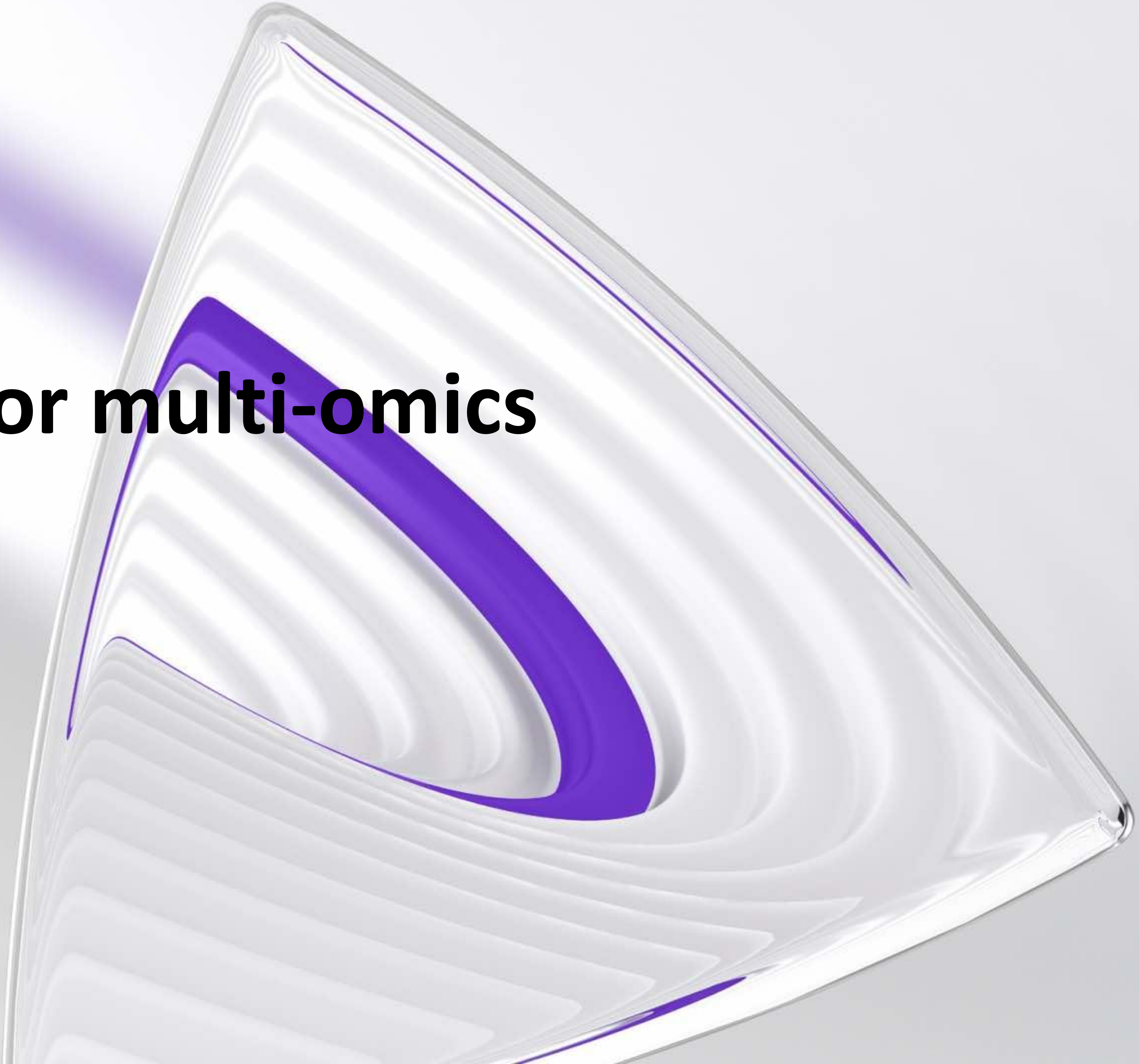
Using MetaCore for multi-omics analysis



Nuria.forns@Clarivate.com

Customer Education Specialist

April 2022

Agenda

1. Learn:
   - How to approach analyzing multi-omics data in MetaCore.
   - Use metabolic networks (endogenous) enrichment to analyze metabolites and expression data.
   - Find pathways where the metabolic and proteomic data are both involved.
2. Questions:
   - What relationships can we find between the metabolic and RNA-seq data?
   - What changes in metabolites and protein concentrations could be biomarkers for disrupted processes?

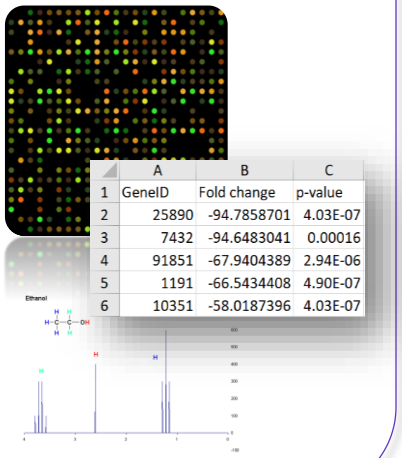
MetaCore, a Cortellis solution

Your GPS in pathway analysis

INPUT

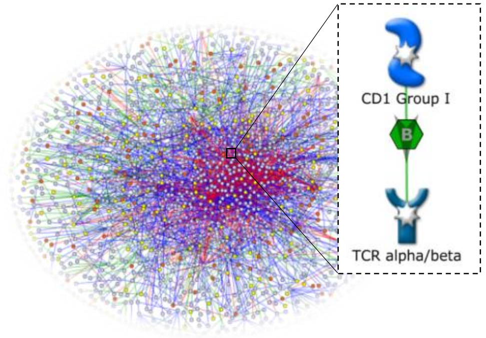
Data mining
Content Browsing

Gene lists or
OMICs analysis



	A	B	C
1	GeneID	Fold change	p-value
2	25890	-94.7858701	4.03E-07
3	7432	-94.6483041	0.00016
4	91851	-67.9404389	2.94E-06
5	1191	-66.5434408	4.90E-07
6	10351	-58.0187396	4.03E-07

METABASE



> 3,300,000 molecular interactions

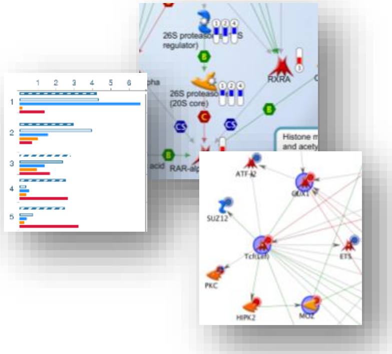
From Human, mouse and rat

Manually curated by editorial team

(>50 PhD, MD)

3,701 journals

METACORE



1,500+ Pathway Maps

- **Search & browse**
- **Enrichment analysis**
- **Compare experiments**
- **Network building**
- **Interactome analysis**
- **Pathway Map creation**

- **Understand omics data in the context of validated biology.**
- **Generate and confirm hypotheses for novel targets, biomarkers or drug mechanisms of action.**

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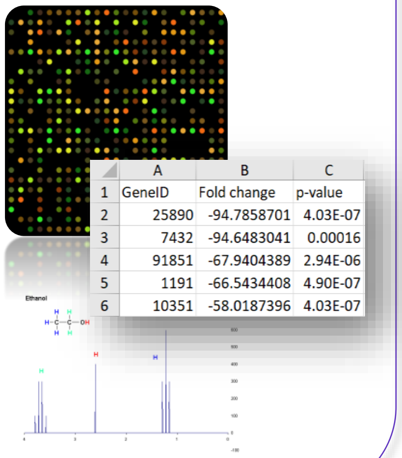

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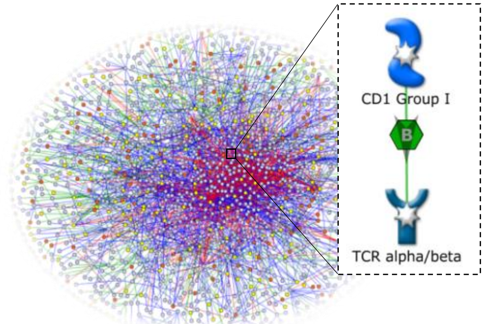

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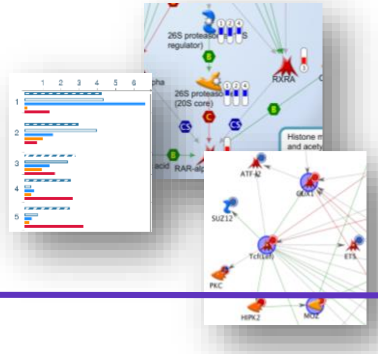

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- **Compare experiments**
- **Network building**
- **Interactome analysis**
- **Pathway Map creation**

Type	Number
All	3,301,030
Protein - Protein	1,455,811
Compound - Protein	1,012,689
Compound - Compound	12,291
Metabolic enzyme - Reaction	62,070
Substrate, Product - Reaction	136,068
RNA - Protein	616,754

MetaCore, a Cortellis solution

Your GPS in pathway analysis

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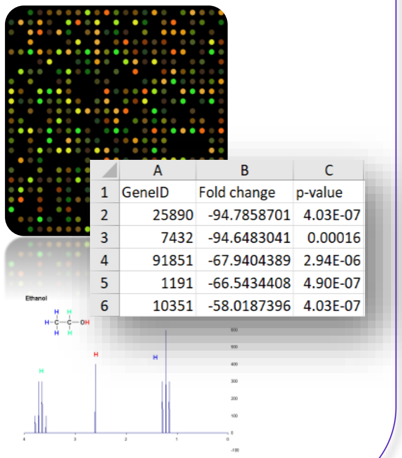
Content Browsing

Gene lists or
OMICs analysis



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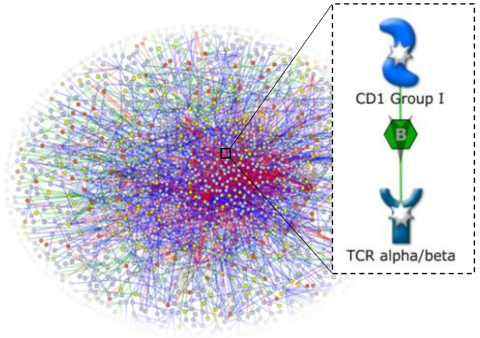

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METACORE

1,500+ Pathway Maps

- **Search & browse**
- **Enrichment analysis**
- **Compare experiments**
- **Network building**
- **Interactome analysis**
- **Pathway Map creation**

- **~ 1600 canonical and disease signaling pathways**
- **250 metabolic networks**
- **118 endogenous metabolic networks**

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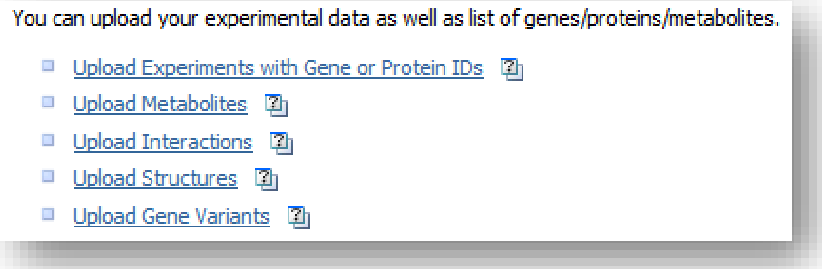
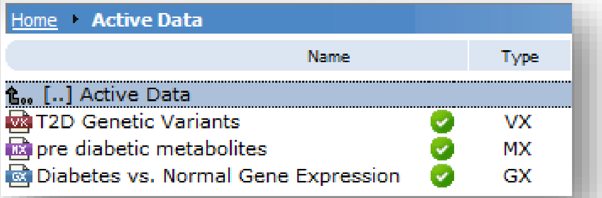
Multi-omics simultaneous analysis

Combining metabolomic, transcriptomic and gene variants for side by side –omics enrichment analysis



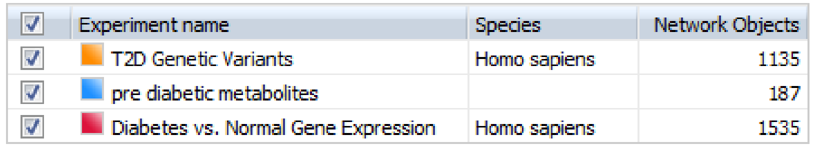
You can upload your experimental data as well as list of genes/proteins/metabolites.

- Upload Experiments with Gene or Protein IDs
- Upload Metabolites
- Upload Interactions
- Upload Structures
- Upload Gene Variants

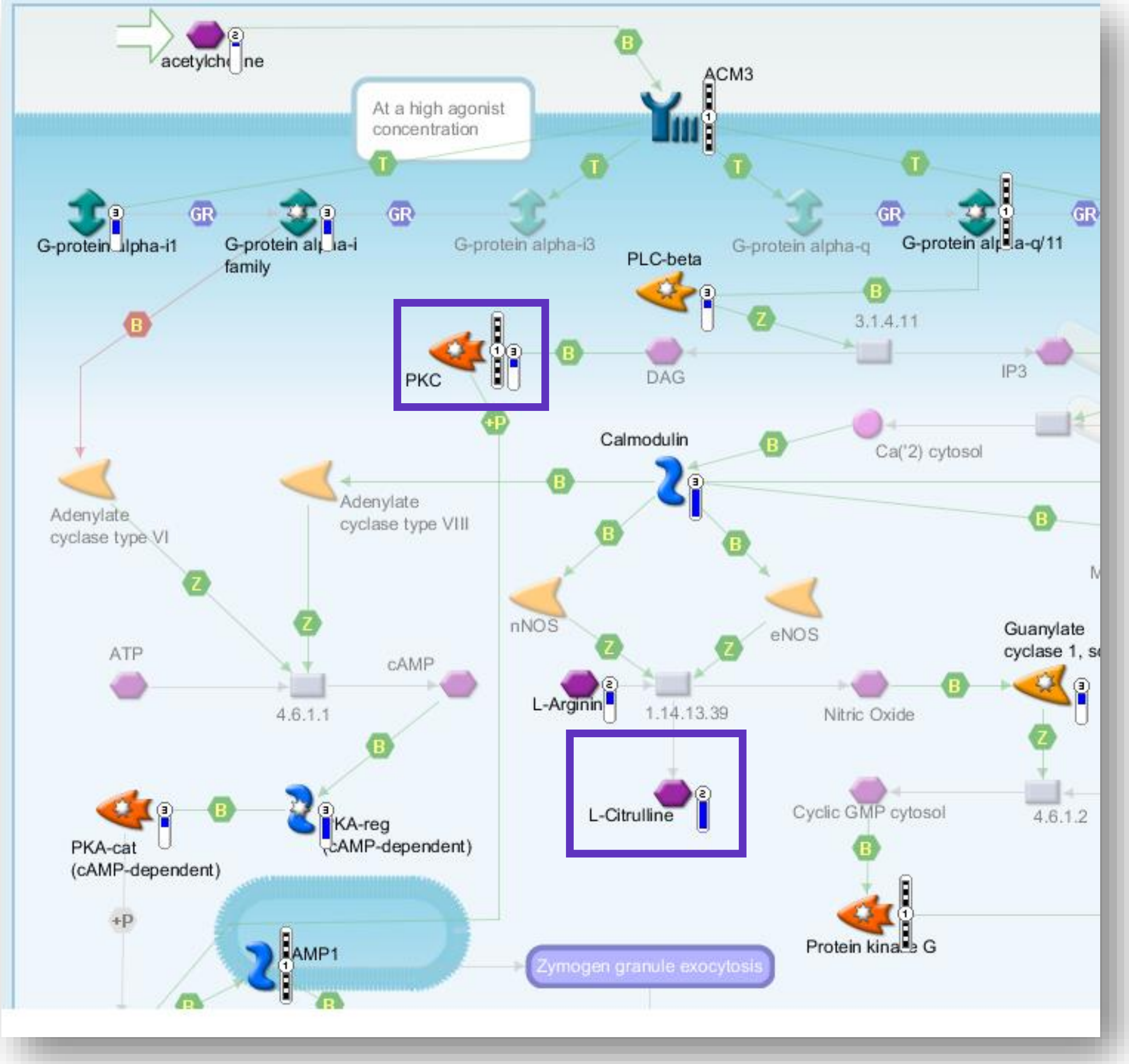


Home ▸ **Active Data**

Name		Type
[..] Active Data		
T2D Genetic Variants	✓	VX
pre diabetic metabolites	✓	MX
Diabetes vs. Normal Gene Expression	✓	GX



☑	Experiment name	Species	Network Objects
☑	🟧 T2D Genetic Variants	Homo sapiens	1135
☑	🟦 pre diabetic metabolites		187
☑	🟥 Diabetes vs. Normal Gene Expression	Homo sapiens	1535



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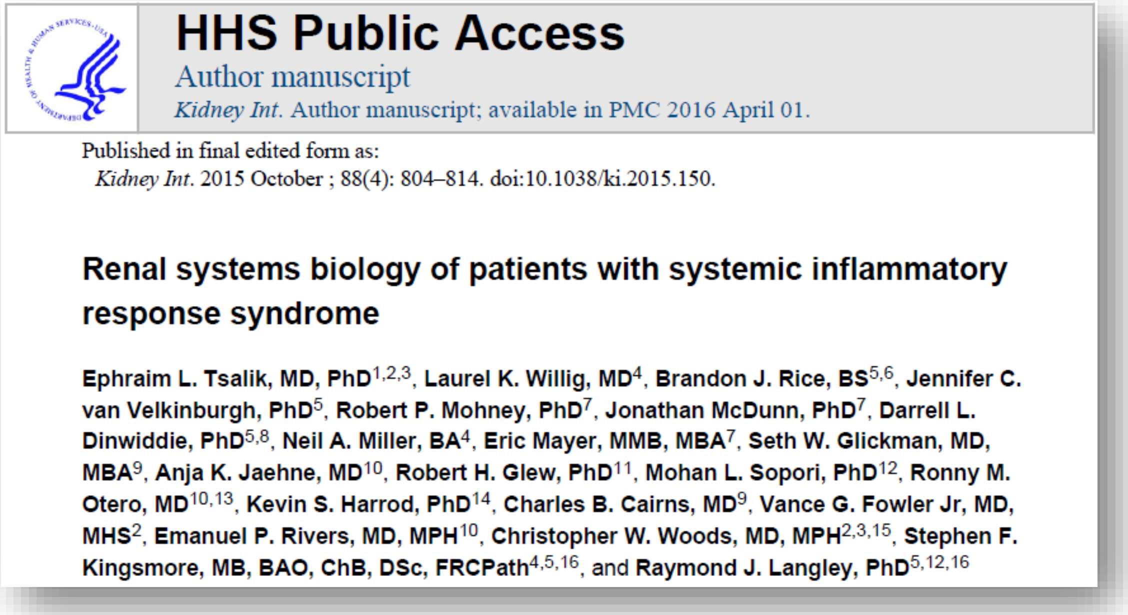
Acute kidney injury (AKI) public datasets

- **CAPSOD study** - 150 patients with sepsis or pneumonia with varying renal dysfunction.
- Renal dysfunction was classified using the **Acute Kidney Injury** Network (AKIN) criteria.
  - **AKI0** (no significant increase in serum creatinine) n=65 **(control)**
  - **AKI1** (serum creatinine increase of ≥ 0.3 mg/dl, or 150% to 200% above baseline) n=41
  - **AKI2/3** (serum creatinine increase more that 200% above baseline, or ≥ 4.0 mg/dl with an acute increase of at least 0.5 mg/dl) n=20
  - **HD** (Chronic hemodialysis) n=24



HHS Public Access

Author manuscript

Kidney Int. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:
Kidney Int. 2015 October ; 88(4): 804–814. doi:10.1038/ki.2015.150.

Renal systems biology of patients with systemic inflammatory response syndrome

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Datasets

- Levels of plasma proteins
  - Measured with mass spectrometry
  - 164 proteins were identified using peptide sequences
  - 46 were significantly different from the AKI0 control group using ANOVA with 5% false discovery rate correction.
- Levels of plasma metabolites
  - Measured with mass spectrometry
  - 241 metabolites were annotated
  - Clinical assays of serum creatine, capillary lactate, and serum glucose was used to validate the use of the MS data in a semiquantitative fashion.
  - 138 annotated metabolites were significantly different from the AKI0 control group using ANOVA with 1% false discovery rate correction.
- Blood transcriptome
  - Measured with RNA-seq
  - 133 out of 150 patients were used due to poor insufficient quality.
  - 1,997 genes were significantly differentially expressed across all groups using ANOVA with 1% false discovery rate correction.

AKI0 (control)

AKI1
Stage 1

AKI2-3
Stage 2

HD
Stage 3

TIPS FOR ANALYZING MULTI OMICS DATA

1. Calculate enrichment p-values for each experiment independently using the appropriate background list.

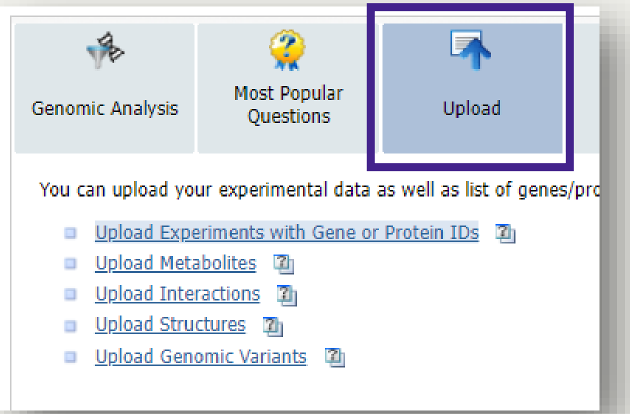
2. When comparing different omics types, think about how they would be related.

   - ✓ Metabolites concentration and transcriptome expression could **identify channels and enzymes impacting the metabolites.**
   - ✓ Proteome abundance and transcriptome expression could be useful for **correlating expression to translation.**
   - ✓ Metabolites and proteome abundance could be useful for **finding biomarkers** from non-invasive mediums.

Let’s go live

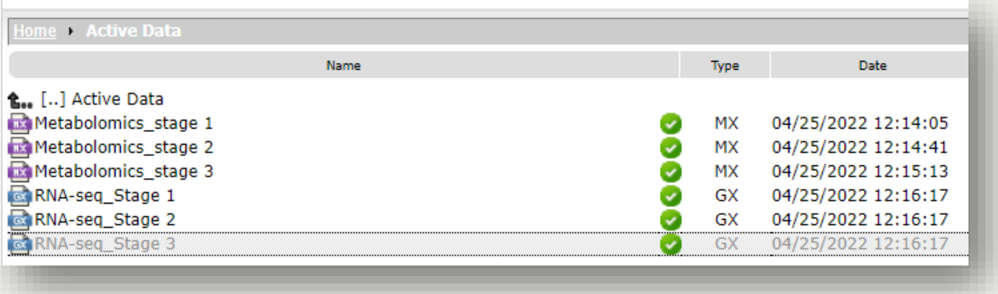
➢ What is the relationship between the metabolomic and expression data?

1. Upload your data



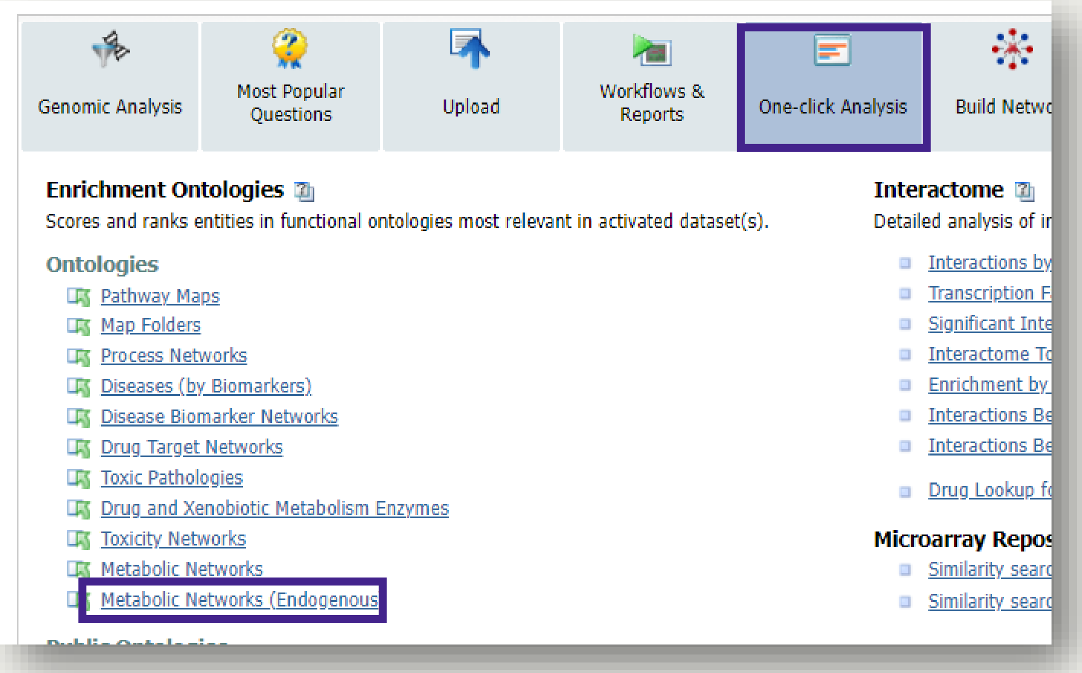
You can upload your experimental data as well as list of genes/pro

- Upload Experiments with Gene or Protein IDs
- Upload Metabolites
- Upload Interactions
- Upload Structures
- Upload Genomic Variants


Home ▸ Active Data

Name		Type	Date
[..] Active Data			
Metabolomics_stage 1	✓	MX	04/25/2022 12:14:05
Metabolomics_stage 2	✓	MX	04/25/2022 12:14:41
Metabolomics_stage 3	✓	MX	04/25/2022 12:15:13
RNA-seq_Stage 1	✓	GX	04/25/2022 12:16:17
RNA-seq_Stage 2	✓	GX	04/25/2022 12:16:17
RNA-seq_Stage 3	✓	GX	04/25/2022 12:16:17

2. Use metabolic networks (endogenous) to analyze metabolite and transcriptomic data



Enrichment Ontologies

Scores and ranks entities in functional ontologies most relevant in activated dataset(s).

Ontologies

- Pathway Maps
- Map Folders
- Process Networks
- Diseases (by Biomarkers)
- Disease Biomarker Networks
- Drug Target Networks
- Toxic Pathologies
- Drug and Xenobiotic Metabolism Enzymes
- Toxicity Networks
- Metabolic Networks
- Metabolic Networks (Endogenous

Interactome

Detailed analysis of in

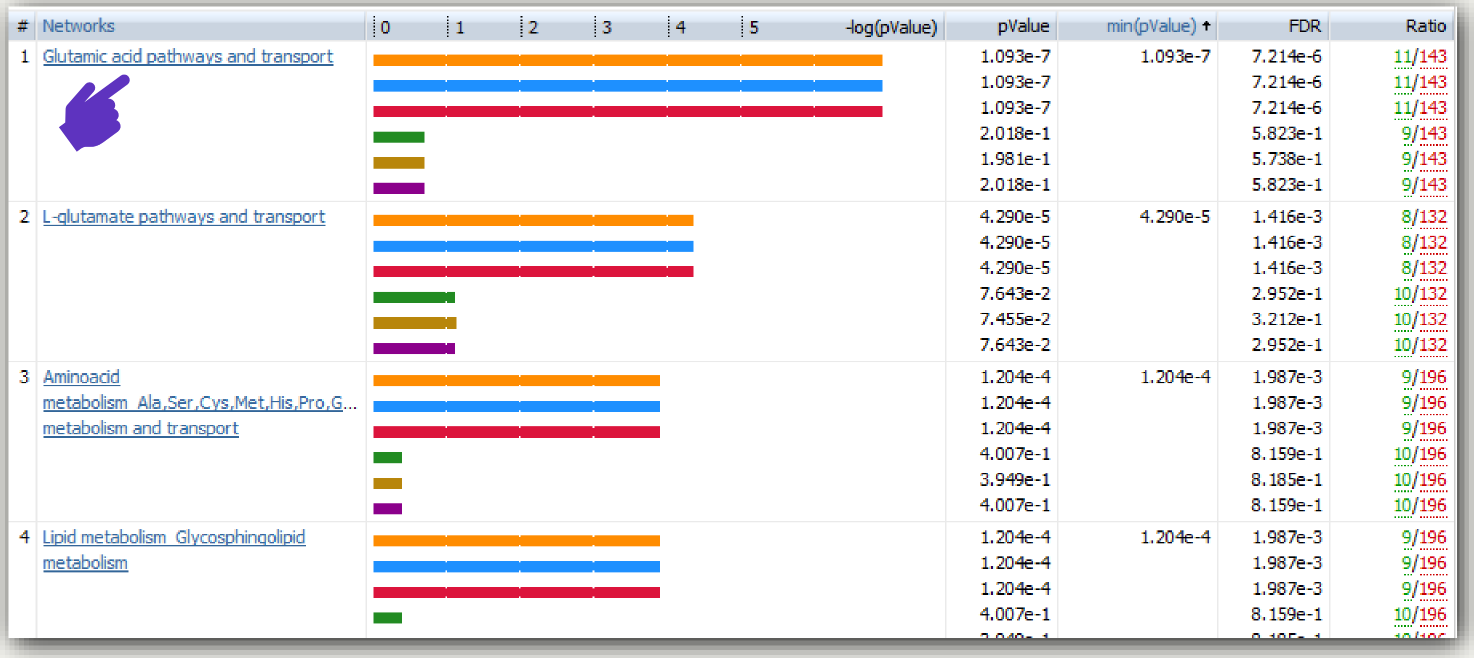
- Interactions by
- Transcription F
- Significant Inte
- Interactome To
- Enrichment by
- Interactions Be
- Interactions Be
- Drug Lookup fo

Microarray Repos

- Similarity searc
- Similarity searc

➢ What is the relationship between the metabolomic and expression data?

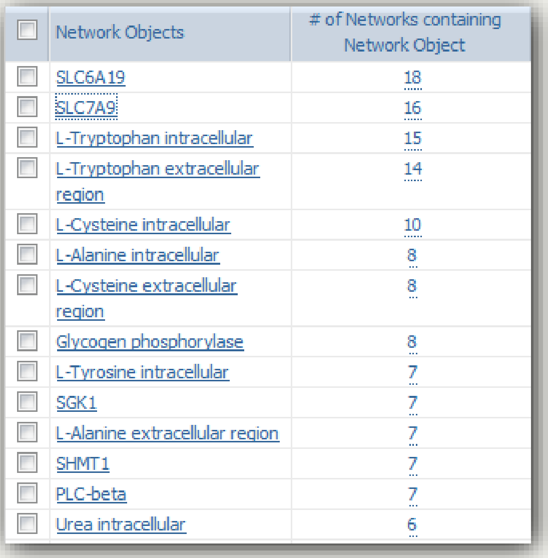
✓ Top 10 networks involved amino acid metabolism and glutamic acid processes.



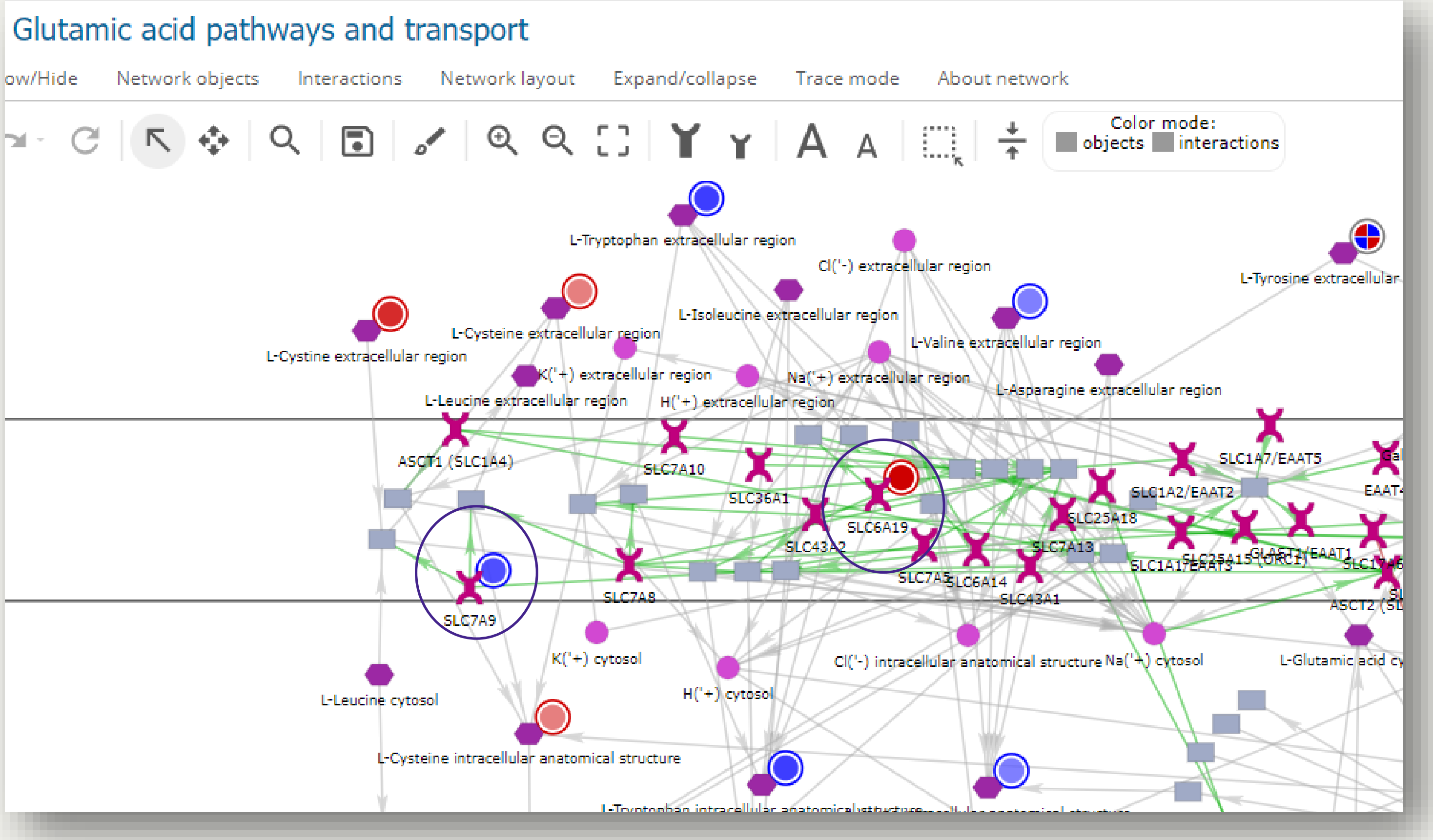
#	Networks	0 1 2 3 4 5 -log(pValue)	pValue	min(pValue) ↑	FDR	Ratio
1	Glutamic acid pathways and transport		1.093e-7	1.093e-7	7.214e-6	11/143
			1.093e-7		7.214e-6	11/143
			1.093e-7		7.214e-6	11/143
			2.018e-1		5.823e-1	9/143
			1.981e-1		5.738e-1	9/143
			2.018e-1		5.823e-1	9/143
2	L-glutamate pathways and transport		4.290e-5	4.290e-5	1.416e-3	8/132
			4.290e-5		1.416e-3	8/132
			4.290e-5		1.416e-3	8/132
			7.643e-2		2.952e-1	10/132
			7.455e-2		3.212e-1	10/132
			7.643e-2		2.952e-1	10/132
3	Aminoacid metabolism_Ala,Ser,Cys,Met,His,Pro,G... metabolism and transport		1.204e-4	1.204e-4	1.987e-3	9/196
			1.204e-4		1.987e-3	9/196
			1.204e-4		1.987e-3	9/196
			4.007e-1		8.159e-1	10/196
			3.949e-1		8.185e-1	10/196
			4.007e-1		8.159e-1	10/196
4	Lipid metabolism_Glycosphingolipid metabolism		1.204e-4	1.204e-4	1.987e-3	9/196
			1.204e-4		1.987e-3	9/196
			1.204e-4		1.987e-3	9/196
			4.007e-1		8.159e-1	10/196

➤ What is the relationship between the metabolomic and expression data?

- ✓ Expression changes in SLC7A9 and SLC6A19 could be influencing the dysregulation of amino acid concentrations.

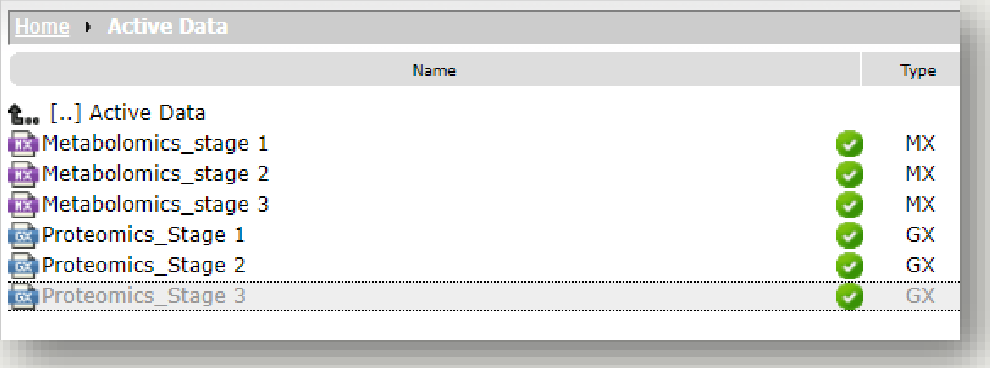


☐	Network Objects	# of Networks containing Network Object
☐	SLC6A19	18
☐	SLC7A9	16
☐	L-Tryptophan intracellular	15
☐	L-Tryptophan extracellular region	14
☐	L-Cysteine intracellular	10
☐	L-Alanine intracellular	8
☐	L-Cysteine extracellular region	8
☐	Glycogen phosphorylase	8
☐	L-Tyrosine intracellular	7
☐	SGK1	7
☐	L-Alanine extracellular region	7
☐	SHMT1	7
☐	PLC-beta	7
☐	Urea intracellular	6



➢ What changes in metabolites and protein concentrations could be biomarkers for disrupted processes?

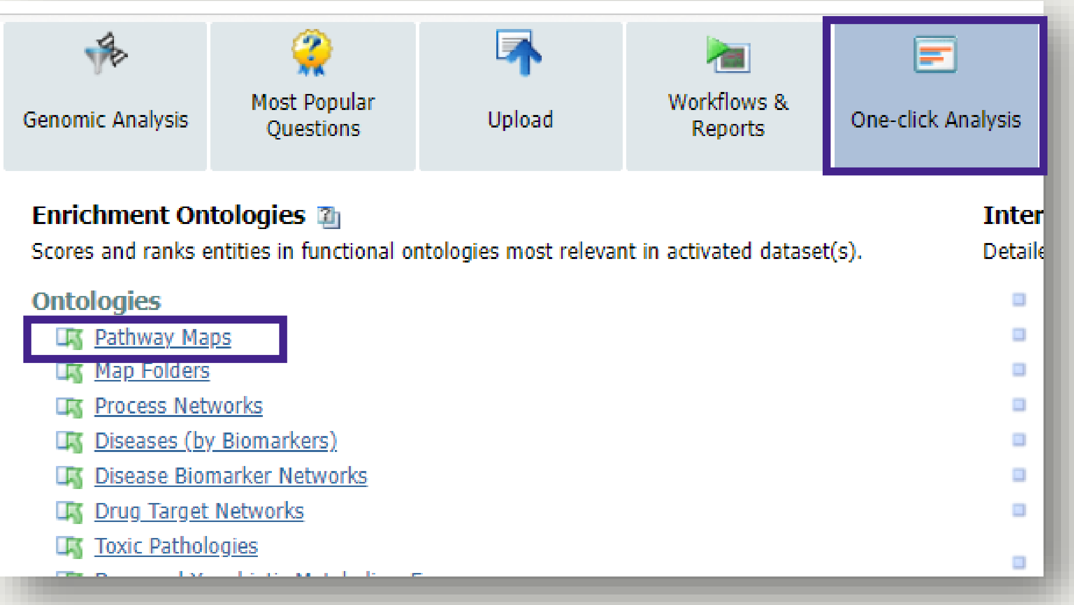
1. Activate metabolomic and proteomic data



Home ▸ **Active Data**

Name		Type
[..] Active Data		
Metabolomics_stage 1	✓	MX
Metabolomics_stage 2	✓	MX
Metabolomics_stage 3	✓	MX
Proteomics_Stage 1	✓	GX
Proteomics_Stage 2	✓	GX
Proteomics_Stage 3	✓	GX

2. Find pathways where both data sets are involved



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Inter

Detaile

Ontologies

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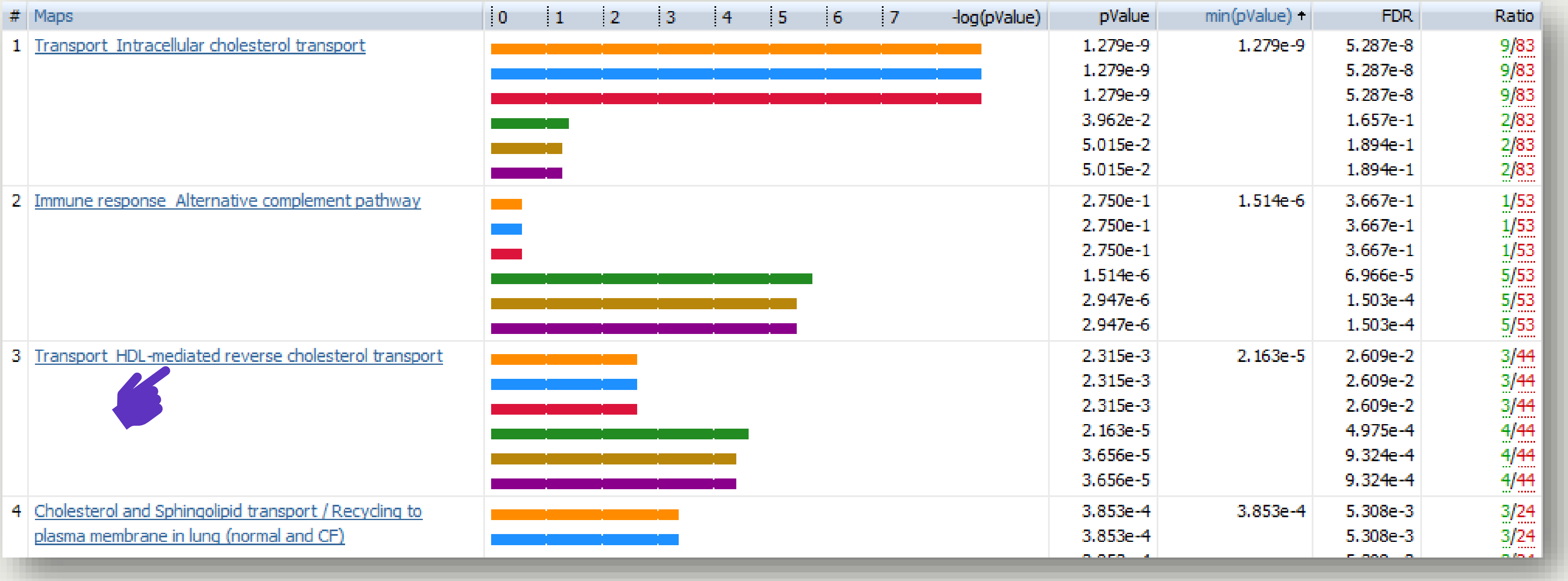
- Map Folders
- Process Networks
- Diseases (by Biomarkers)
- Disease Biomarker Networks
- Drug Target Networks
- Toxic Pathologies

➢ What changes in metabolites and protein concentrations could be biomarkers for disrupted processes?

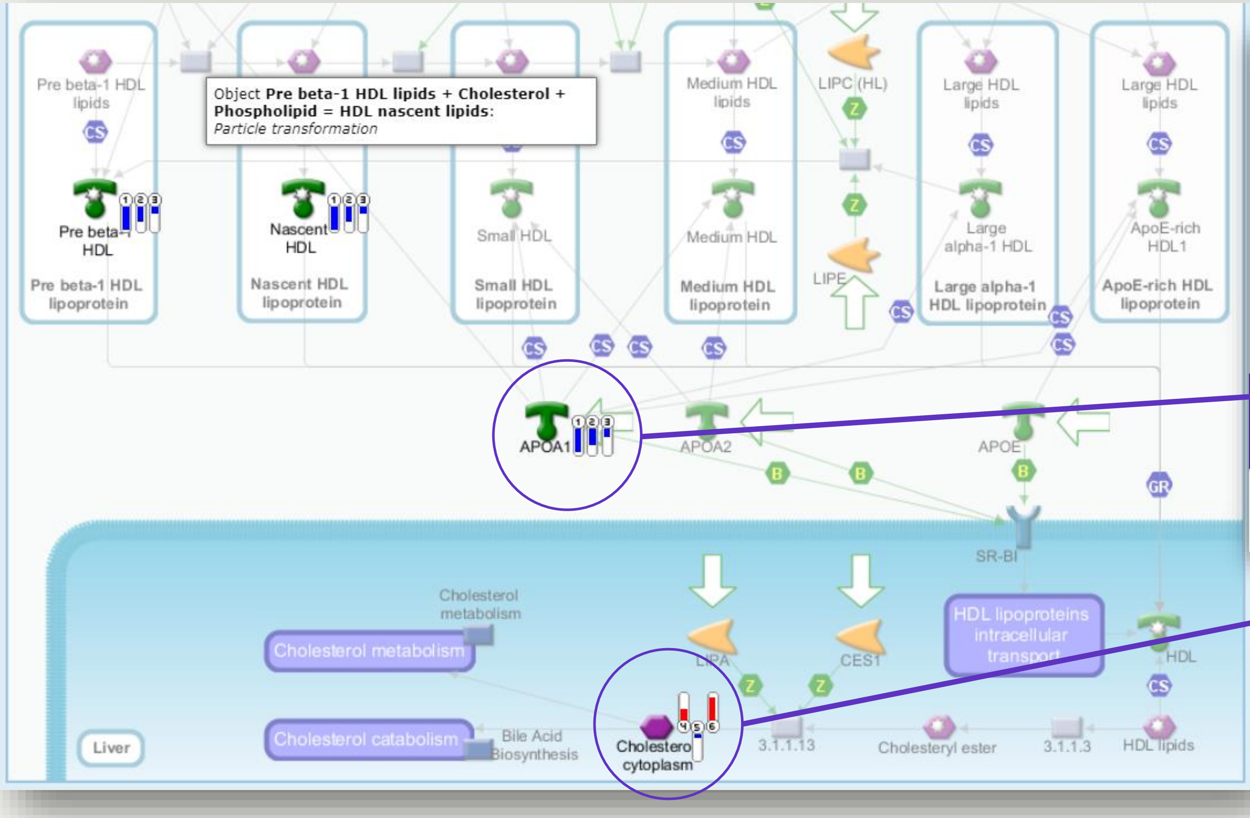
- ✓ Cholesterol related and complement pathways are both involved with the changes in these datasets



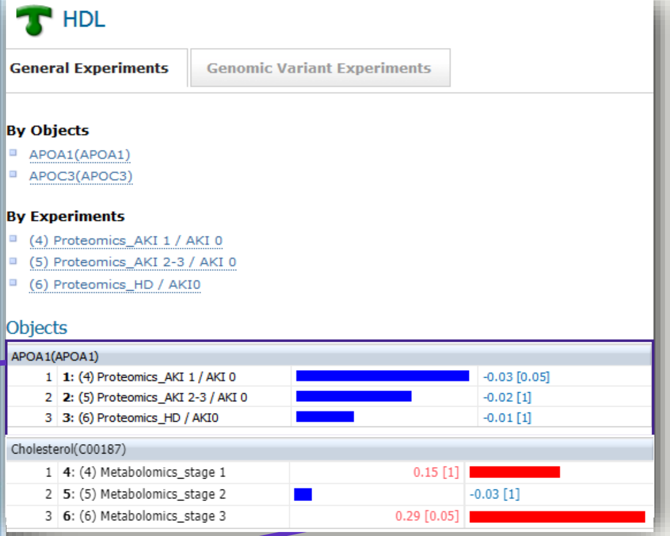
#	Maps	0 1 2 3 4 5 6 7 -log(pValue)	pValue	min(pValue) ↑	FDR	Ratio
1	Transport_Intracellular cholesterol transport	🟧	1.279e-9	1.279e-9	5.287e-8	9/83
		🟦	1.279e-9		5.287e-8	9/83
		🟥	1.279e-9		5.287e-8	9/83
		🟩	3.962e-2		1.657e-1	2/83
		🟫	5.015e-2		1.894e-1	2/83
		🟪	5.015e-2		1.894e-1	2/83
2	Immune response_Alternative complement pathway	🟧	2.750e-1	1.514e-6	3.667e-1	1/53
		🟦	2.750e-1		3.667e-1	1/53
		🟥	2.750e-1		3.667e-1	1/53
		🟩	1.514e-6		6.966e-5	5/53
		🟫	2.947e-6		1.503e-4	5/53
		🟪	2.947e-6		1.503e-4	5/53
3	Transport_HDL-mediated reverse cholesterol transport	🟧	2.315e-3	2.163e-5	2.609e-2	3/44
		🟦	2.315e-3		2.609e-2	3/44
		🟥	2.315e-3		2.609e-2	3/44
		🟩	2.163e-5		4.975e-4	4/44
		🟫	3.656e-5		9.324e-4	4/44
		🟪	3.656e-5		9.324e-4	4/44
4	Cholesterol and Sphingolipid transport / Recycling to plasma membrane in lung (normal and CF)	🟧	3.853e-4	3.853e-4	5.308e-3	3/24
		🟦	3.853e-4		5.308e-3	3/24

➢ What changes in metabolites and protein concentrations could be biomarkers for disrupted processes?

- ✓ APOA1 and Cholesterol levels change with kidney failure



Object **Pre beta-1 HDL lipids + Cholesterol + Phospholipid = HDL nascent lipids**:
Particle transformation



HDL

By Objects

- APOA1(APOA1)
- APOC3(APOC3)

By Experiments

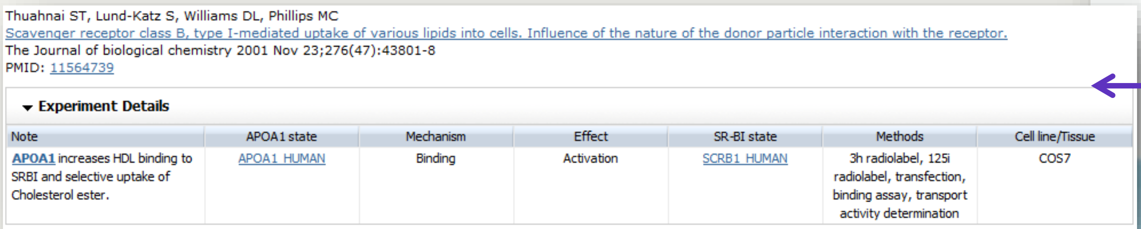
- (4) Proteomics_AKI 1 / AKI 0
- (5) Proteomics_AKI 2-3 / AKI 0
- (6) Proteomics_HD / AKI0

Objects

APOA1(APOA1)		
1	**1:** (4) Proteomics_AKI 1 / AKI 0	-0.03 [0.05]
2	**2:** (5) Proteomics_AKI 2-3 / AKI 0	-0.02 [1]
3	**3:** (6) Proteomics_HD / AKI0	-0.01 [1]
Cholesterol(C00187)		
1	**4:** (4) Metabolomics_stage 1	0.15 [1]
2	**5:** (5) Metabolomics_stage 2	-0.03 [1]
3	**6:** (6) Metabolomics_stage 3	0.29 [0.05]

➢ What changes in metabolites and protein concentrations could be biomarkers for disrupted processes?

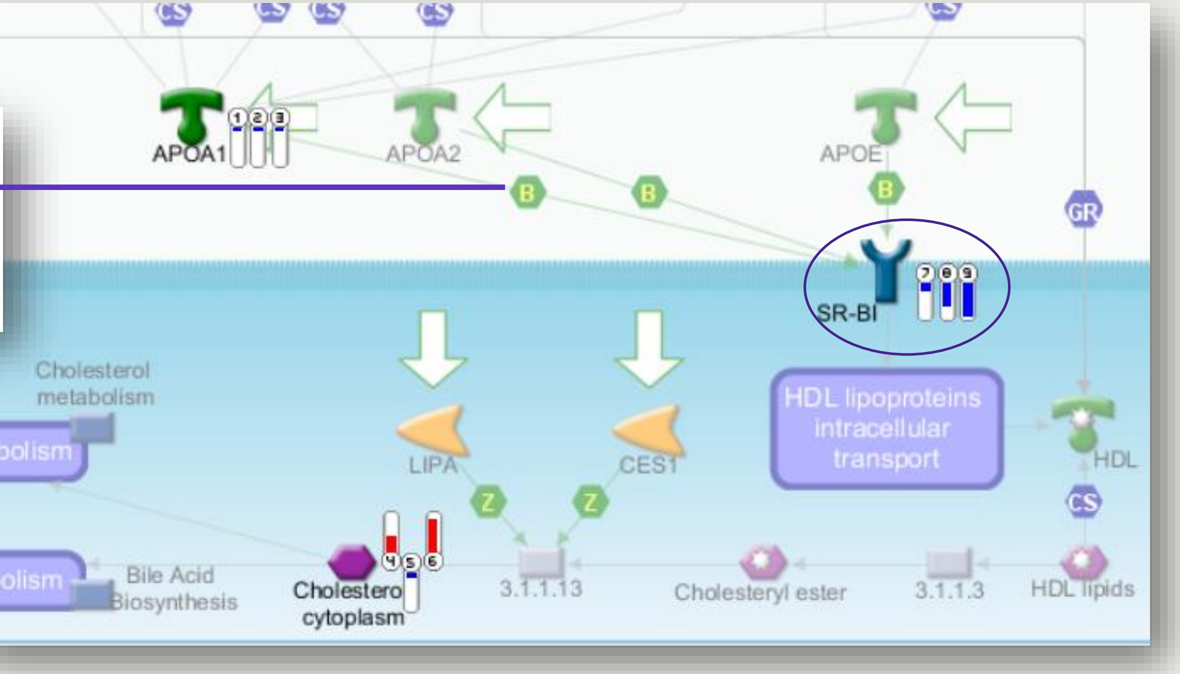
- ✓ SR-B1 expression appears to decrease as kidney injury worsens and could be indicative of cholesterol metabolism dysregulation.



Thuahnai ST, Lund-Katz S, Williams DL, Phillips MC
Scavenger receptor class B, type I-mediated uptake of various lipids into cells. Influence of the nature of the donor particle interaction with the receptor.
The Journal of biological chemistry 2001 Nov 23;276(47):43801-8
PMID: 11564739

▾ Experiment Details

Note	APOA1 state	Mechanism	Effect	SR-BI state	Methods	Cell line/Tissue
APOA1 increases HDL binding to SRBI and selective uptake of Cholesterol ester.	APOA1_HUMAN	Binding	Activation	SCRB1_HUMAN	3h radiolabel, 125i radiolabel, transfection, binding assay, transport activity determination	COS7



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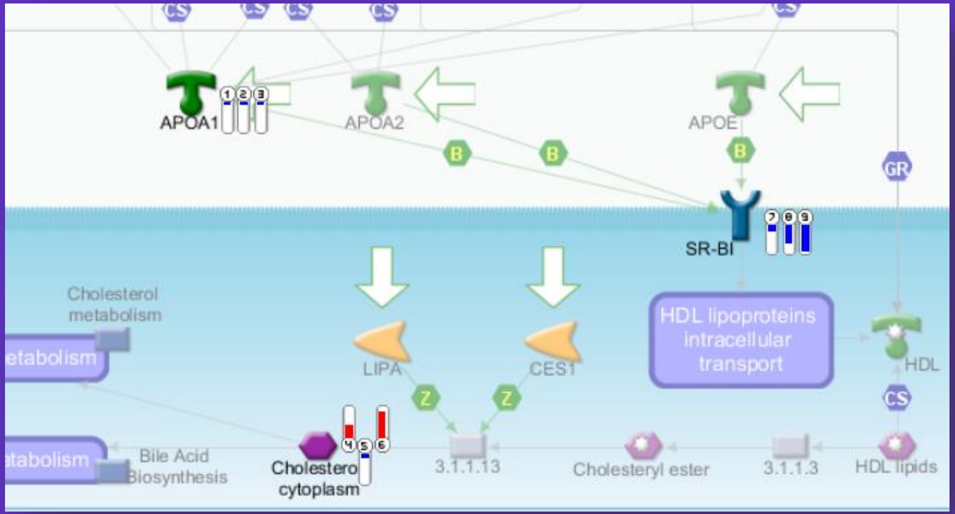
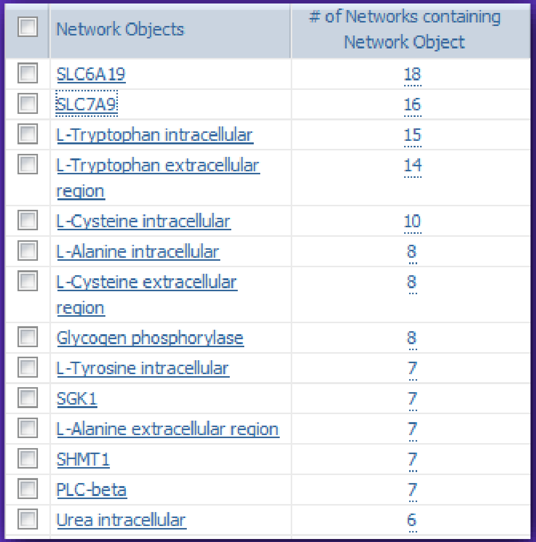
SUMMARY

- ✓ Used metabolomic and RNA-seq analysis and identified channels such as SLC7A9 and SLC6A19 could be playing a role in the transport of amino acids in and out of cells.
- ✓ Used metabolomic and proteomic analysis to identify potential biomarkers for disrupted processes.
- ✓ Added the RNA-seq analysis to find that a decrease SR-B1 expression (associated to kidney injury) could be indicative of cholesterol metabolism dysregulation.





☐	Network Objects	# of Networks containing Network Object
☐	SLC6A19	18
☐	SLC7A9	16
☐	L-Tryptophan intracellular	15
☐	L-Tryptophan extracellular region	14
☐	L-Cysteine intracellular	10
☐	L-Alanine intracellular	8
☐	L-Cysteine extracellular region	8
☐	Glycogen phosphorylase	8
☐	L-Tyrosine intracellular	7
☐	SGK1	7
☐	L-Alanine extracellular region	7
☐	SHMT1	7
☐	PLC-beta	7
☐	Urea intracellular	6

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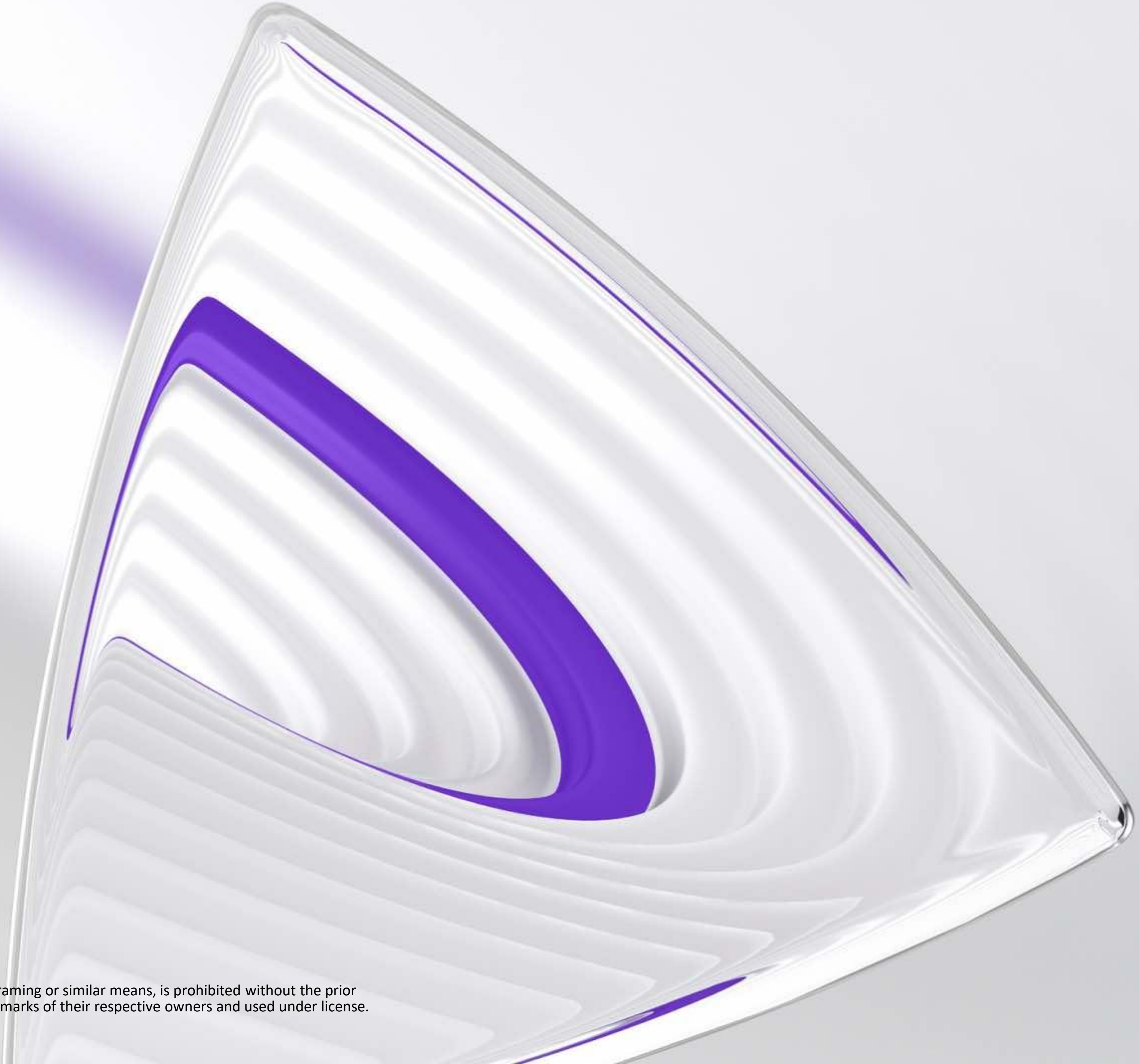
Thank you



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