Type of data (A1)	
T..	Ontology
W..	Pathway
G..	Genomics/Epigenomics
F..	Functional genomics
P..	Proteomics
M..	Chemical Perturbations
B..	Metabolomics
R..	PAGER data
N..	Single Gene

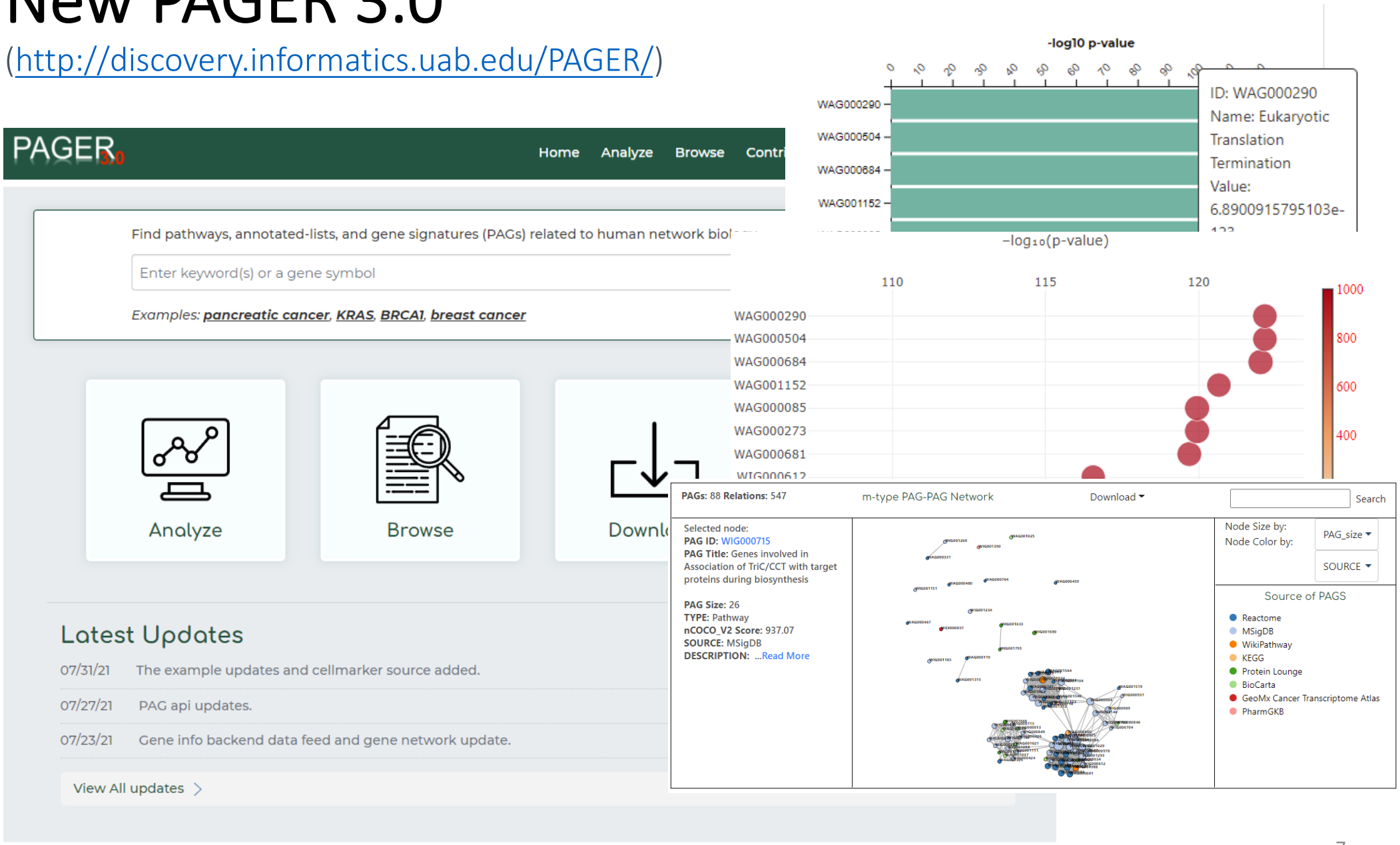
Pos #2: Derivation method (A2)	
.E.	Experimentally derived
.O.	Computationally predicted
.A.	Curated from literature
.U.	Unknown/Uncharacterized
.I.	Known missing curation

Pos #3: Relationship details (A3)	
..X	No relationship mapped
..I	Some interactions
..J	Interactions + interaction parameters
..G	Some regulatory data
..H	Regulatory data + regulation parameters
..R	Some chemical reaction data
..S	Chemical reactions + reaction parameters
..M	Model (regulatory and reaction data)
..P	Parameterized model (regulatory and reaction data + parameters)

Yue et al (2015) Bioinformatics, Vol. 31, No. 12, pp. i250-i257

New PAGER 3.0

(http://discovery.informatics.uab.edu/PAGER/)



Yue, et al, PAGER 3.0: an update to a comprehensive database of human pathways, annotated gene lists, and gene signatures for system-scale characterization of Omics data (unpublished)

PAG data coverage in PAGER 3.0

Data Type	Data Source	Number	Type	Version
Diseases	GAD	1671	G	1
	GWAS Catalog	1230	G	1
	Phewas	1358	G	2
Gene Expression Signatures	MSigDB	8,377	P,G	1
	GeneSigDB	2942	G	1
	MSigDB-ImmuneSigDB	4852	G	2
Drug-Gene Interactions	PharmGKB	102	P	1
	DSigDB	22455	G	2
Genes	Genome Data	17363	N	1
Proteins	Protein Lounge	388	P	1
	Pfam	1161	A	2
	Isozyme	484	G	2
	HPA-normProtein	105	G	3
Pathways	SPIKE	28	P	1
	WikiPathway	144	P	1
	HPD-Reactome	528	P	1
	HPD-BioCarta	252	P	1
	HPD-NCI_Nature Curated	132	P	1
	HPD-KEGG	199	P	1
	GeoMx Cancer Transcriptome Atlas	110	P	3
miRNA-Gene Interactions	Microcosm Targets	851	G	2
	TargetScan	390	G	2
	mirTARbase	2603	G	2
Tissue Specific Expressions	NGS Catalog	56	G	1
	GTEx	92	A	2
	HPA-TCGA	7932	G	3
	HPA-PathologyAtlas	20	G	3
	HPA-GTEx	34	G	3
	HPA-FANTOM5	45	G	3
	HPA-normRNA	43	G	3
	HPA-RNAcon	62	G	3
Functional Annotations	GOA	21894	A	2
Interactome	I2D	15874	G	3
Literature curated	Cell	22	A	3
Cell Specific Expression	HPA-CellAtlas	31	G	3

Data summary

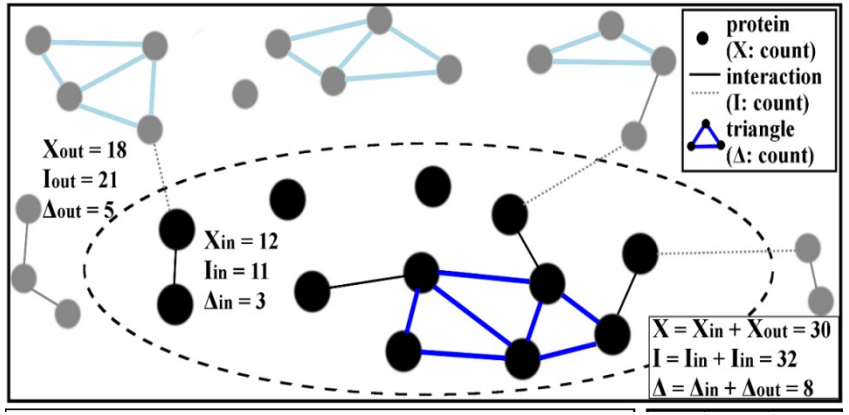
	PAGER3
Genes in PAGs	27,746
Gene-Gene Relationships	601,164
PPI	578,587
Gene Regulation	22,127
PAG	113,830
singleton PAG	33,083
multiton PAG	80,747
with CoCo score >=1	74,461
PAG-PAG pairs	42,960,619
m-type (similarity>=0.15,-logPMF>=10)	40,753,308
r-type (-logPMF>=5)	2,207,311

CoCo score: gauging biological relatedness of genes inside a PAG

Yue et al (2015) Bioinformatics, Vol. 31, No. 12, pp. i250-i257

CoCo (Cohesion Coefficient):

- ***CoCo = CoI + CoT***
- ***CoI***: Cohesion from enriched protein-protein interaction pairs
- ***CoT***: Cohesion from enriched protein-protein interaction triangles



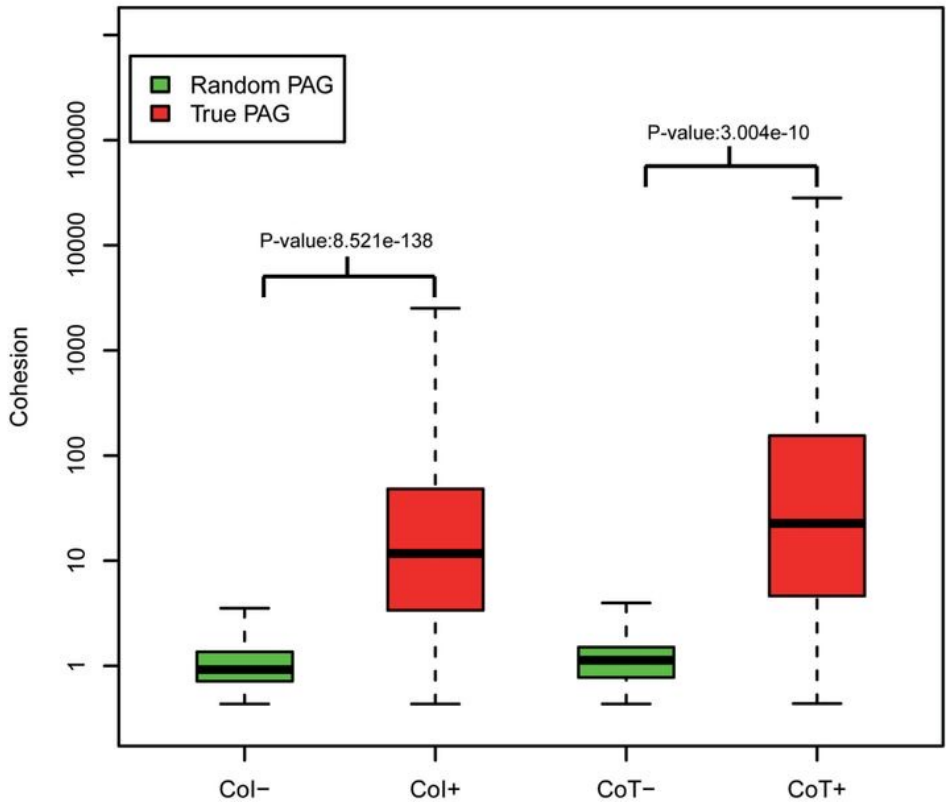
The score indicates the significance test results of enriched interaction pairs (I) and enriched interaction triangles (T) within a PAG.

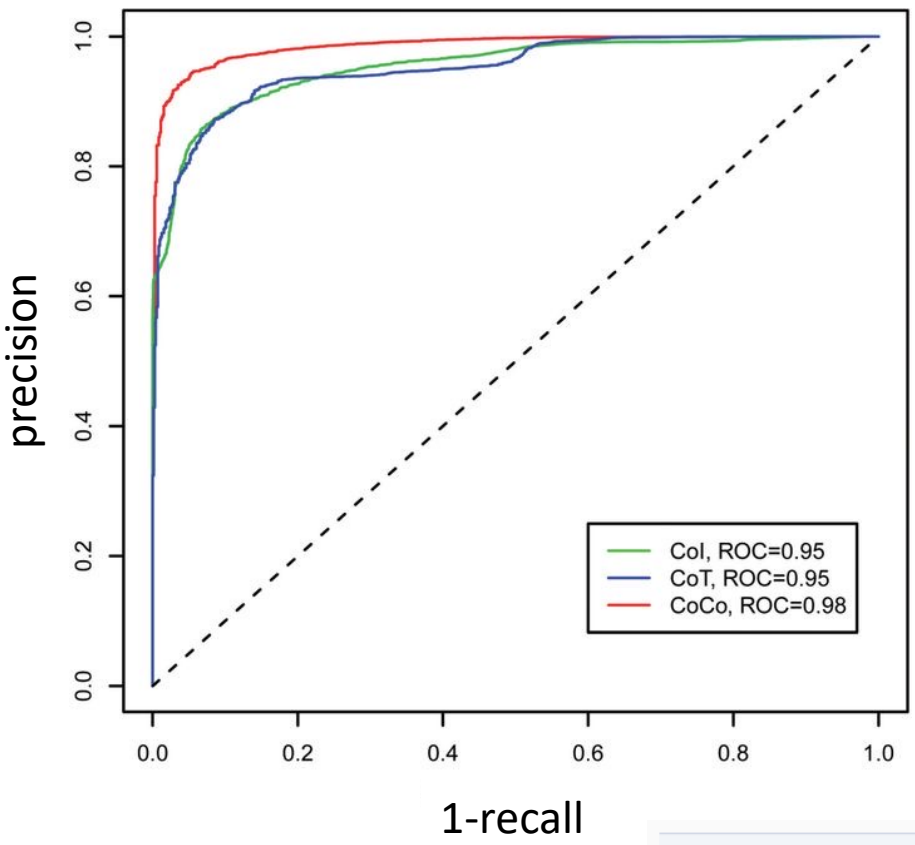
We calculate hypergeometric cumulative distribution function (CDF) value for CoI, e.g., using the formula:

$$CoI(p) = sign\left(\frac{n}{k} - \frac{N}{K}\right) \times -log_{10}\left(\sum_{t=k}^{min\,(n,K)} \frac{\binom{K}{t}\binom{N-K}{n-t}}{\binom{N}{n}}\right)$$

in which N is the number of theoretical PPIs in Π, $K = |I_\Pi|$ is the number of actual PPIs in the referenced database, n=(|PAG_i|×(|PAG_i|−1))/2n=(|PAG_i|×(|PAG_i|−1))/2is the theoretical number of PPIs inside PAG *i*, and $k = |I_i|$ is the number of actual PPIs inside PAG *i*.

CoI or CoT as a PAG quality metric





Randomly generated PAGs are size-matched to recorded true PAGs.

Yue et al (2015) Bioinformatics, Vol. 31, No. 12, pp. i250-i257

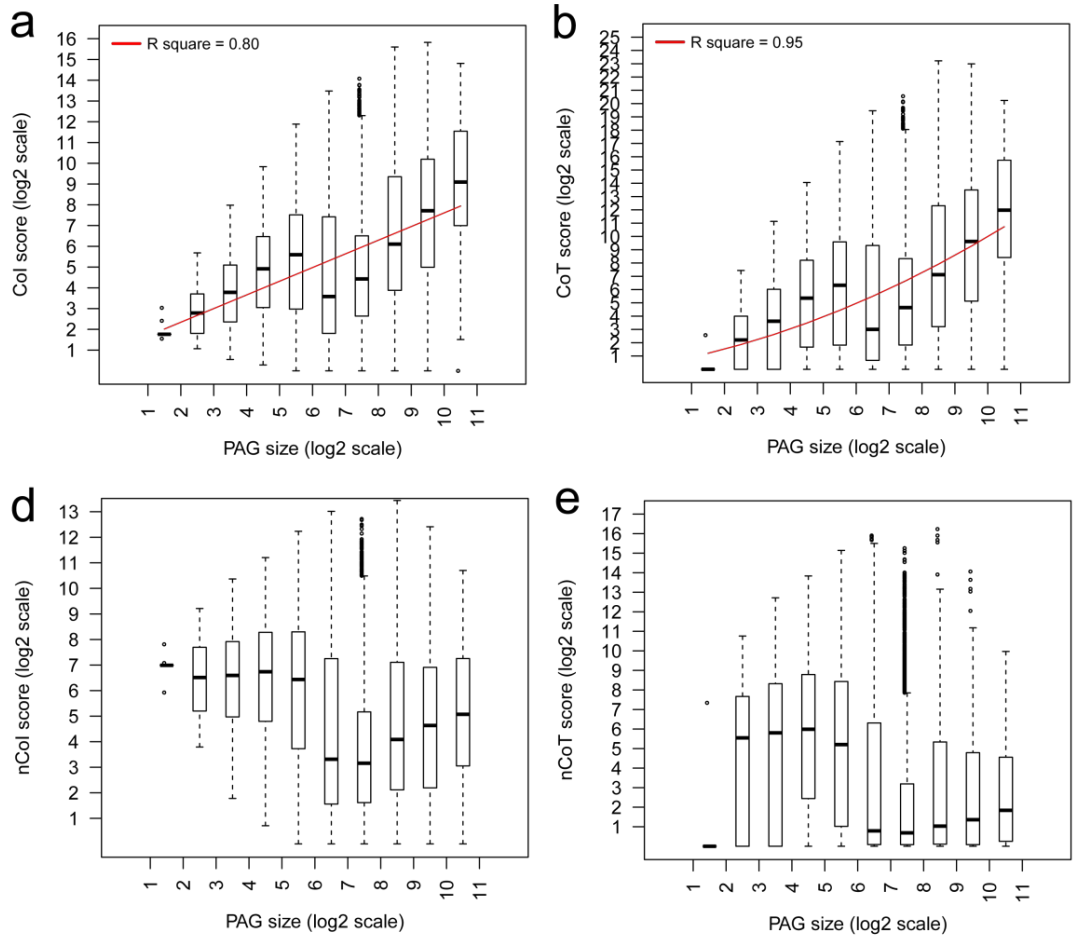
CoI is better for large-sized PAGs
CoT is better for small-sized PAGs
CoCo achieves a good balance overall

	AUC (size <100)	AUC (size >300)
CoI	0.953	**0.987**
CoT	**0.962**	0.979

Size bias and corrections (nCoCo)

Before

After



***CoI* and *CoT* normalization.** (a) The relationship of PAG size and *CoI* score, (b) the relationship of PAG size and *nCoI* score, (d) the relationship of PAG size and *nCoT* score, (e) the *CoI*, *CoT*, *CoCo* score distribution of PAGER

An example of comparing the PAG quality using *nCoCo* score

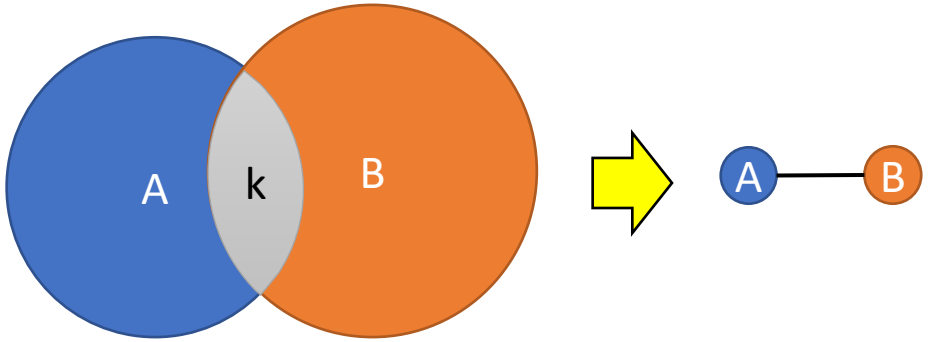
PAG Id	Type	PAG name	PAG size	Theoretical PPI	PPI	*CoCo*	*nCoCo*
WIG001980	P	Non-homologous end joining	6	15	13	88	1153
WIG001424	P	Actin Nucleation and Branching	101	5050	612	2094	130

Yue, et al, Nucleic Acids Research, Volume 46, Issue D1, 4 January 2018

Defining PAG-to-PAG relationships

co-membership based PAG-to-PAG relationship (m-type)

- **PAG Co-membership networks** connect PAGs if there is a significant number of shared genes between the two PAGs.



$$\frac{\binom{K}{k}\binom{N-K}{n-k}}{\binom{N}{n}}$$

- Hypergeometric distribution
  - N is the total number of genes
  - n is the number of genes in gene set A
  - K is the number of genes in gene set B
  - k is the number of shared genes

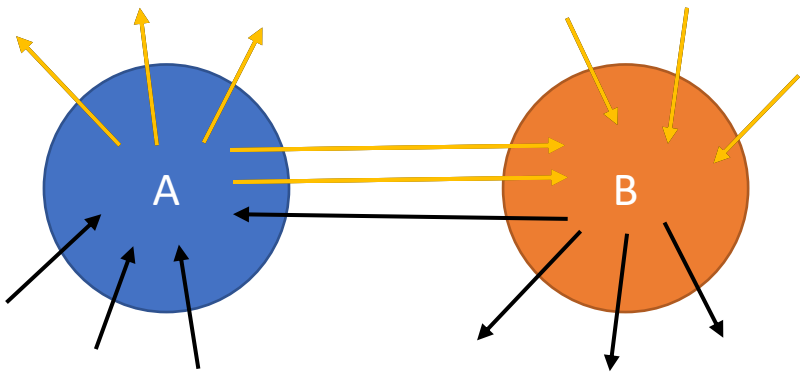
__k__ successes in __n__ draws without replacement from a finite population of size __N__ containing a maximum of successes __K__

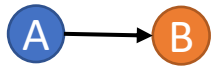
- Control false discovery rate using BH procedure (q-value = 0.05)

Yue et al (2015) Bioinformatics, Vol. 31, No. 12, pp. i250-i257

Constructing Regulatory PAG relationships

- **Regulatory PAGs** are constructed from PAG A to PAG B if there is a significant number of gene regulations from the unique genes of A to B.





$$\frac{\binom{K}{k}\binom{N-K}{n-k}}{\binom{N}{n}}$$

k *successes in* ***n*** *draws without replacement from a finite population of size* ***N*** *containing a maximum of successes* ***K***

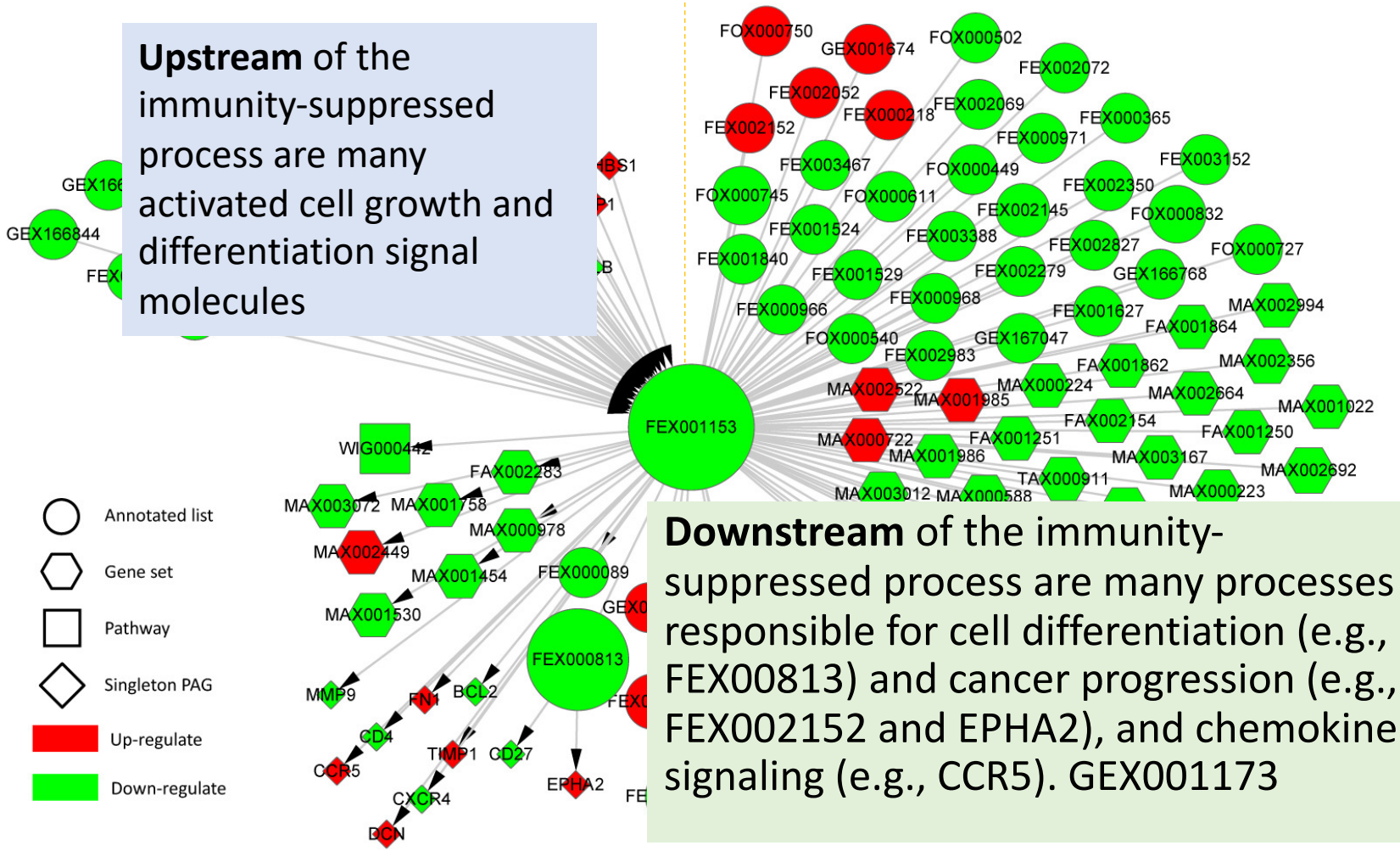
- Hypergeometric distribution
  - N is the total number of gene regulations
  - n is the number of gene regulations where genes in A regulate genes outside A
  - K is the number of gene regulations where genes in B are regulated from genes outside B
  - k is the number of gene regulations from (not shared) genes in A to B
- Control false discovery rate using BH procedure (q-value = 0.05)

Yue et al (2015) Bioinformatics, Vol. 31, No. 12, pp. i250-i257

Myeloid-derived suppressor cell (MDSC) Regulatory PAG-PAG Network Reveals Key Immunity Impacts

A large (n=4568) PAG containing genes responsible for immunity functions

Upstream of the immunity-suppressed process are many activated cell growth and differentiation signal molecules



Downstream of the immunity-suppressed process are many processes responsible for cell differentiation (e.g., FEX00813) and cancer progression (e.g., FEX002152 and EPHA2), and chemokine signaling (e.g., CCR5). GEX001173

Yue et al (2015) Bioinformatics, Vol. 31, No. 12, pp. i250-i257

Demo

Basic search: Retrieve PAGs using keywords, e.g., the pancreatic cancer related PAGs

C

PAGER 3.0

Contribute Download FAQ About Us

Result: PAGs with names including substring 'pancreatic cancer'

Showing 51 results out of 51

download

1

Query Term Matches

2

TYPE

- A (Annotated-lists) 41
- G (Gene signatures) 8
- P (Pathways) 2

SOURCE

- Cell 12
- HPA-PathologyAtlas 1
- GAD 1
- GWAS Catalog 5
- PheWAS 1
- MSigDB 30
- KEGG 1

ORGANISM

- Homo sapiens 51

PAG SIZE RANGE

[3 , 1556]

NCOCO SCORE ≥

0

Reset filters

3

GSEA Hallmark Pancreatic Cancer Tissue Explants (Extracellular Vesicles) - - Epithelial Mesenchymal Transition

PAG_ID:	FAX003040
PAG_SIZE:	53
ORGANISM:	Homo sapiens
DESCRIPTION:	Top 3 pathways enriched in pancreatic cancer tissue extract extracellular vesicle particles compared to matched pancreas adjacent tissue using Hallmark gene sets (GSEA)
nCoCo SCORE:	708.83
SOURCE:	Cell

GSEA Hallmark Pancreatic Cancer Tissue Explants (Extracellular Vesicles) - - Coagulation

PAG_ID:	FAX003041
PAG_SIZE:	49
ORGANISM:	Homo sapiens
DESCRIPTION:	Top 3 pathways enriched in pancreatic cancer tissue extract extracellular vesicle particles compared to matched pancreas adjacent tissue using Hallmark gene sets (GSEA)
nCoCo SCORE:	512.24
SOURCE:	Cell

aimed

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Demo

- Analysis: Retrieve PAGs using list of genes

C

1

Search Query

Total number of input genes: 314 (Show/Hide)

LIST OF M-TYPE PAGS SIMILAR TO YOUR GENE LIST

Analysis Filters

Type of PAG

All

Size of PAGs

Min 2 Max 5000

PAGs Similarity Score

0.05

Number of Overlapping Genes

1

Cohesion 0 P-Value 0.05

Species

All

Data Source

BioCarta
DSigDB
GAD
GeneSigDB
GOA
GTEx
GWAS Catalog
Isozyme
KEGG_2021_HUMAN
Microcosm Targets
mirTARbase
MSigDB

ANALYZE

2

List of PAGs similar to your gene list: Show Bar Plot Show Scatter Plot Advance Analysis

Show 15 rows Download As

Search:

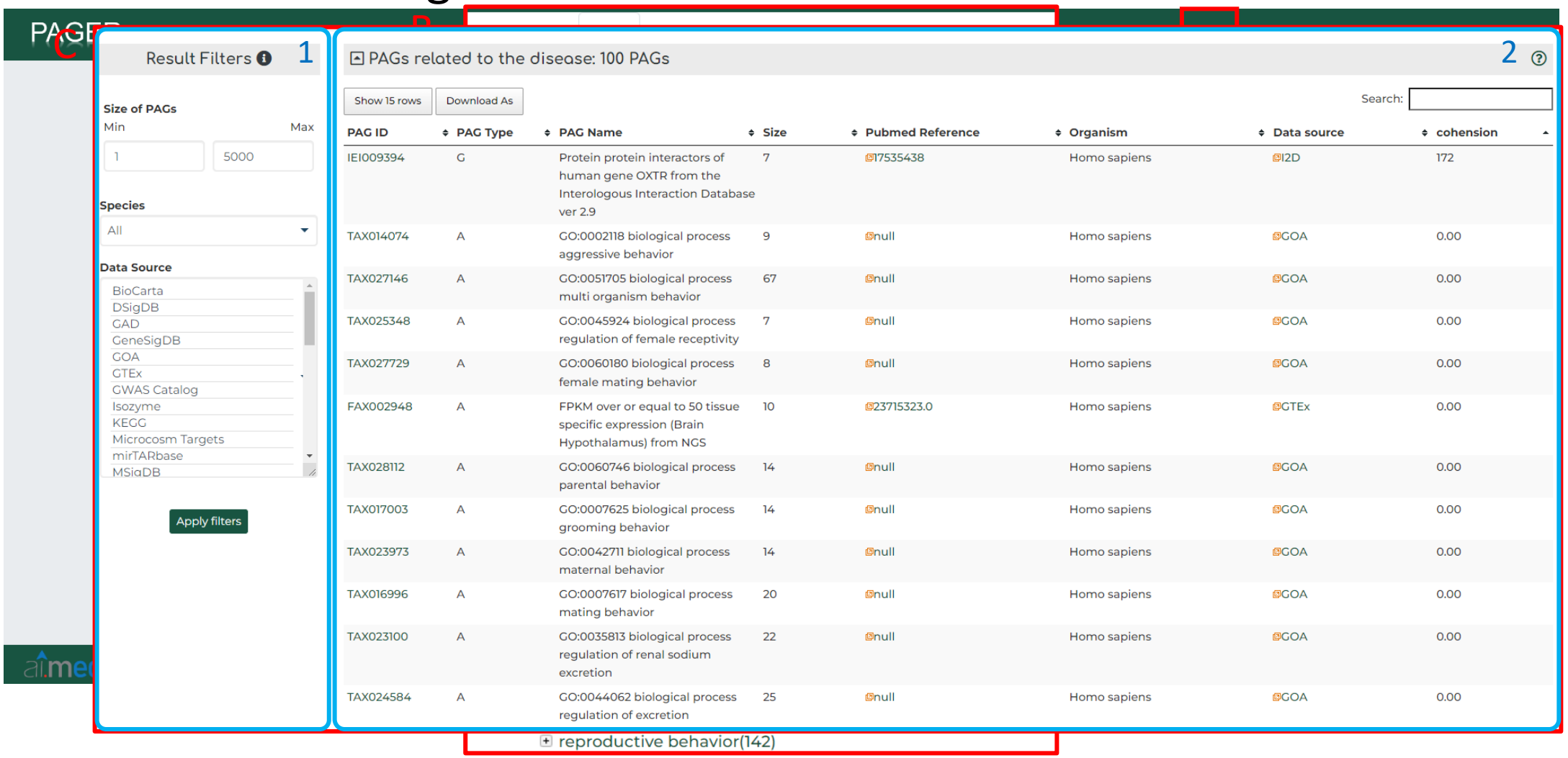
PAG ID	Type	Name	Size	Species	Data source	Overlap	Similarity score	CoCo score	p-value	FDR
TAX014776	A	GO:0003723 molecular function RNA binding	1601	Homo sapiens	GOA	159	0.17	0.00	1.98e-142	1.25e-139
TAX016314	A	GO:0006413 biological process translational initiation	139	Homo sapiens	GOA	70	0.25	0.00	2.96e-114	1.87e-111
TAX016473	A	GO:0006614 biological process SRP dependent cotranslational protein targeting to membrane	89	Homo sapiens	GOA	62	0.28	0.00	3.83e-114	2.41e-111
TAX013299	A	GO:0000184 biological process nuclear transcribed mRNA catabolic process, nonsense mediated decay	117	Homo sapiens	GOA	66	0.26	0.00	3.38e-112	2.12e-109
TAX024909	A	GO:0045047 biological process protein targeting to ER	99	Homo sapiens	GOA	63	0.27	0.00	5.45e-112	3.42e-109
TAX016472	A	GO:0006613 biological process cotranslational protein targeting to membrane	94	Homo sapiens	GOA	62	0.28	0.00	1.01e-111	6.35e-109
TAX030084	A	GO:0072599 biological process establishment of protein localization to endoplasmic reticulum	103	Homo sapiens	GOA	63	0.26	0.00	2.58e-110	1.61e-107
TAX029220	A	GO:0070972 biological process protein localization to endoplasmic reticulum	110	Homo sapiens	GOA	64	0.26	0.00	5.26e-110	3.28e-107
TAX034390	A	GO:1990904 cellular component ribonucleoprotein complex	812	Homo sapiens	GOA	109	0.16	0.00	5.88e-108	3.66e-105
TAX015958	A	GO:0005829 cellular component cytosol	4846	Homo sapiens	GOA	193	0.15	0.00	6.14e-104	3.82e-101
TAX021916	A	GO:0032991 cellular component protein containing complex	4915	Homo sapiens	GOA	193	0.15	0.00	8.03e-103	4.99e-100
TAX016471	A	GO:0006612 biological process protein targeting to membrane	129	Homo sapiens	GOA	62	0.23	0.00	2.74e-99	1.7e-96
TAX016305	A	GO:0006402 biological process mRNA catabolic process	207	Homo sapiens	GOA	70	0.19	0.00	8.36e-99	5.17e-96
TAX013553	A	GO:0000956 biological process nuclear transcribed mRNA catabolic process	191	Homo sapiens	GOA	68	0.20	0.00	9.26e-98	5.72e-95
TAX016304	A	GO:0006401 biological process RNA catabolic process	237	Homo sapiens	GOA	72	0.18	0.00	1.02e-97	6.27e-95

Showing 1 to 15 of 315 entries

Previous 1 2 3 4 5 ... 21 Next

Demo

- Browse: knowledge-based search



PAG ID	PAG Type	PAG Name	Size	Pubmed Reference	Organism	Data source	cohension
IEI009394	G	Protein protein interactors of human gene OXTR from the Interologous Interaction Database ver 2.9	7	17535438	Homo sapiens	I2D	172
TAX014074	A	GO:0002118 biological process aggressive behavior	9	null	Homo sapiens	GOA	0.00
TAX027146	A	GO:0051705 biological process multi organism behavior	67	null	Homo sapiens	GOA	0.00
TAX025348	A	GO:0045924 biological process regulation of female receptivity	7	null	Homo sapiens	GOA	0.00
TAX027729	A	GO:0060180 biological process female mating behavior	8	null	Homo sapiens	GOA	0.00
FAX002948	A	FPKM over or equal to 50 tissue specific expression (Brain Hypothalamus) from NGS	10	23715323.0	Homo sapiens	GTEx	0.00
TAX028112	A	GO:0060746 biological process parental behavior	14	null	Homo sapiens	GOA	0.00
TAX017003	A	GO:0007625 biological process grooming behavior	14	null	Homo sapiens	GOA	0.00
TAX023973	A	GO:0042711 biological process maternal behavior	14	null	Homo sapiens	GOA	0.00
TAX016996	A	GO:0007617 biological process mating behavior	20	null	Homo sapiens	GOA	0.00
TAX023100	A	GO:0035813 biological process regulation of renal sodium excretion	22	null	Homo sapiens	GOA	0.00
TAX024584	A	GO:0044062 biological process regulation of excretion	25	null	Homo sapiens	GOA	0.00

Demo

- API example http://discovery.informatics.uab.edu/PAGER/index.php/pages/help

PAGER 3.0

Home Analyze Browse Contribute Download FAQ About Us

WHAT IS A PAG?

WHAT IS PAGER?

HOW IS PAGER IMPLEMENTED?

HOW COMPREHENSIVE IS PAGER?

WHAT ARE THE FEATURES OF PAGER?

HOW DO I PERFORM A BASIC SEARCH IN PAGER?

HOW DO I SEARCH FOR PAGS IN PAGER BY A QUERIED GENE LIST?

WHAT ARE R-TYPE AND M-TYPE PAG-TO-PAG RELATIONSHIPS?

WHAT IS RP-SCORE AND HOW IS IT DERIVED?

WHAT IS nCoCo SCORE AND HOW IS IT DERIVED?

CAN I SUBMIT MY PAG TO PAGER?

WHAT IS API FOR PAGER ANALYSIS?

A BRIEF HISTORY OF PAGER DATABASE

The PAGER API allows developers to analyze gene lists, get enrichment results, and download files of enrichment results. We provide a demo using two R scripts and python scripts in performing the PAGER analysis using API.

The core function R script for accessing the PAGER API:

- PAGER.r

The R script of calling the functions:

- PAGER_API_CALL.r

The core function python script for accessing the PAGER API:

- PAGER.py

The python script of calling the functions:

- PAGER_API_CALL.ipynb

Demo

- PAG details: http://discovery.informatics.uab.edu/PAGER/index.php/geneset/view/[PAG_ID]

WAG002693 Sandbox pathway test

1

PAG Summary

PAG Title	Sandbox pathway test
PAG ID	WAG002693
Type	P (Pathways)
Source Link	WikiPathway_2021
Publication Reference	NA
PAG Description	Sandbox pathway test
Species	Homo sapiens
Curator	Zongliang Yue
Curator Contact	zongyue@uab.edu
nCoCo Score	189
Base PAG ID	WAG002693
Human Phenotyte Annotation	

PAG Members

2

Total number of genes: 5

Show 15 rows Download As Search:

Gene ID	Gene symbol	Gene name	RP_score
7157	TP53	tumor protein p53	2.94
672	BRCA1	BRCA1 DNA repair associated	2.00
675	BRCA2	BRCA2 DNA repair associated	1.99
4313	MMP2	matrix metallopeptidase 2	0.95
100422915	MIR3065	microRNA 3065	0.00

Showing 1 to 5 of 5 entries Previous 1 Next

Gene-Gene Interactions within the PAG Network Visualization

Interactions of 3 Star or greater rating from HAPPI-2

Show 15 rows Download As Search:

Gene A	Gene B	Source	SCORE
BRCA1	BRCA2	HAPPI-2	1.00
BRCA1	TP53	HAPPI-2	1.00
BRCA2	TP53	HAPPI-2	0.99
MMP2	TP53	HAPPI-2	0.98

Showing 1 to 4 of 4 entries Previous 1 Next

Gene-Gene regulations within the PAG Network Visualization

Directed Regulations from Gene A to Gene B

Show 15 rows Download As Search:

Related PAGs

3

Top-ranked neighbors

1. GO:0006978 biological_process DNA damage response, signal transduction by p53 class mediator resulting in transcription of p21 class mediator
2. GO:0042772 biological_process DNA damage response, signal transduction resulting in transcription
3. Role of BRCA1, BRCA2 and ATR in Cancer Susceptibility
4. breast cancer
5. role of brca1 brca2 and atr in cancer susceptibility

more...

Top-ranked upstream regulatory PAGs

1. GO:0010468 biological_process regulation of gene expression
2. GO:0010604 biological_process positive regulation of macromolecule metabolic process
3. GO:0031325 biological_process positive regulation of cellular metabolic process
4. GO:0009893 biological_process positive regulation of metabolic process
5. GO:0051173 biological_process positive regulation of nitrogen compound metabolic process

more...

Top-ranked downstream regulatory PAGs

1. MAPK9
2. HIPK1
3. AIFM2
4. GML
5. PathwayGeneSet, Reactome

more...

Demo

- Full text of our publication and how to cite us

PAGER 3.0

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A BRIEF HISTORY OF PAGER DATABASE DEVELOPMENT

HOW TO CITE US?

To cite the latest database, i.e., PAGER 2.0:

- Yue, Z., Q. Zheng, M. T. Neylon, M. Yoo, J. Shin, Z. Zhao, A. C. Tan and J. Y. Chen (2018). "PAGER 2.0: an update to the pathway, annotated-list and gene-signature electronic repository for Human Network Biology." Nucleic acids research 46(D1): D668-D676.

Cite Full text PubMed

To cite the representation of PAG-2-PAG networks:

- Chen, J. Y., C. Shen, Z. Yan, D. P. Brown and M. Wang (2006). "A systems biology case study of ovarian cancer drug resistance." Comput Syst Bioinformatics Conf: 389-398.

Cite Full text PubMed

- Yue, Z., M. M. Kshirsagar, T. Nguyen, C. Suphavilai, M. T. Neylon, L. Zhu, T. Ratliff and J. Y. Chen (2015). "PAGER: constructing PAGs and new PAG–PAG relationships for network biology." Bioinformatics 31(12): i250-i257.

Cite Full text PubMed

To cite the new PAGER analysis workflow:

- Yue, Z., R. Slominski, S. Bharti and J. Y. Chen (2022). "PAGER Web APP: An Interactive, Online Gene Set and Network Interpretation Tool for Functional Genomics." Front Genet 13: 820361.

Cite Full text PubMed

To review the research and development history of biological pathway analysis from our lab:

- Chen, J. Y., C. Shen, Z. Yan, D. P. Brown and M. Wang (2006). "A systems biology case study of ovarian cancer drug resistance." Comput Syst Bioinformatics Conf: 389-398.
- Chowbina, S. R., X. Wu, F. Zhang, P. M. Li, R. Pandey, H. N. Kasamsetty and J. Y. Chen (2009). HPD: an online integrated human pathway database enabling systems biology studies. BMC bioinformatics. BioMed Central.

PAGER web app

An interactive online application to perform the gene set enrichment analysis and network interpretation of the functional genomics result

Features:

- Online data analytics: https://aimed-lab.shinyapps.io/PAGERwebapp/
- Bundled with UALCAN TCGA data sets (http://ualcan.path.uab.edu/).
- Interactive visualization apps for biological network analysis.

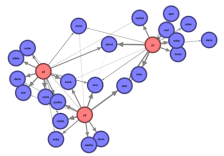
Underlying Technology:

Shiny

PAGER 3.0

UALCAN

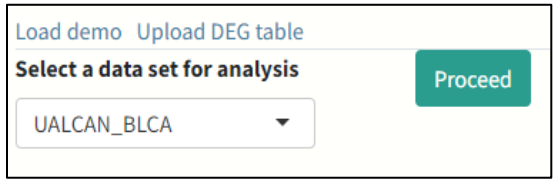
Analyze, Integrate, Discover

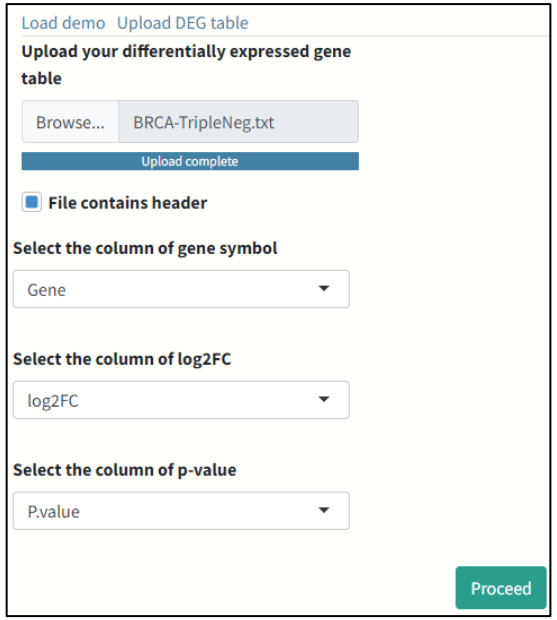


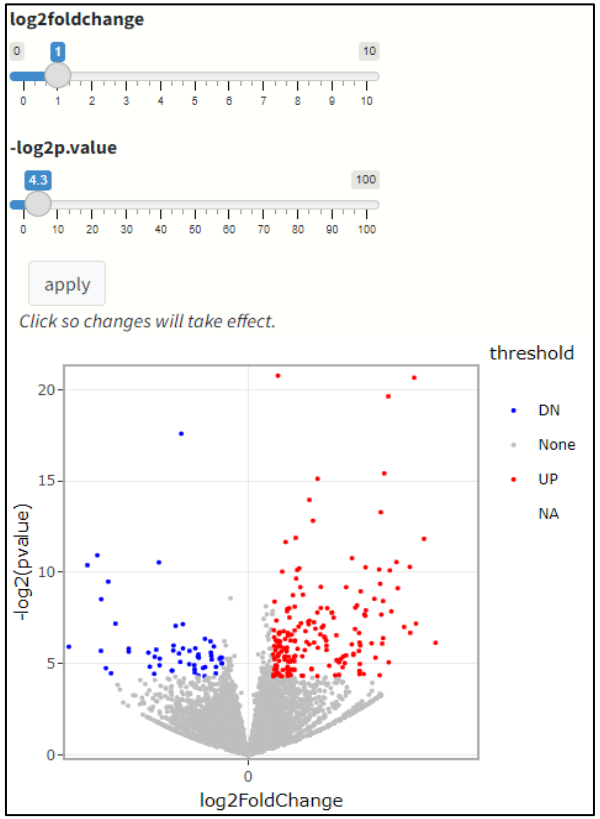
Network Visualization

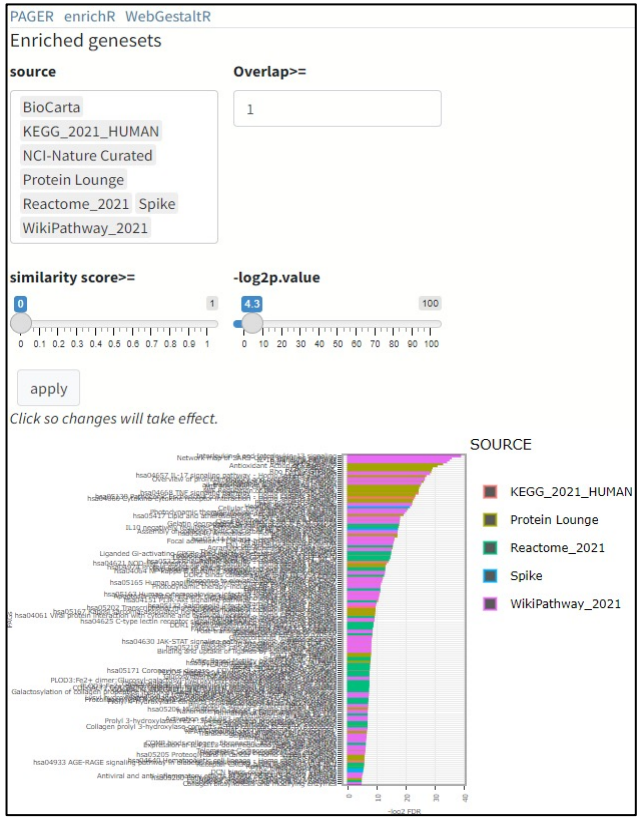
PAGER web app workflow

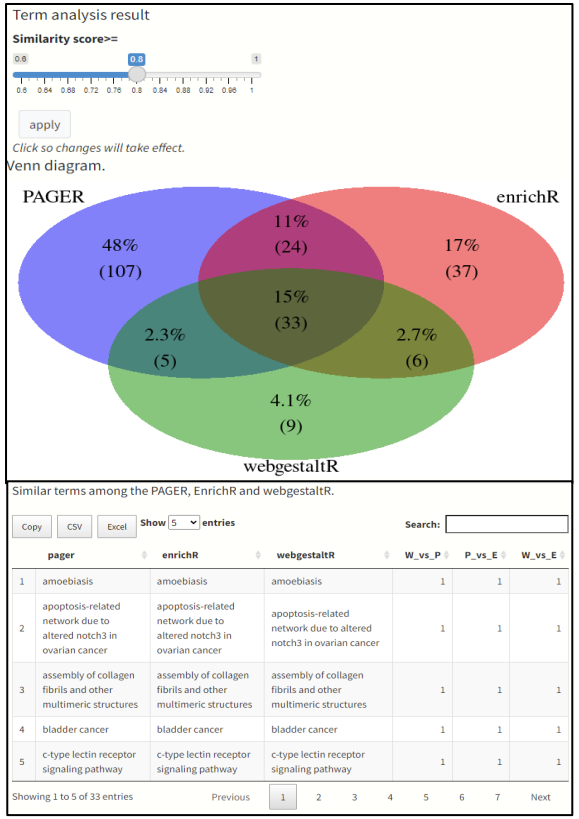
Load → Filter → Enrich → Compare











https://aimed-lab.shinyapps.io/PAGERwebapp/

http://discovery.informatics.uab.edu/PAGER-COV/

PAGER-COV

Home Analyze Contribute Download FAQ News About Us

Find pathways, annotated-lists, and gene signatures (PAGs) related to coronavirus diseases

Enter keyword(s) or a gene symbol

Search for PAGs

Exam

33 data sources

11,835 PAGs (pathways, annotated gene lists, and gene signatures)

19,996,993 PAG-to-PAG relationships stored in the database

Yue et al Nucleic Acids Research, Vol. 49 (D1), 2021, pp D589-D599, doi.org/10.1093/nar/gkaa1094

PAGER-CoV data source: immune response related PubMed, PubChem, and related functional databases

PubChem	PubChem	A compiled list of PubChem data related to COVID-19 (Coronavirus Disease 2019) and SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2).	1549	1549

1549 repositioning targets

Curation	Am J Respir Crit Care Med	Clinical journals related to pulmonary, critical care, and sleep-related fields.	2	271
	Microbiology and Molecular Biology Reviews	Research journals related to immunology, molecular, and cell biology.	1	
	Zenodo	general-purpose open-access repository developed under the European OpenAIRE program and operated by CERN.	1	
	Mouse Genome Informatics Database	international database resource for the laboratory mouse, providing integrated genetic, genomic, and biological data for researching human health.	5	
	Nature Cell Discovery	Cell molecular biology journal.	4	
	GenBank/UniProt	Databases used to manually curate gene to protein mapping and protein annotations.	33	
	Cell	A research journal relating to cell biology.	5	
	The Annual Review of Cell and Developmental Biology	A research journal relating to developments in the field of cell and developmental biology.	1	
	Nature	A leading multidisciplinary science journal.	111	
	Drugbank	Unique bioinformatics and cheminformatics resource that combines detailed drug data with comprehensive drug target information.	96	
	Nature Medicine	A monthly journal publishing original peer-reviewed research in all areas of medicine.	1	
	Cell Host and Microbe	A research journal that focuses broadly on the study of microbes, with an emphasis on the interface between the microbe and its host.	1	
	bioRxiv	COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv.	10	

271 curated SARS-CoV-2 gene set

PAGER	PAGER-MSigDB	Immune signatures from GSEA (imported from PAGER 2.0).	6139	10015
	PAGER-GOA_EXCL	Gene Ontology Annotation database.	1030	
	PAGER-GAD	Gene signatures from Genetic Association Database.	70	
	PAGER-GOA	Gene Ontology Annotation database (is_a relation aggregation).	1888	
	PAGER-Pfam	A Large collection of protein families represented by multiple sequence alignments and hidden Markov models (HMMs).	82	
	PAGER-GeneSigDB	A curated database of gene expression signatures.	390	
	PAGER-Protein Lounge	Interactive web-based biological database.	30	
	PAGER-Spike	Signaling Pathways Integrated Knowledge Engine, regulation from highly curated human pathway information.	3	
	PAGER-PheWAS	Phenome-wide association studies database.	57	
	PAGER-PharmGKB	A database containing information relating to human genetic variation on drug response.	4	
	PAGER-Reactome	A pathway database.	25	
	PAGER-BioCarta	Online maps of metabolic and signaling pathways.	105	
	PAGER-GWAS Catalog	GWAS Catalog A Catalog of Published Genome-Wide Association Studies provided by NHGRI	79	
	PAGER-KEGG	A database containing high-level functions and utilities of the biological system.	38	
	PAGER-NGS Catalog	A Database of Next Generation Sequencing Studies in Humans.	1	
	PAGER-DSigDB	A drug signatures database for gene set analysis	49	
	PAGER-GTEx	The Genotype-Tissue Expression (GTEx) project	2	
	PAGER-NCI-Nature Curated	Gathered from published research literature and reviewed by expert scientists before publication.	13	
	PAGER-WikiPathway	A database of biological pathways maintained by and for the scientific community.	10	

10015 immune response gene signatures

Yue et al Nucleic Acids Research, Vol. 49 (D1), 2021, pp D589-D599, doi.org/10.1093/nar/gkaa1094

PAGER-CoV-Run

A web-based python-scripted interactive tool for COVID-19 SARS-CoV-2 functional genomic and downstream analysis

Features:

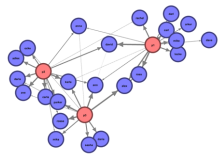
- Online data analytics: https://pager-cov-run.herokuapp.com/
- Bundled with example COVID-19 functional genomic data sets (GEO database).
- Interactive visualization apps for biological network analysis.

Underlying Technology:

Tutorial video: https://youtu.be/AArN4zdG94E

Streamlit

PAGER-CoV



Network Visualization

PAGER-CoV_Run user interface

https://youtu.be/AArN4zdG94E

Data

The COVID-19 transcriptional response data is from GSE147507

```
1.NHBE: Primary human lung epithelium.
2.A549: Lung alveolar.
3.Calu3:The transformed lung-derived Ca
4.Lung: The lung samples.
5.NP: The nasopharyngeal samples.
6.PBMC: The peripheral blood mononuclea
```

select a cell line or tissue:

PBMC

You selected PBMC

Adjust PAGER-CoV Parameters

The PAGER-CoV database detail http://discovery.informatics.uab.edu/PAGER-COV/

Available Data Sources

PubChem ×

Overlap ≥

1

Similarity score ≥

0.10

0.00 1.00

-log2-based FDR Cutoff

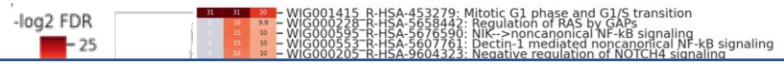
27

0 300

Section 1 out of 4: Show the conditions of samples

Section 2 out of 4: Parse DEG Results

Section 3 out of 4: Run PAGER-CoV Analysis



Section 4 out of 4: Generate the network of the selected PAG

Select a PAG_ID here:

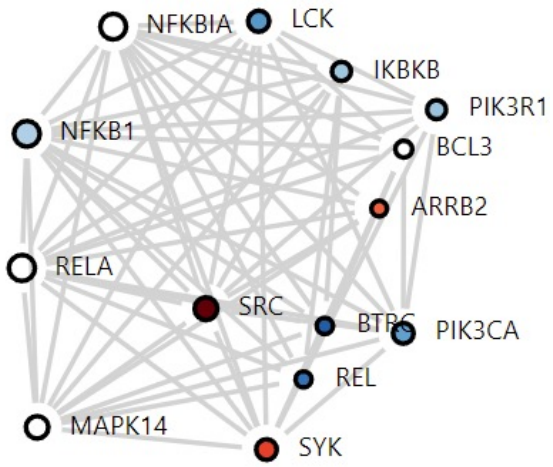
Available PAG_IDs

WIG001001_nfkappabatypicalpathway: Atypical NF-kappaB pathway

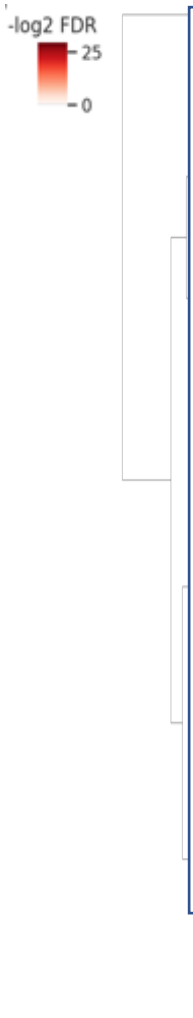
For the selected PAG WIG001001_nfkappabatypicalpathway: Atypical NF-kappaB pathway's gene information. (http://discovery.informatics.uab.edu/PAGER-COV/index.php/geneset/view/WIG001001)

	GS_ID	GENE_SYM	RP_SCORE	ENTREZ_ID	DESCRIPTION	node_size
0	WIG001001	RELA	12.4351	5970	RELA proto-oncogene, N…	49.740
1	WIG001001	NFKB1	12.1186	4790	nuclear factor kappa B…	48.474
2	WIG001001	NFKBIA	12.1069	4792	NFKB inhibitor alpha	48.427
3	WIG001001	SRC	9.5490	6714	SRC proto-oncogene, no…	38.196
4	WIG001001	MAPK14	9.2622	1432	mitogen-activated prot…	37.049
5	WIG001001	LCK	8.1861	3932	LCK proto-oncogene, Sr…	32.744
6	WIG001001	SYK	7.8020	6850	spleen associated tyro…	31.207
7	WIG001001	PIK3CA	7.7992	5290	phosphatidylinositol-4…	31.196
8	WIG001001	PIK3R1	6.6667	5295	phosphoinositide-3-kin…	26.666
9	WIG001001	IKBKB	6.6579	3551	inhibitor of nuclear f…	26.631
10	WIG001001	BCL3	5.2365	602	BCL3 transcription coa…	20.946

Download txt file for PBMC WIG001001

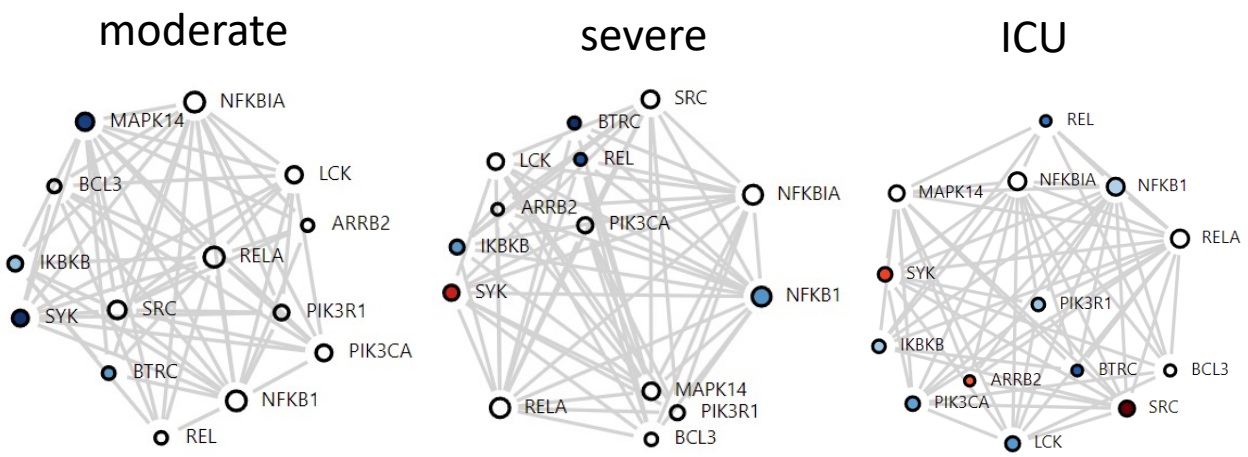


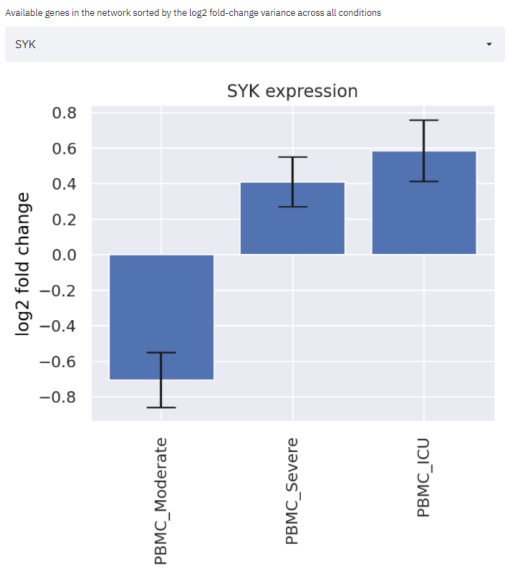
Case study: Peripheral blood samples from ICU, severe, and moderate enriched pathway comparison

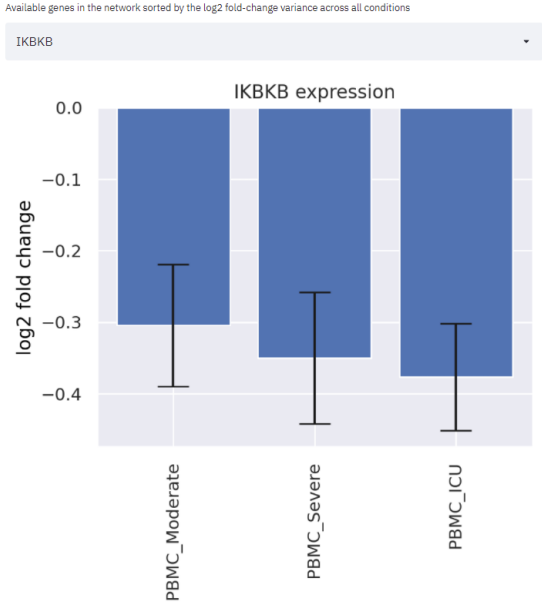


Ranked genes in "Atypical NF-kappaB pathway"

GENE_SYM	RP_SCORE	ENTREZ_ID	DESCRIPTION
RELA	12.44	5970	RELA proto-oncogene, NF-kB subunit
NFKB1	12.12	4790	nuclear factor kappa B subunit 1
NFKBIA	12.11	4792	NFKB inhibitor alpha
SRC	9.55	6714	SRC proto-oncogene, non-receptor tyrosine kinase
MAPK14	9.26	1432	mitogen-activated protein kinase 14
LCK	8.19	3932	LCK proto-oncogene, Src family tyrosine kinase
SYK	**7.80**	**6850**	**spleen associated tyrosine kinase**
PIK3CA	7.80	5290	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PIK3R1	6.67	5295	phosphoinositide-3-kinase regulatory subunit 1
IKBKB	**6.66**	**3551**	**inhibitor of nuclear factor kappa B kinase subunit beta**
BCL3	5.24	602	BCL3 transcription coactivator
BTRC	4.91	8945	beta-transducin repeat containing E3 ubiquitin protein ligase
REL	4.71	5966	REL proto-oncogene, NF-kB subunit
ARRB2	4.53	409	arrestin beta 2







References

- PAGER-3 webserver: http://discovery.informatics.uab.edu/PAGER/
- PAGER-web-app Demo: https://aimed-lab.shinyapps.io/PAGERwebapp/
- PAGER-CoV webserver: http://discovery.informatics.uab.edu/PAGER-COV/
- PAGER-CoV-Run Source code: https://github.com/aimed-uab/PAGER-COV_RUN
- PAGER-CoV-Run Demo: https://pager-cov-run.herokuapp.com/
- YouTube Tutorial: https://youtu.be/AArN4zdG94E

U54TR002731
U01CA223976
R01AI134023
R01AR073850