

Data resources at EMBL-EBI

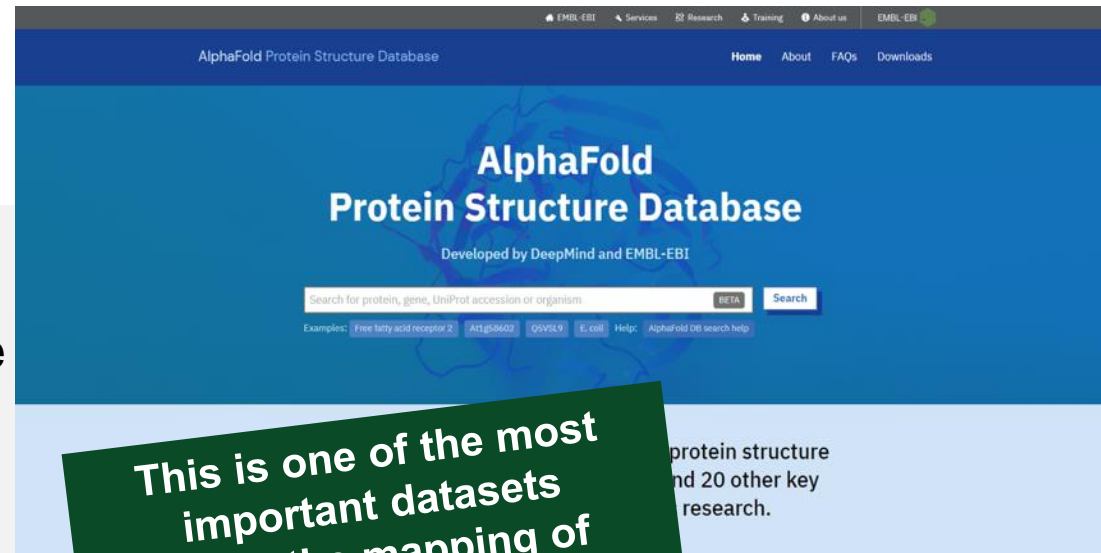


Henning Hermjakob
hhe@ebi.ac.uk

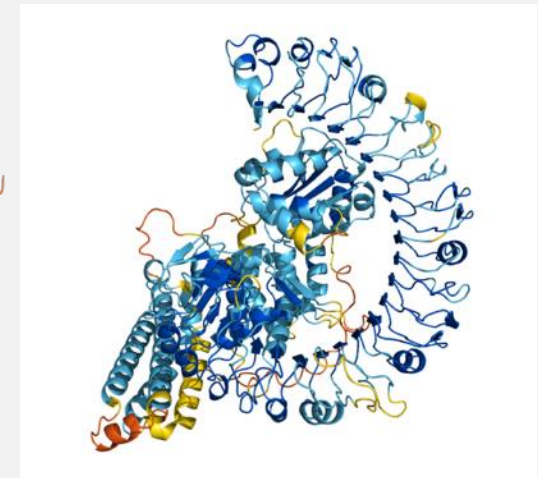
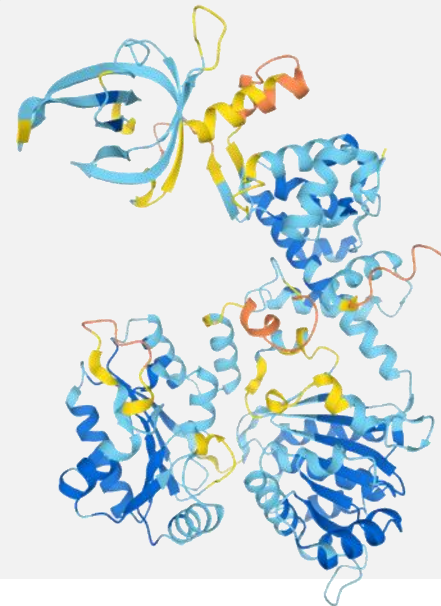
AlphaFold Protein Structure Database

- Launched on 22nd July 2021
 - Open access (CC-BY-4.0 license) to all structure models
- V1: ~365,000 models (21 proteomes)
- V2: >800,000 models (SwissProt entries)
- V3: ~1,000,000 Structures (focus on pathogens and neglected diseases; 49 proteomes)
- Later in 2022: >100,000,000 models

NAR paper on AlphaFold DB: bit.ly/NAR-AFDB-2022

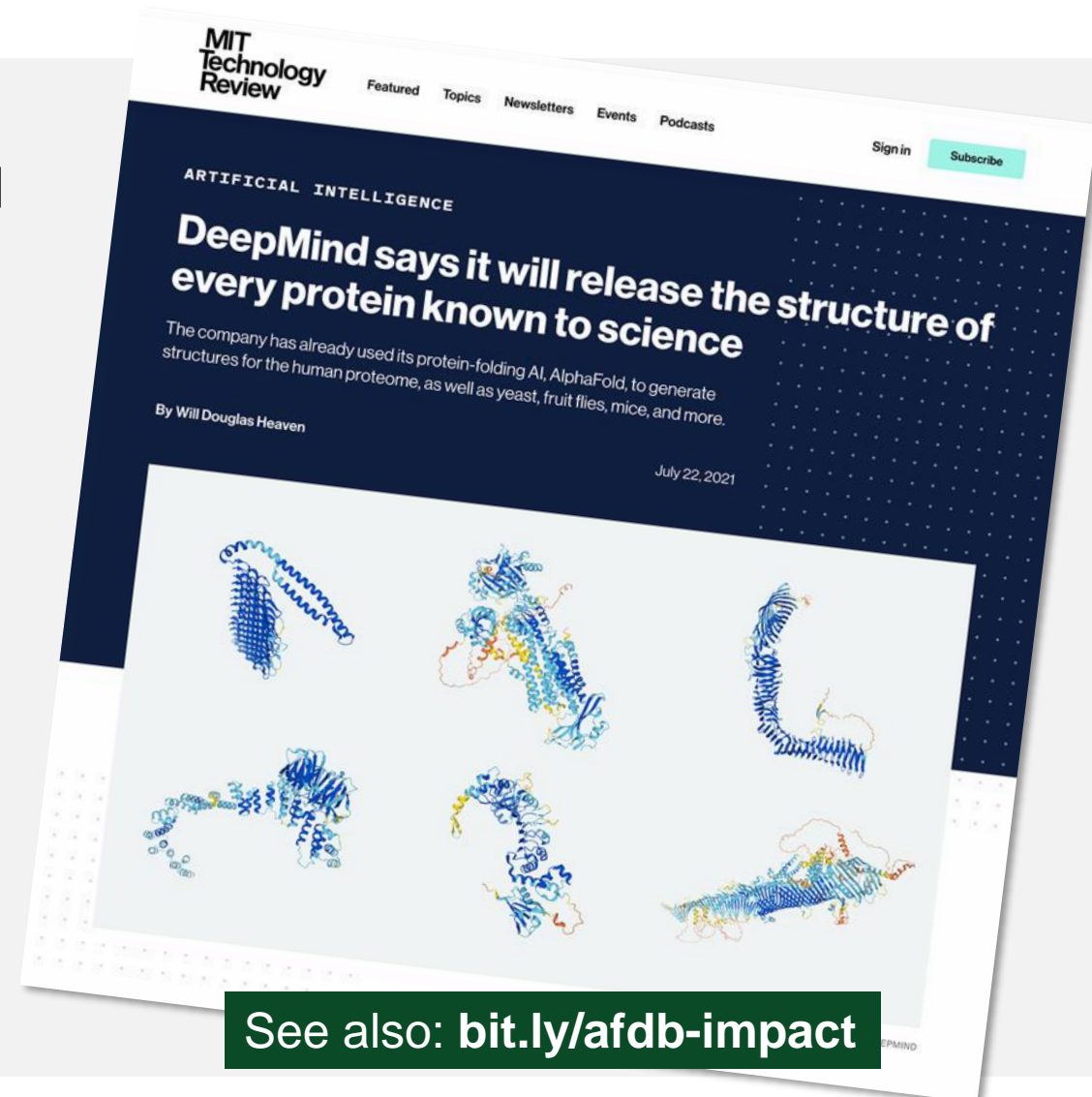


This is one of the most important datasets since the mapping of the Human Genome



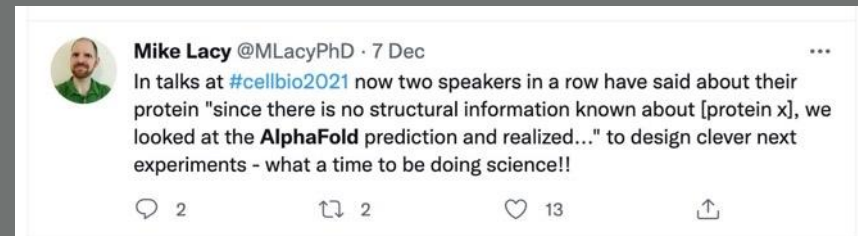
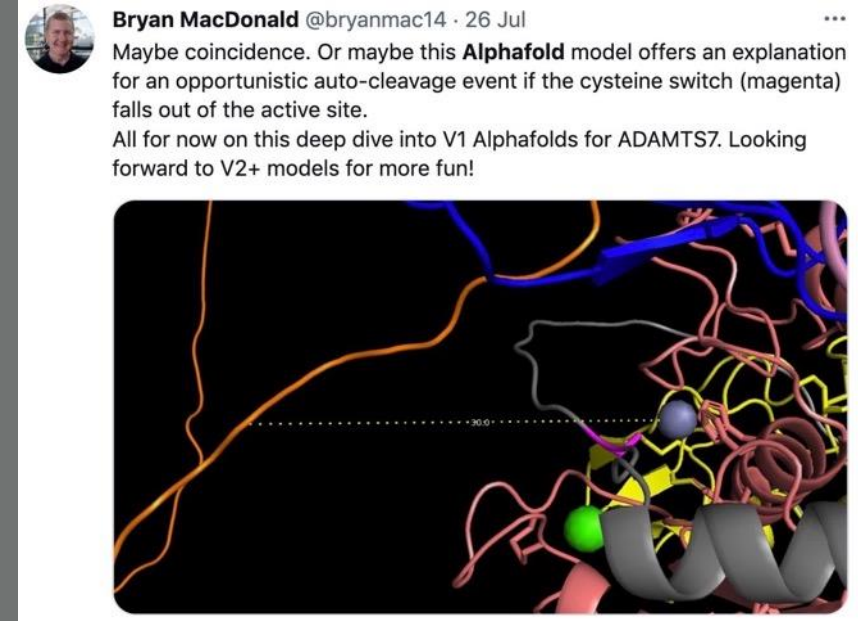
Impact of AlphaFold database on life science research

- Structure for every known protein in UniProt database will be available or can be modelled
- 3-D structures for virtually all (98.5%) of the human proteome
 - 92.5% residues are covered
 - 58% of all residues have very confident(36%) or confident (22%) predictions
 - ~30-40% are disordered and are not expected to have good prediction
- Protein Data Bank content
 - Only ~17% of the human proteome residues covered in the PDB

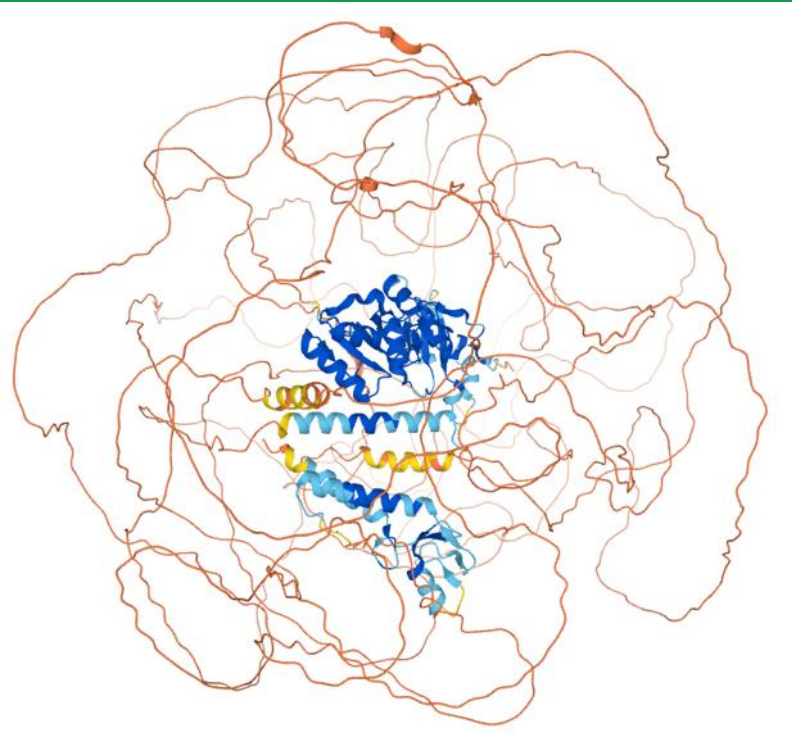


New normal for biology

- Many studies of proteins can now start with a 3D model as the basis for hypotheses
- Does a model explain previously known data on function, binding, specificity, ...?
- Design experiments based on the model (e.g., introduce mutations)



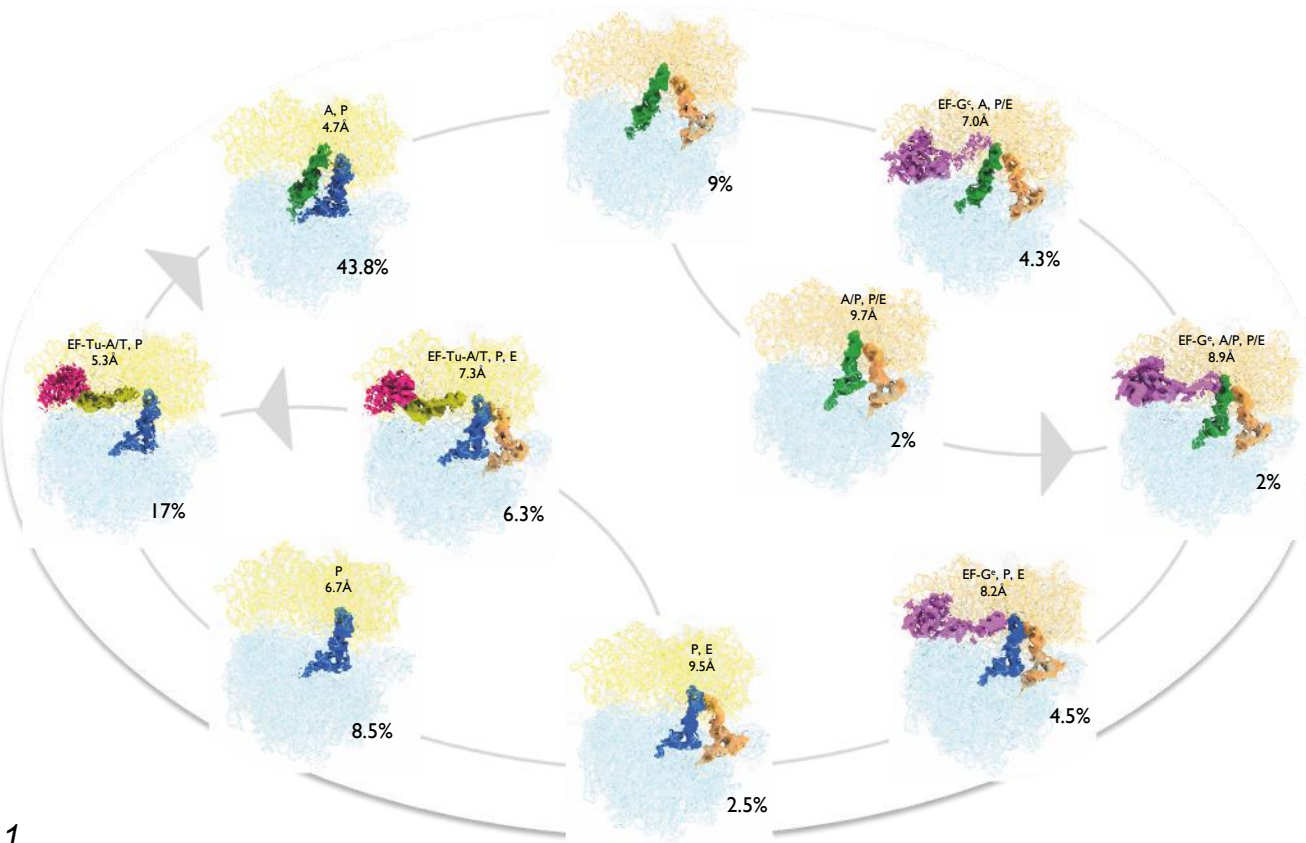
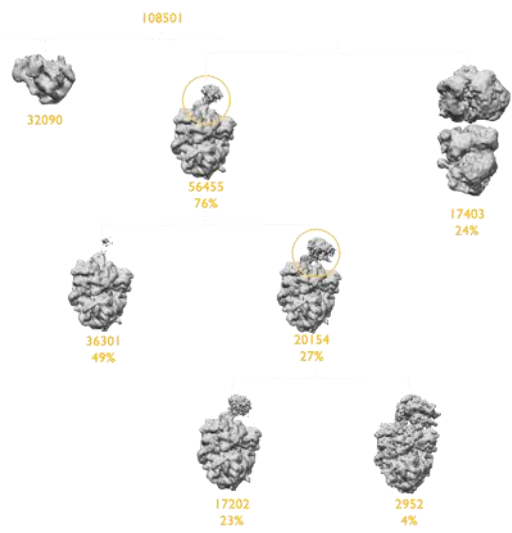
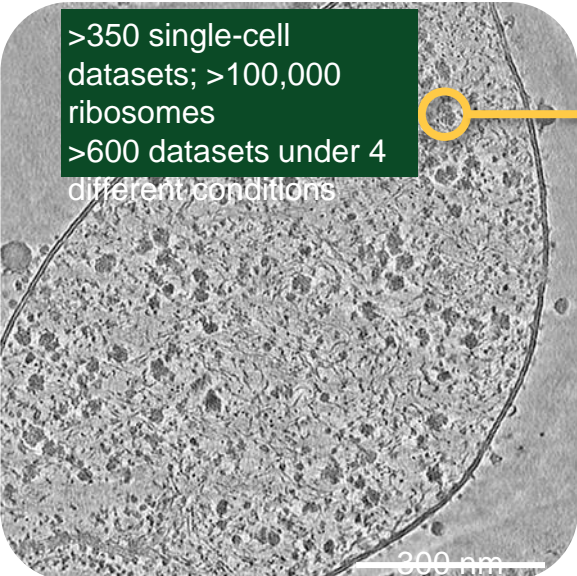
Impact of AlphaFold database on life science research



- “An unexpected effect of the AFDB is that it visually demonstrates the prevalence of intrinsically disordered regions (IDRs) in the human proteome”
- Ried Alderson et al. doi:
<https://doi.org/10.1101/2022.02.18.481080>
- “Proteins” are no longer seen as having a well defined and compact structure
- Inclusion of unstructured regions with pLDDT <70 in AFDB structures was a conscious decision

From Structural Inventories to Processes: Visual proteomics

Single-cell translation profiles
Molecular sociology of ribosomes
Translation landscapes reshaped by antibiotics



Tegunov, Xue, Dienemann, Cramer & Mahamid. *Nature Methods* 2021
O'Reilly*, Xue*, Graziadei *, Sinn, Lenz, Tegunov, Blötz, Hagen, Cramer, Stülke, Mahamid & Rappsilber. *Science* 2020

Xue, Lenz, Zimmermann-Kogadeeva, Tegunov, Cramer, Bork, Rappsilber & Mahamid. *Biorxiv* 2021; under review

Data resources at EMBL-EBI

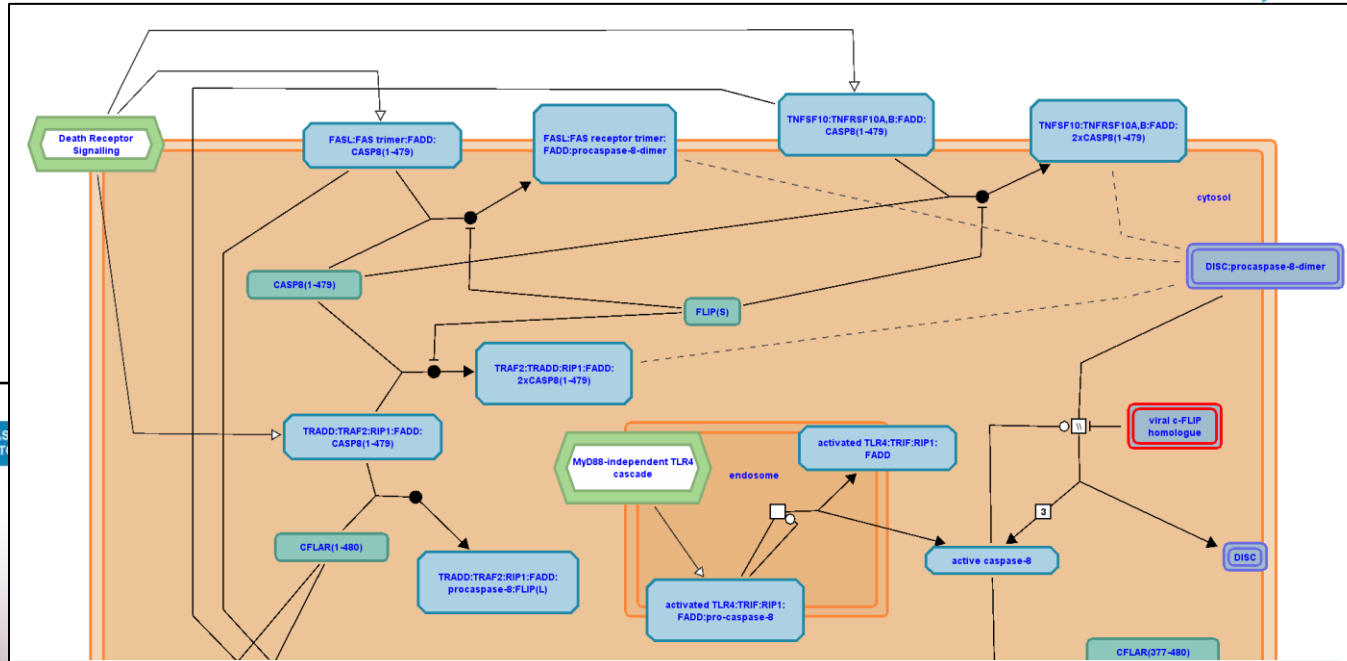
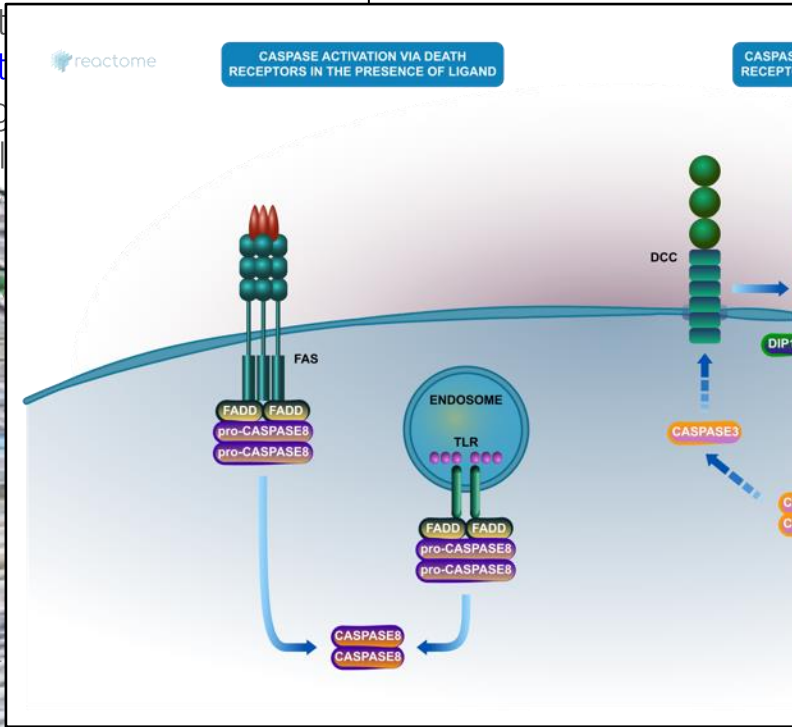




Reactome: Computationally Accessible Pathway Reviews

Nature 407(6805):770-6. The Biochemistry of Apoptosis.

“Caspase-8 is the key initiator caspase in the death-receptor pathway. Upon ligand binding, death receptors (Apo-1/Fas) aggregate membrane-bound signaling proteins (Box 3). These complex through recruitment of pro-caspase-8 and pro-caspase-10. The proximity of these proteases is sufficient to activate each other, a process including caspase-8 activation.



Summation

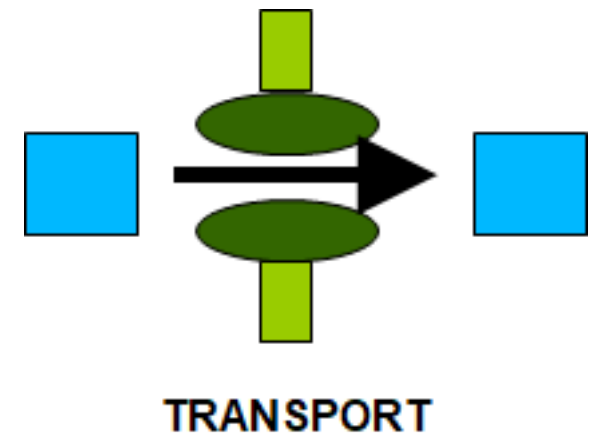
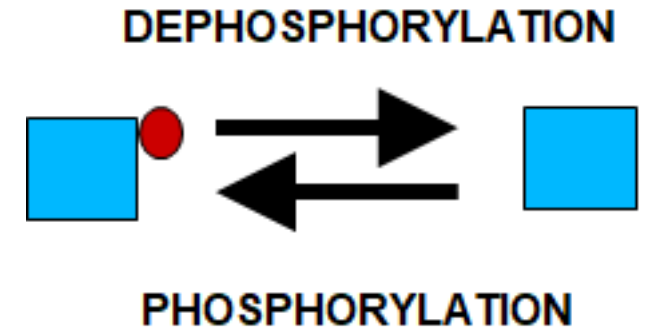
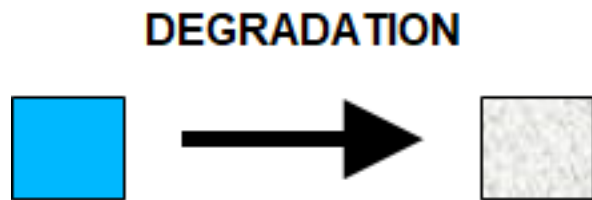
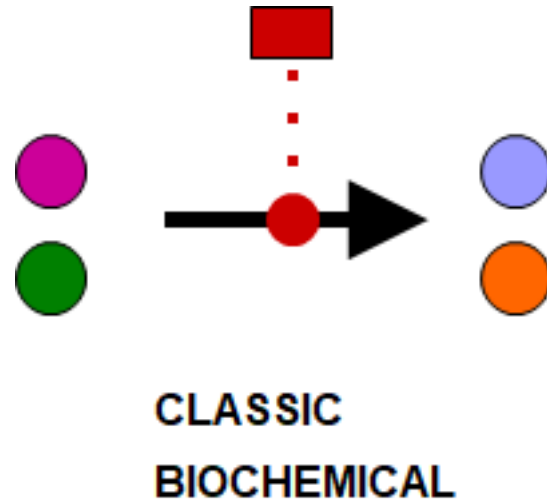
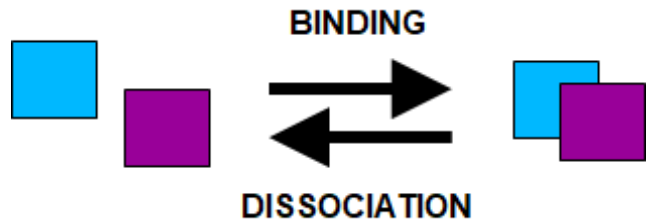
Caspase-8 is synthesized as zymogen (procaspase-8) and is formed from procaspase-8 as a cleavage product. However, the cleavage itself appears not to be sufficient for the efficient activation in vitro and apoptosis in cellular systems [Boatright KM and Salvesen GS 2003; Keller N et al 2010; Oberst A et al 2010].

The caspase-8 zymogens are present in the cells as inactive monomers, which are recruited to the death-inducing signaling complex (DISC) by homophilic interactions with the cytosolic tails of the receptors. The subsequent conformational changes at the receptor complex, which results in the formation of catalytically active form of procaspase-8. [Boatright KM et al 2003; Doneudi M et al 2003]

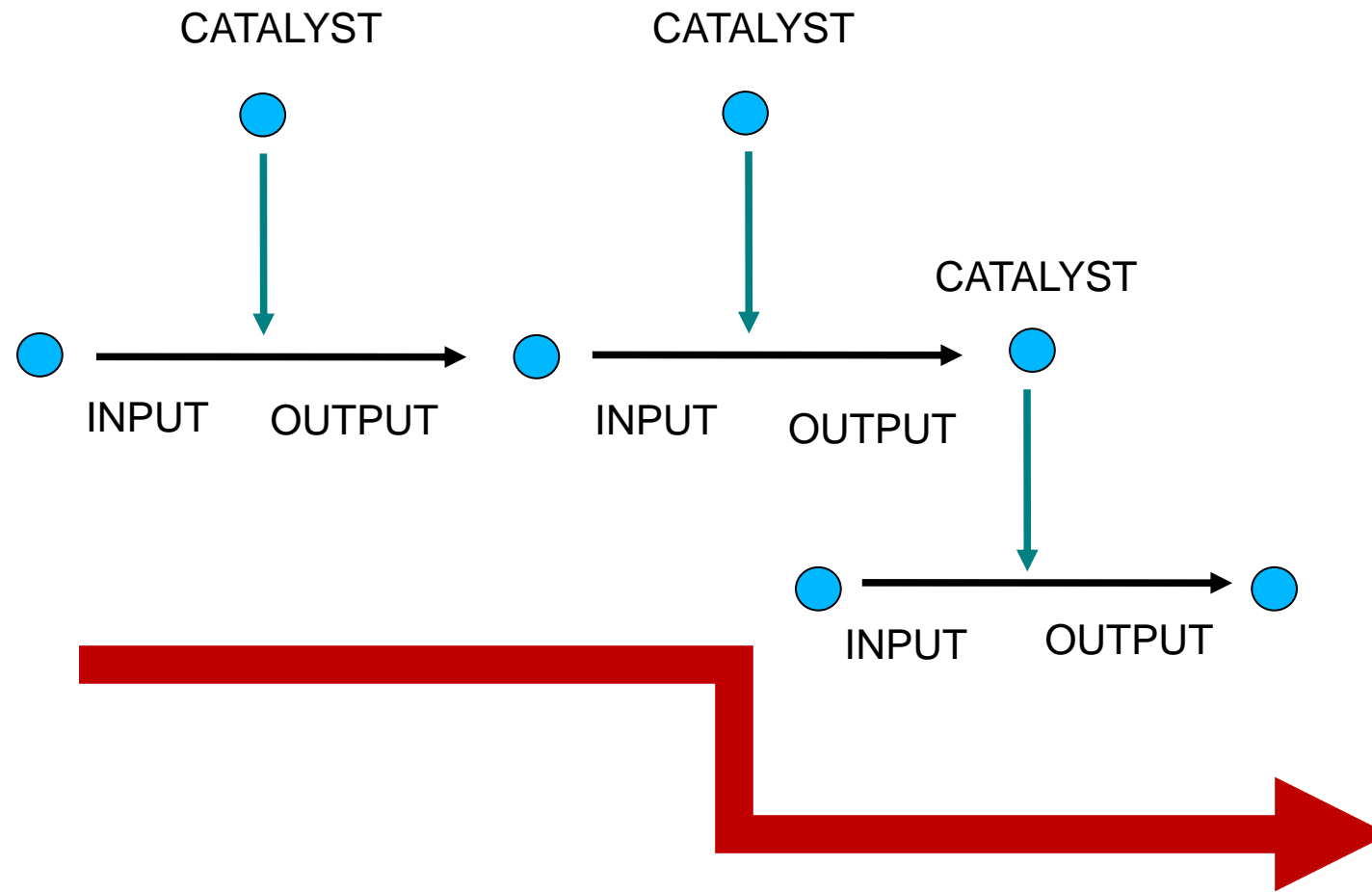
Caspase activation via Death Receptors in the presence of ligand



Reactions as Building Blocks

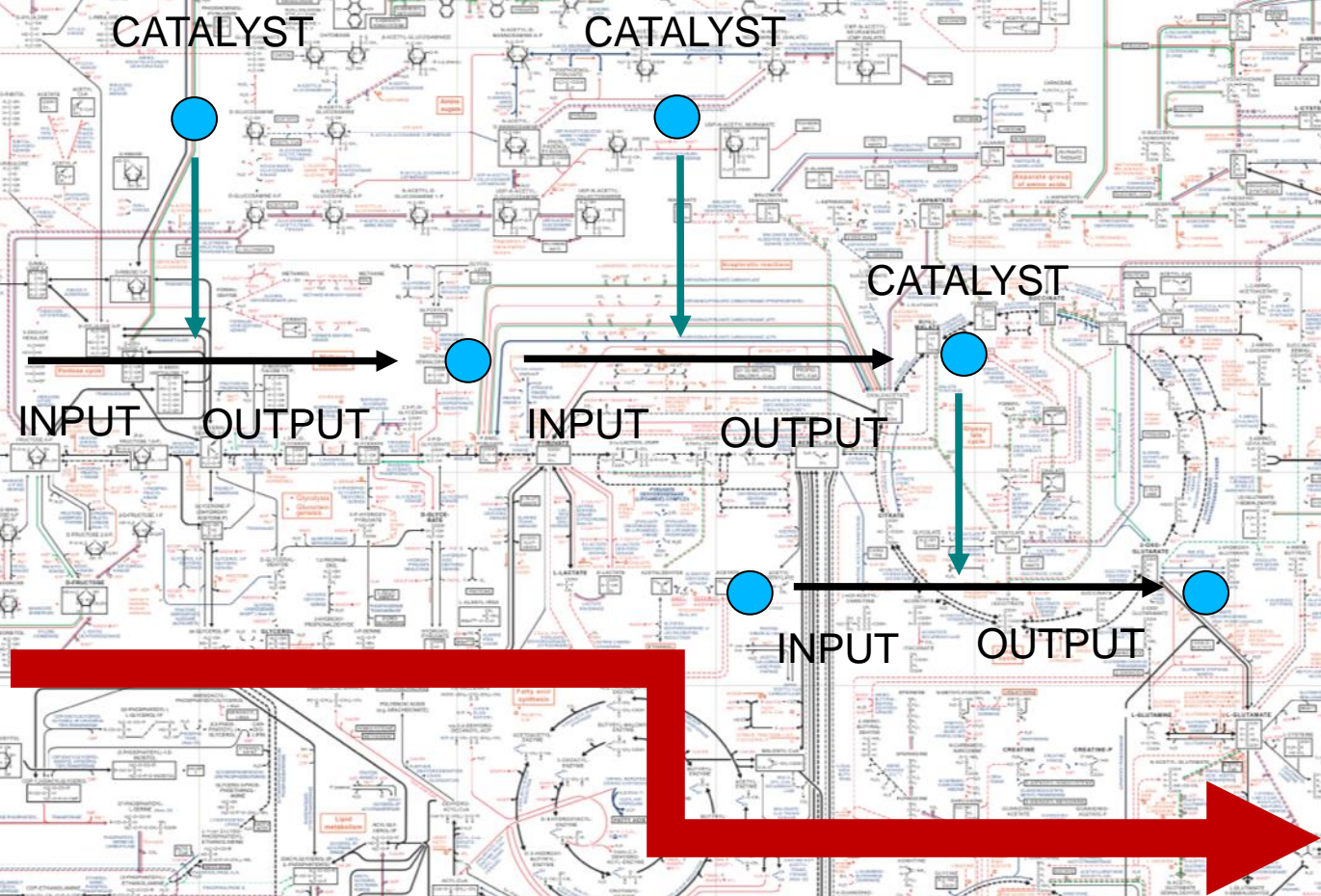


Reactions Connect into Pathways





... which are parts of a vast, connected network!



Pathway Browser



The screenshot displays the Reactome Pathway Browser interface. At the top, the Reactome logo and version (3.7) are visible, along with a dropdown menu for 'Pathways for: Homo sapiens'. Navigation tools for Citation, Analysis, Tour, and Layout are provided. On the left, an 'Event Hierarchy' tree lists various biological processes, with 'Hemostasis' and 'Platelet homeostasis' expanded. The central area shows a complex pathway map with several sub-sections highlighted in colored boxes: 'Platelet calcium homeostasis' (green), 'Prostacyclin signalling through prostacyclin receptor' (red), 'Nitric oxide stimulates guanylate cyclase' (blue), and 'Platelet sensitization by LDL' (grey). The bottom panel contains tabs for Description, Molecules, Structures, Expression, Analysis, and Downloads. The 'Description' tab is active, showing a 'Summation' section with a detailed text description of platelet homeostasis. Metadata includes 'Id: R-HSA-418346.2' and 'Species: Homo sapiens'.

Hierarchy

Mol. Map

Details



Description Molecules Structures Expression Analysis Downloads

Platelet homeostasis Id: R-HSA-418346.2 Species: Homo sapiens

Summation

Under normal conditions the vascular endothelium supports vasodilation, inhibits platelet adhesion and activation, suppresses coagulation, enhances fibrin cleavage and is anti-inflammatory in character. Under acute vascular trauma, vasoconstrictor mechanisms predominate and the endothelium becomes prothrombotic, procoagulatory and proinflammatory in nature. This is achieved by a reduction of endothelial dilating agents: adenosine, NO and prostacyclin; and by the direct action of ADP, serotonin and thromboxane on vascular smooth muscle cells to elicit their contraction (Becker et al. 2000). Cyclooxygenase-2 (COX-2) and endothelial nitric oxide synthase (eNOS) are primarily expressed in endothelial cells. Both are important regulators of vascular function. Under normal conditions, laminar flow induces vascular endothelial COX-2 expression and synthesis of Prostacyclin (PGI₂) which in turn stimulates endothelial Nitric Oxide Synthase (eNOS) activity. PGI₂ and NO both oppose platelet activation and aggregation, as does the CD39 ecto-

Pathway Browser



Hierarchy

The screenshot displays the Reactome Pathway Browser interface. At the top, it shows the Reactome logo, version 3.7, and the pathway name 'Pathways for: Homo sapiens'. The main area is a metabolic pathway diagram set in a 'cytosol' compartment. Key components include LDL binding to LRP8, FGR binding to LDL:LRP8, and subsequent phosphorylation events involving MAPK14 and p-T180,Y182-MAPK14. The diagram uses various shapes and colors to represent molecules and their interactions, with some molecules highlighted in blue boxes. On the left side, there is a 'Event Hierarchy' panel with a tree view of biological processes, including 'Platelet sensitization by LDL'. At the bottom, there is a 'Details' section with tabs for 'Description', 'Molecules', 'Structures', 'Expression', 'Analysis', and 'Downloads'. The 'Structures' tab is active, showing a 3D protein structure of MAPK14 (UniProt: Q16539) with a resolution of 1.6 Å.

Mol. Map

Details

Pathway Analysis



Analysis tools

Ever

- Analyse gene list
- Analyse gene expression
- Species Comparison
- Tissue Distribution
- Reactome v79
- Click to learn more about our analysis tools

Your data

Options

Analysis

Step 1: Select a file from your computer or paste your own data and click on the corresponding "Continue" button.

Select data file for analysis: No file chosen

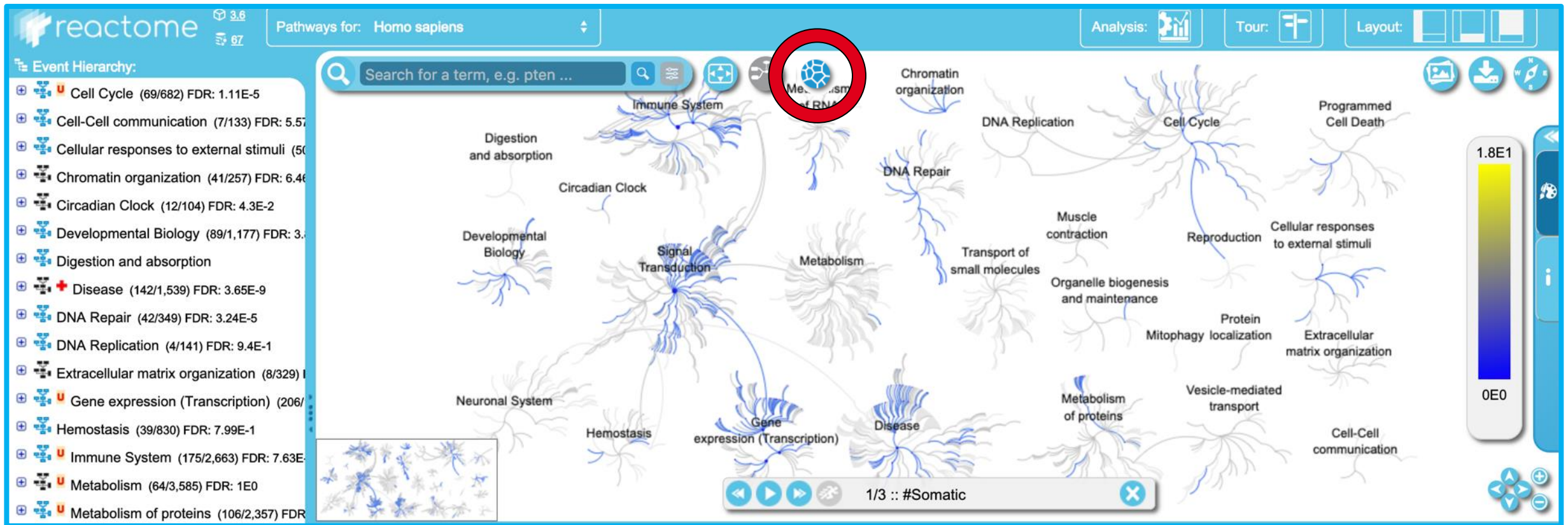
Paste your data to analyse or try example data sets:

```
#GBM Uniprot
P01023
Q99758
O15439
O43184
Q13444
P82987
P04083
Q7Z5R6
P27540
Q13315
P36543
Q13535
```

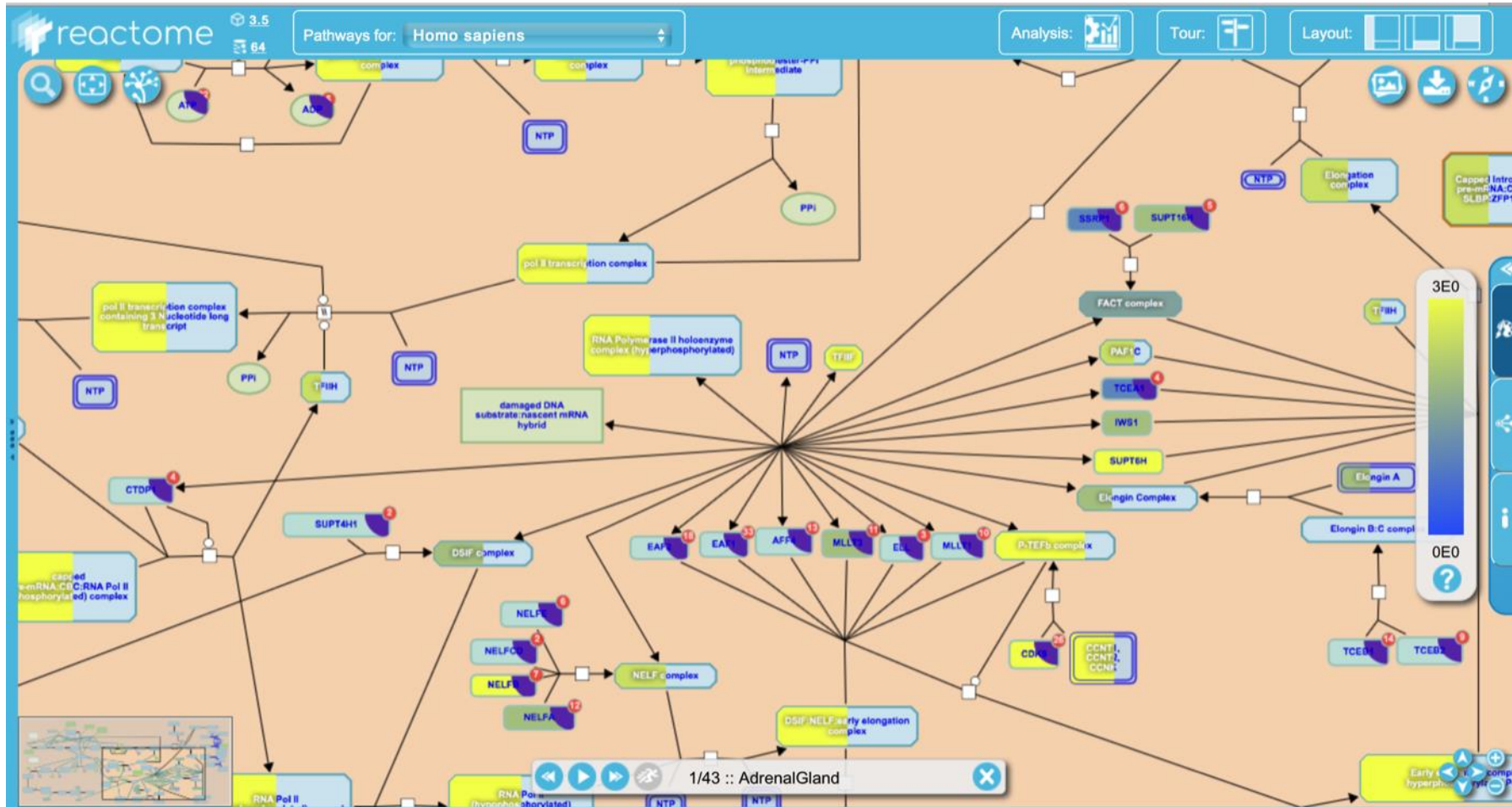
Some examples:

- UniProt accession list
- Gene name list
- Gene NCBI / Entrez list
- Small molecules (ChEBI)
- Small molecules (KEGG)
- Microarray data
- Metabolomics data
- Cancer Gene Census (COSMIC)
- Tissue Specific Expression (HPA)

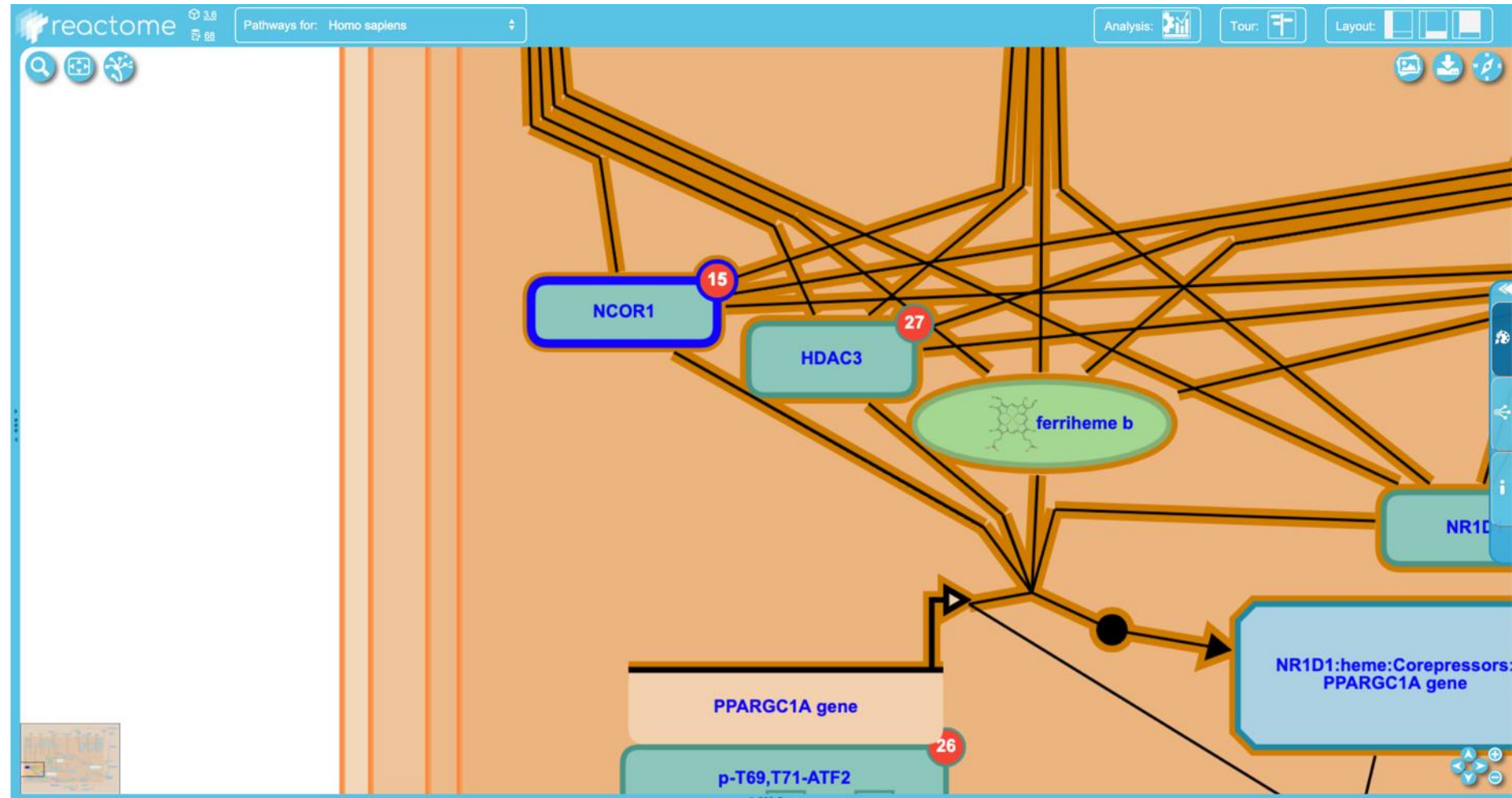
Pathway Analysis: Results overview - Fireworks



Pathway Analysis: Detail view



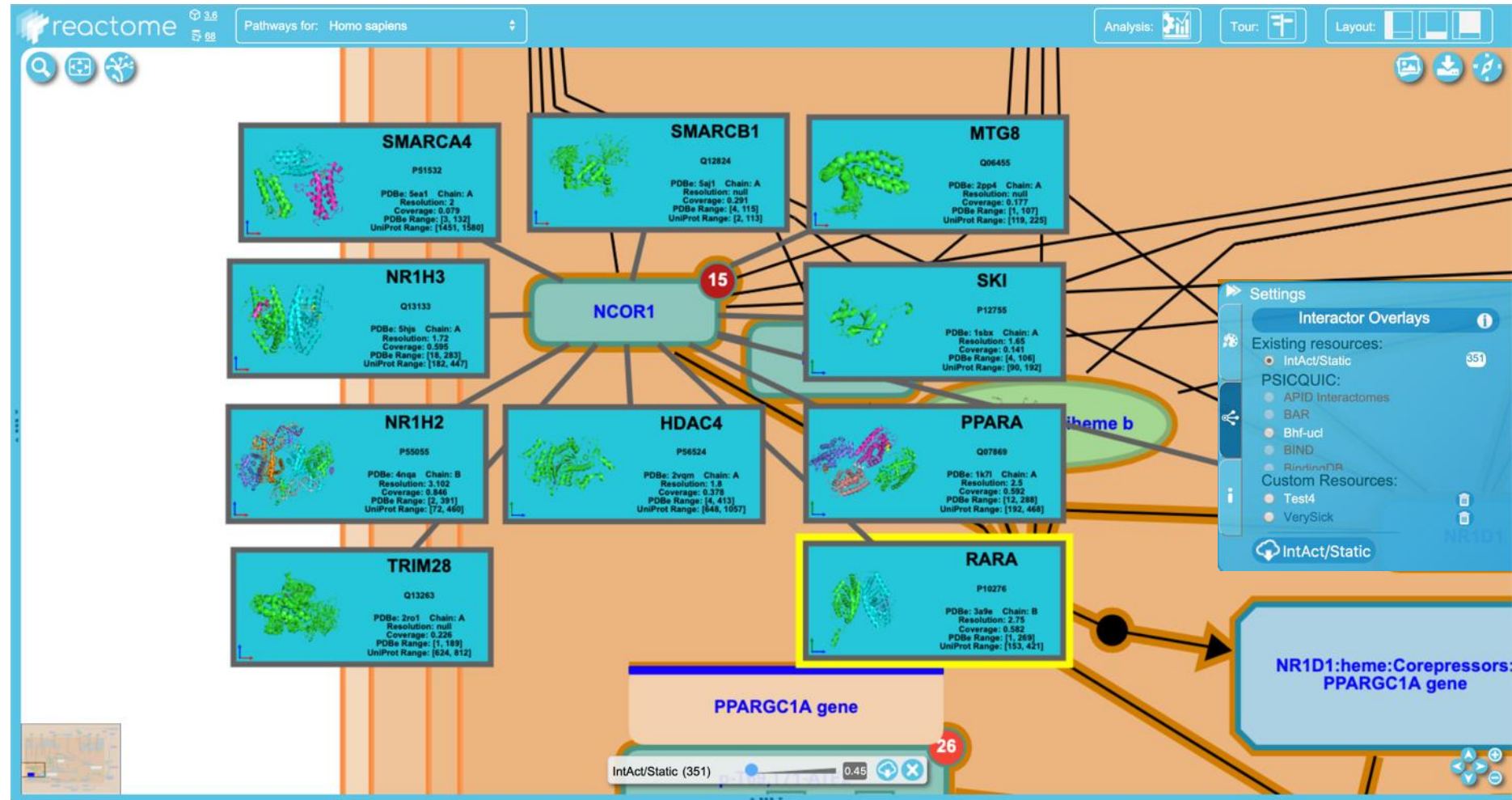
Pathway Analysis: Detail view



Inclusion of External Data: IntAct

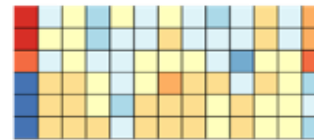
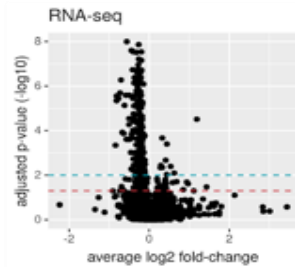
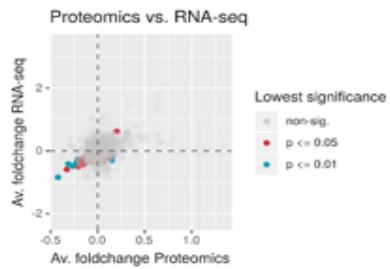
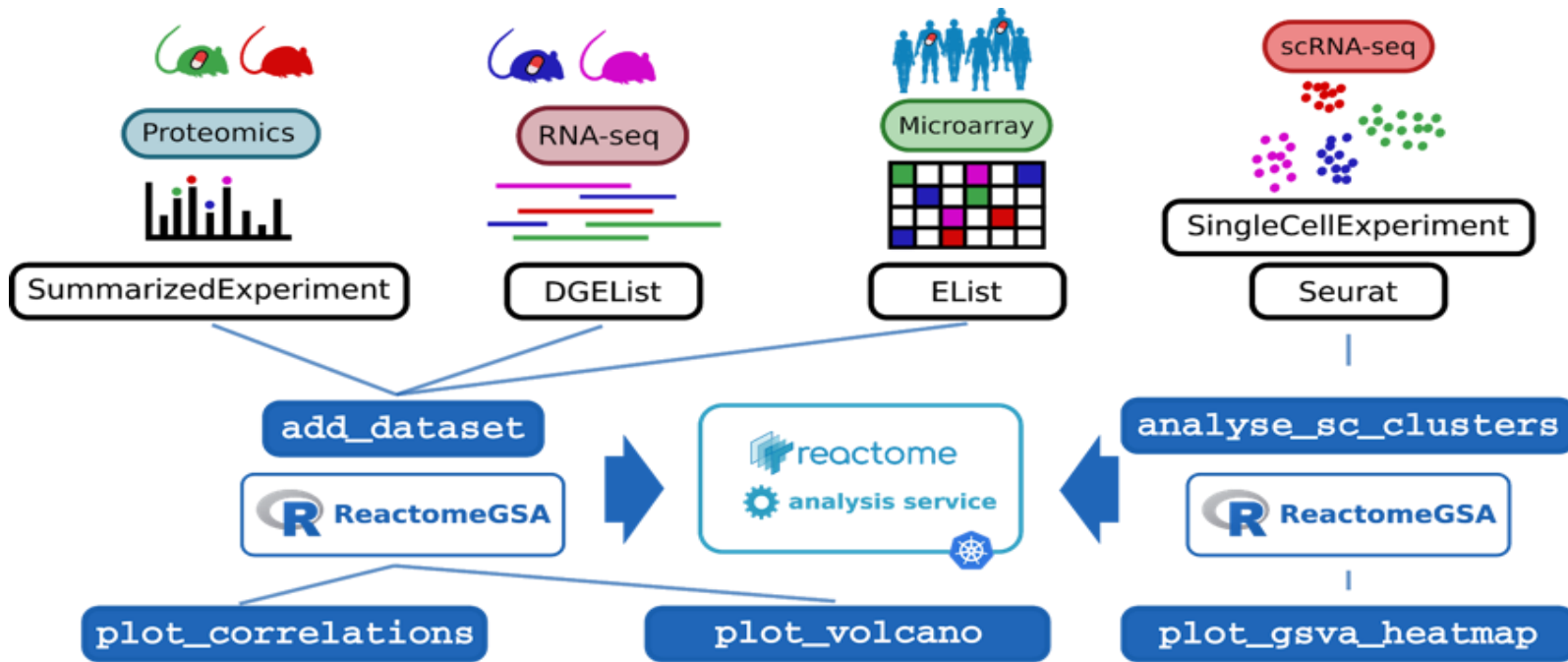


- Medium to high confidence interactors from IntAct are included in the Reactome pathway database
- Where available, PDB structure pictograms are included in high zoom levels
- Many other resources available through PSICQUIC web services





ReactomeGSA - Quantitative Multi-Omics Analysis



ASBMB - MOLECULAR & CELLULAR PROTEOMICS

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Technological Innovation and Resources

ReactomeGSA - Efficient Multi-Omics Comparative Pathway Analysis

Johannes Griss, Guilherme Viteri, Konstantinos Sidiropoulos, Vy Nguyen, Antonio Fabregat and Hanning Hermjakob

Molecular & Cellular Proteomics September 9, 2020. mcp.TIR120.002155; https://doi.org/10.1074/mcp.TIR120.002155

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Recommended for you

Extracting Pathway-Level S Breast Cancer Using Indep Editors' Choice, Wenke Liu 2019

Graph algorithms for condense analysis results Sara R. Savage et al., Mol

Multi-omics data integration Tumor microenvironment Cancer immunology Bioinformatics software Cancer Biology Data evaluation Melanoma Pathway Analysis

Quantitative Analysis



```
# S4 request class
my_request <- new("ReactomeAnalysisRequest", method="Camera")

# directly import limma dataset
data("griss_melanoma_proteomics")
my_request <- add_dataset(request = my_request,
                          expression_values = griss_melanoma_proteomics,
                          name = "Proteomics",
                          type = "proteomics-int",
                          comparison_factor = "condition",
                          comparison_group_1 = "MOCK",
                          comparison_group_2 = "MCM",
                          additional_factors = c("cell.type", "patient.id"))

# directly import edgeR dataset
data("griss_melanoma_rnaseq")
my_request <- add_dataset(request = my_request,
                          expression_values = griss_melanoma_rnaseq,
                          name = "RNA-seq",
                          type = "rnaseq",
                          comparison_factor = "treatment",
                          comparison_group_1 = "MOCK",
                          comparison_group_2 = "MCM",
                          additional_factors = c("cell_type", "patient"))
```

<https://bioconductor.org/packages/release/bioc/html/ReactomeGSA.html>

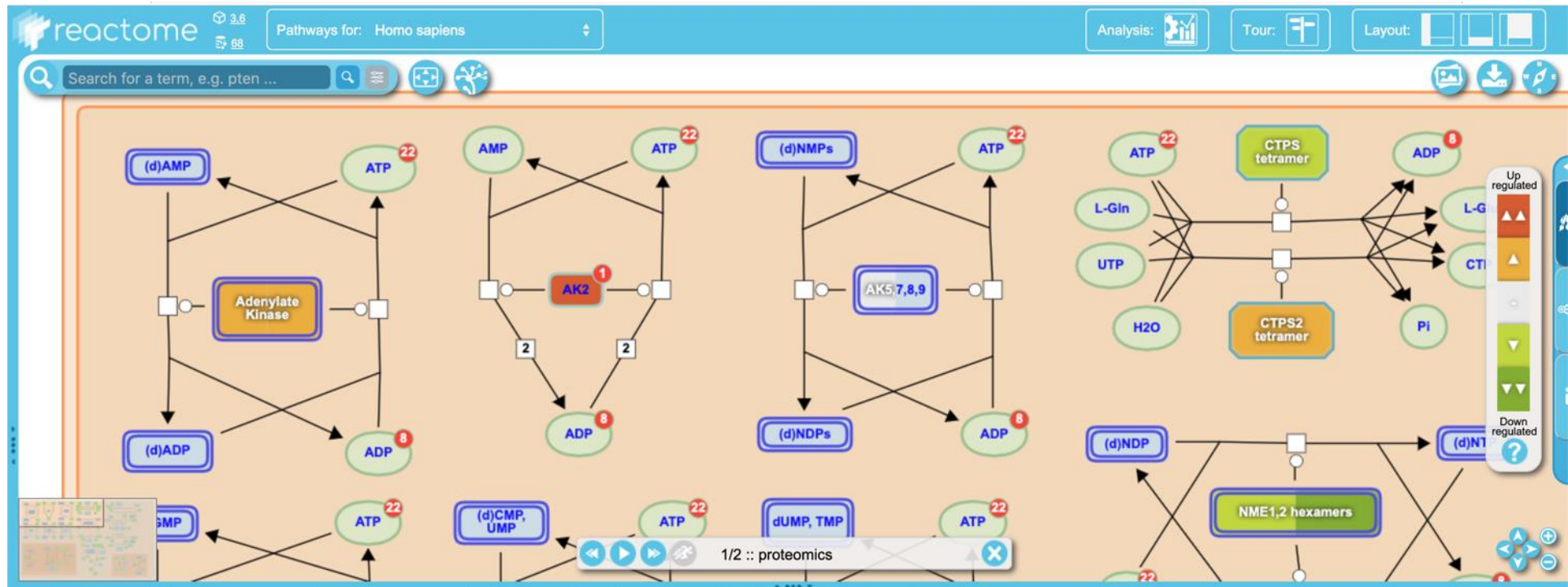
Combined Visualization



```
# perform the analysis
analysis_result <- perform_reactome_analysis(my_request)

# get the pathway statistics
pathway_result <- pathways(analysis_result)

# open the visualization
open_reactome(analysis_result)
```



Description | Molecules | Structures | Expression | Analysis 2,108 | Downloads

Gsa Regulation analysis results for TOTAL [Data: Multi-sample analysis]

Results	Pathway name	Entities found	Entities Total	Entities ratio	Entities pValue	Entities FDR	Reactions found	Reactions total	Reactions ratio	proteomics	maseq	Species name
	Propionyl-CoA catabolism	5	14	0.001	1.48E-2	7.4E-2	3	3	0	▲▲▲	▲	Homo sapiens
905	Signaling by FGFR	68	106	0.007	1.49E-2	7.44E-2	139	142	0.012	▼	▼	Homo sapiens
	Mitochondrial protein import	57	69	0.005	1.49E-2	7.44E-2	14	14	0.001	▲▲	▼	Homo sapiens
Not found	Interferon gamma signaling	179	250	0.018	1.52E-2	7.53E-2	15	15	0.001	▲	▲	Homo sapiens
	Intracellular metabolism of fatty acids regulates insulin secretion	3	9	0.001	1.6E-2	7.92E-2	2	2	0	▲	▼	Homo sapiens

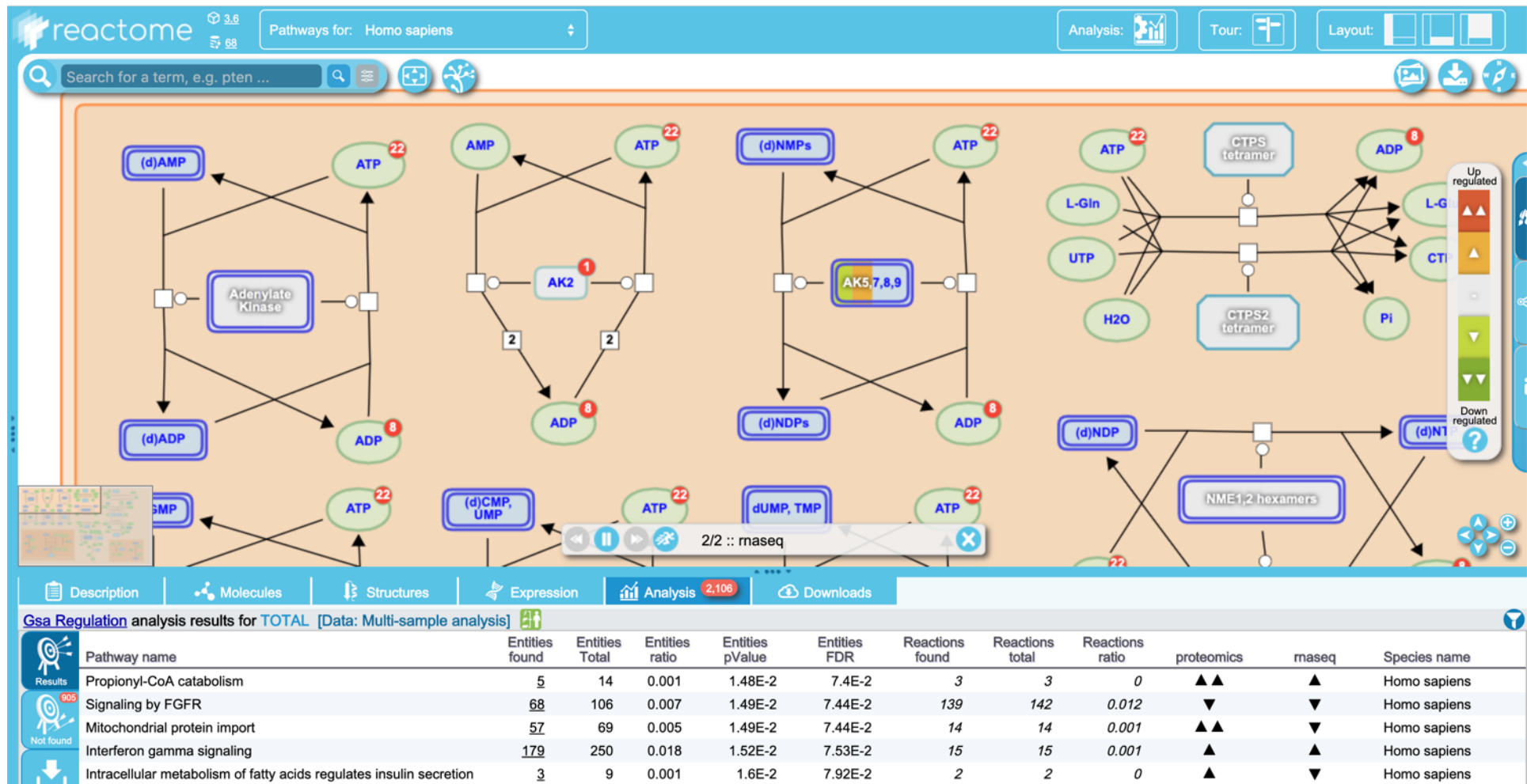


Combined Visualization

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# get the pathway statistics
pathway_result <- pathways(analysis_result)

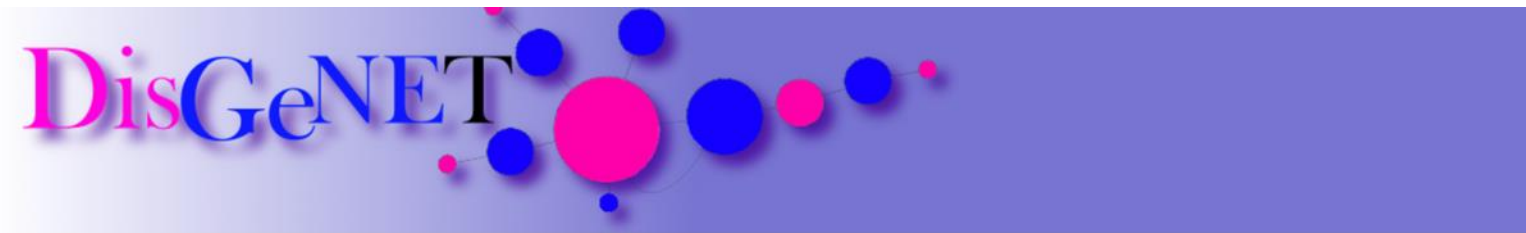
# open the visualization
open_reactome(analysis_result)
```





External Binary Data Overlay: DisGeNET

- Many types of binary association data:
 - Disease-Gene, Drug-Target, Antibody-Antigen, ...
- Example: DisGeNet



DisGeNET is a discovery platform containing one of the largest publicly available collections of genes and variants associated to human diseases (Piñero *et al.*, 2016; Piñero *et al.*, 2015). DisGeNET integrates data from expert curated repositories, GWAS catalogues, animal models and the scientific literature. DisGeNET data are homogeneously annotated with controlled vocabularies and community-driven ontologies. Additionally, several original metrics are provided to assist the prioritization of genotype-phenotype relationships.

	A	B	C	D	E	F	G	H	I
1	geneld	geneSymbol	DSI	DPI	diseaseId	diseaseName	diseaseType	diseaseClass	diseaseSemanticType
1421	3949	LDLR	0.475	0.828	C0519066	Acute Q fever	disease	C01	Disease or Syndrome
1422	4047	LSS	0.676	0.448	C0519066	Acute Q fever	disease	C01	Disease or Syndrome
1423	10211	FLOT1	0.727	0.414	C0519066	Acute Q fever	disease	C01	Disease or Syndrome
1424	1152	CKB	0.636	0.483	C0857501	Acute schizophrenia	disease		Mental or Behavioral Dysfunc
1425	3458	IFNG	0.323	0.897	C0857501	Acute schizophrenia	disease		Mental or Behavioral Dysfunc
1426	7167	TP11	0.564	0.655	C0857501	Acute schizophrenia	disease		Mental or Behavioral Dysfunc
1427	4297	KMT2A	0.46	0.793	C0280141	Acute Undifferentiated Leukemia	disease		Neoplastic Process
1428	283	ANG	0.547	0.69	C0001349	Acute-Phase Reaction	phenotype	C23	Pathologic Function
1429	28976	ACAD9	0.727	0.345	C1970173	Acyl-CoA Dehydrogenase Family, Member 9, Deficient	disease	C05;C10;C14;C1	Disease or Syndrome
1430	673	BRAF	0.352	0.793	C0431129	Adamantinous Craniopharyngioma	disease	C04	Neoplastic Process

DisGeNET overlay of gene-disease associations



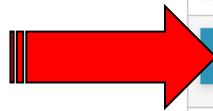
DisGeNET (Pinerio J, et al, *Nucleic Acids Res.* 2019) is a database of gene-disease associations. We have pre-processed DisGeNET curated gene-disease associations (Release v7.0) for overlay onto Reactome. For each disease, clicking on the "Analysis" button will show the results of Reactome pathway analysis with the set of genes associated with that disease. If you are interested in overlaying other data sources onto Reactome in a similar manner, please [contact us](#).

Parameters

Parameter	Option	Description
Minimum number of genes per disease	<input type="range" value="10"/>	The Reactome pathway analysis presented here only makes sense for multiple genes. Diseases with less gene associations than this parameter are not displayed in the table. For small numbers of genes, it might be helpful to switch from "pValue" to "coverage" at the bottom of the visualisation.
Score	<input checked="" type="radio"/> Low (no filter) <input type="radio"/> Medium (> 0.33) <input type="radio"/> High (> 0.66)	Score of the gene-disease association as provided by DisGeNET.
Include interactors	<input type="checkbox"/>	Include high confidence interactors from IntAct in Reactome.
Default result view	<input checked="" type="radio"/> ReactFoam <input type="radio"/> Fireworks	Reactome provides two different options for the first view of the analysis results. Choose your preference.
Reset the filters	<input type="button" value="Reset"/>	Clear disease name filter, and reset to default values.

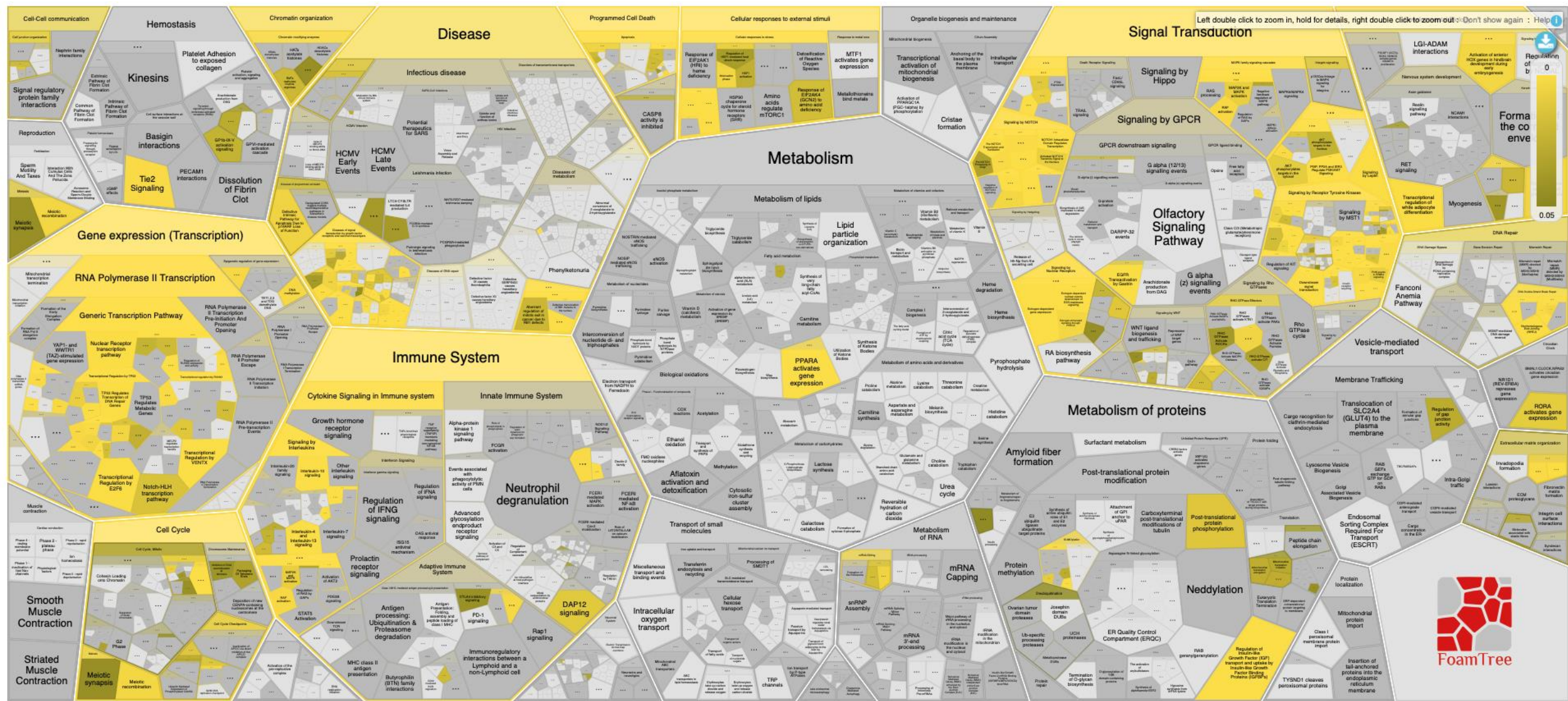
Overlay Table

Check in Pathway Browser	Disease name <input type="text" value="Disease name filter"/>	Number of genes	Gene list	Disease id
Analysis	Malignant_Neoplasm_Of_Breast	1074	ABCA3, ABCA4, ABCB1, ABCB10, ABCB6, ABCB8, ABCC1, ABCG2, ABHD12B, ABL1, ABRAXAS1, ACADM, ACAP1, ACCS, ACHE, ACO2, ACTA2, ACVR1, ACY1, ADAM10, ADAM12, ADAM33, ADAMTS1, ADAMTS19, ADAR, ADAT3, ADGRF4, ADHFE1, ADRA1A, AEF1, AEP, ACAD7, ACB2, AUP, ABCA3B, AKAP13, AKAP9	C0006142
Analysis	Schizophrenia	883	A1BG, ABCA1, ABCA13, ABCB1, ACE, ACHE, ACOT6, ACP1, ACSL6, ACSM1, ACTB, ACTR2, ADAM12, ADAMTS12, ADAMTS3, ADAMTSL3, ADARB1, ADCY7, ADCYAP1, ADCYAP1R1, ADGRF4, ADK, ADM, ADNP, ADNP2, ADORA1, ADORA2A, ADORA2B, ADORA2C, ADORA2D, ADRD1, ADRD2, ADRD3, ADRD4, ADRD5, ADRD6, ADRD7, ADRD8, ADRD9, ADRD10, ADRD11, ADRD12, ADRD13, ADRD14, ADRD15, ADRD16, ADRD17, ADRD18, ADRD19, ADRD20, ADRD21, ADRD22, ADRD23, ADRD24, ADRD25, ADRD26, ADRD27, ADRD28, ADRD29, ADRD30, ADRD31, ADRD32, ADRD33, ADRD34, ADRD35, ADRD36, ADRD37, ADRD38, ADRD39, ADRD40, ADRD41, ADRD42, ADRD43, ADRD44, ADRD45, ADRD46, ADRD47, ADRD48, ADRD49, ADRD50, ADRD51, ADRD52, ADRD53, ADRD54, ADRD55, ADRD56, ADRD57, ADRD58, ADRD59, ADRD60, ADRD61, ADRD62, ADRD63, ADRD64, ADRD65, ADRD66, ADRD67, ADRD68, ADRD69, ADRD70, ADRD71, ADRD72, ADRD73, ADRD74, ADRD75, ADRD76, ADRD77, ADRD78, ADRD79, ADRD80, ADRD81, ADRD82, ADRD83, ADRD84, ADRD85, ADRD86, ADRD87, ADRD88, ADRD89, ADRD90, ADRD91, ADRD92, ADRD93, ADRD94, ADRD95, ADRD96, ADRD97, ADRD98, ADRD99, ADRD100	C0036341
Analysis	Liver_Cirrhosis_Experimental	774	A2M, AADAC, AADAT, ABAT, ABCB1, ABCC2, ABCC5, ABCG1, ABCG5, ABCG8, ABLIM3, ACAT1, ACBD4, ACHE, ACKR3, ACOT9, ACOX2, ACP5, ACSL1, ACTA2, ACTN1, ADA, ADAM17, ADD3, ADGRE1, ADH4, ADHFE1, ADIPOQ, ADM, ADORA2A, ADORA2B, ADORA2C, ADRD1, ADRD2, ADRD3, ADRD4, ADRD5, ADRD6, ADRD7, ADRD8, ADRD9, ADRD10, ADRD11, ADRD12, ADRD13, ADRD14, ADRD15, ADRD16, ADRD17, ADRD18, ADRD19, ADRD20, ADRD21, ADRD22, ADRD23, ADRD24, ADRD25, ADRD26, ADRD27, ADRD28, ADRD29, ADRD30, ADRD31, ADRD32, ADRD33, ADRD34, ADRD35, ADRD36, ADRD37, ADRD38, ADRD39, ADRD40, ADRD41, ADRD42, ADRD43, ADRD44, ADRD45, ADRD46, ADRD47, ADRD48, ADRD49, ADRD50, ADRD51, ADRD52, ADRD53, ADRD54, ADRD55, ADRD56, ADRD57, ADRD58, ADRD59, ADRD60, ADRD61, ADRD62, ADRD63, ADRD64, ADRD65, ADRD66, ADRD67, ADRD68, ADRD69, ADRD70, ADRD71, ADRD72, ADRD73, ADRD74, ADRD75, ADRD76, ADRD77, ADRD78, ADRD79, ADRD80, ADRD81, ADRD82, ADRD83, ADRD84, ADRD85, ADRD86, ADRD87, ADRD88, ADRD89, ADRD90, ADRD91, ADRD92, ADRD93, ADRD94, ADRD95, ADRD96, ADRD97, ADRD98, ADRD99, ADRD100	C0023893
Analysis	Colorectal_Carcinoma	702	ABCA1, ABCA10, ABCA12, ABCA13, ABCA3, ABCA4, ABCA5, ABCA6, ABCA8, ABCA9, ABCB1, ABCB10, ABCB11, ABCB4, ABCB5, ABCB6, ABCC1, ABCC13, ABCC2, ABCC3, ABCC4, ABCC5, ABCC6, ABCC8, ABCD2, ABCD3, ABCD4, ABCE1, ABCE2, ABCE3, ABCE4, ABCE5, ABCE6, ABCE7, ABCE8, ABCE9, ABCE10, ABCE11, ABCE12, ABCE13, ABCE14, ABCE15, ABCE16, ABCE17, ABCE18, ABCE19, ABCE20, ABCE21, ABCE22, ABCE23, ABCE24, ABCE25, ABCE26, ABCE27, ABCE28, ABCE29, ABCE30, ABCE31, ABCE32, ABCE33, ABCE34, ABCE35, ABCE36, ABCE37, ABCE38, ABCE39, ABCE40, ABCE41, ABCE42, ABCE43, ABCE44, ABCE45, ABCE46, ABCE47, ABCE48, ABCE49, ABCE50, ABCE51, ABCE52, ABCE53, ABCE54, ABCE55, ABCE56, ABCE57, ABCE58, ABCE59, ABCE60, ABCE61, ABCE62, ABCE63, ABCE64, ABCE65, ABCE66, ABCE67, ABCE68, ABCE69, ABCE70, ABCE71, ABCE72, ABCE73, ABCE74, ABCE75, ABCE76, ABCE77, ABCE78, ABCE79, ABCE80, ABCE81, ABCE82, ABCE83, ABCE84, ABCE85, ABCE86, ABCE87, ABCE88, ABCE89, ABCE90, ABCE91, ABCE92, ABCE93, ABCE94, ABCE95, ABCE96, ABCE97, ABCE98, ABCE99, ABCE100	C0009402
Analysis	Prostatic_Neoplasms	616	AAAS, ABCC4, ABCG5, ABO, ABR, ACE, ACHE, ACRBP, ACSL4, ACSM3, ADAM28, ADAM9, ADAMTS8, ADI1, ADRB2, AGR2, AHCYL2, AHR, AKAP13, AKR1C3, AKT1, ALAD, ALDH1A2, ALOX12B, ALOX5, ALOXE3, AMACR, ANTXR2, ANXA1, ANXA3, ANXA4, ANXA5, ANXA6, ANXA7, ANXA8, ANXA9, ANXA10, ANXA11, ANXA12, ANXA13, ANXA14, ANXA15, ANXA16, ANXA17, ANXA18, ANXA19, ANXA20, ANXA21, ANXA22, ANXA23, ANXA24, ANXA25, ANXA26, ANXA27, ANXA28, ANXA29, ANXA30, ANXA31, ANXA32, ANXA33, ANXA34, ANXA35, ANXA36, ANXA37, ANXA38, ANXA39, ANXA40, ANXA41, ANXA42, ANXA43, ANXA44, ANXA45, ANXA46, ANXA47, ANXA48, ANXA49, ANXA50, ANXA51, ANXA52, ANXA53, ANXA54, ANXA55, ANXA56, ANXA57, ANXA58, ANXA59, ANXA60, ANXA61, ANXA62, ANXA63, ANXA64, ANXA65, ANXA66, ANXA67, ANXA68, ANXA69, ANXA70, ANXA71, ANXA72, ANXA73, ANXA74, ANXA75, ANXA76, ANXA77, ANXA78, ANXA79, ANXA80, ANXA81, ANXA82, ANXA83, ANXA84, ANXA85, ANXA86, ANXA87, ANXA88, ANXA89, ANXA90, ANXA91, ANXA92, ANXA93, ANXA94, ANXA95, ANXA96, ANXA97, ANXA98, ANXA99, ANXA100	C0033578
Analysis	Malignant_Neoplasm_Of_Prostate	616	AAAS, ABCC4, ABCG5, ABO, ABR, ACE, ACHE, ACRBP, ACSL4, ACSM3, ADAM28, ADAM9, ADAMTS8, ADI1, ADRB2, AGR2, AHCYL2, AHR, AKAP13, AKR1C3, AKT1, ALAD, ALDH1A2, ALOX12B, ALOX5, ALOXE3, AMACR, ANTXR2, ANXA1, ANXA3, ANXA4, ANXA5, ANXA6, ANXA7, ANXA8, ANXA9, ANXA10, ANXA11, ANXA12, ANXA13, ANXA14, ANXA15, ANXA16, ANXA17, ANXA18, ANXA19, ANXA20, ANXA21, ANXA22, ANXA23, ANXA24, ANXA25, ANXA26, ANXA27, ANXA28, ANXA29, ANXA30, ANXA31, ANXA32, ANXA33, ANXA34, ANXA35, ANXA36, ANXA37, ANXA38, ANXA39, ANXA40, ANXA41, ANXA42, ANXA43, ANXA44, ANXA45, ANXA46, ANXA47, ANXA48, ANXA49, ANXA50, ANXA51, ANXA52, ANXA53, ANXA54, ANXA55, ANXA56, ANXA57, ANXA58, ANXA59, ANXA60, ANXA61, ANXA62, ANXA63, ANXA64, ANXA65, ANXA66, ANXA67, ANXA68, ANXA69, ANXA70, ANXA71, ANXA72, ANXA73, ANXA74, ANXA75, ANXA76, ANXA77, ANXA78, ANXA79, ANXA80, ANXA81, ANXA82, ANXA83, ANXA84, ANXA85, ANXA86, ANXA87, ANXA88, ANXA89, ANXA90, ANXA91, ANXA92, ANXA93, ANXA94, ANXA95, ANXA96, ANXA97, ANXA98, ANXA99, ANXA100	C0376358
Analysis	Breast_Carcinoma	538	ABCB1, ABCC1, ABCG2, ABL1, ACHE, ACTA2, ACVR1, ADAM10, ADAM33, ADAMTS1, ADAR, AFP, AGR2, AHR, AKAP12, AKT1, AKT2, ALDOA, ALK, ALKBH8, ANGPTL4, ANKRD34A, APC2, APOBEC3A, APOBEC3B, APRT, AR, ARAF, AREG, AREG1, AREG2, AREG3, AREG4, AREG5, AREG6, AREG7, AREG8, AREG9, AREG10, AREG11, AREG12, AREG13, AREG14, AREG15, AREG16, AREG17, AREG18, AREG19, AREG20, AREG21, AREG22, AREG23, AREG24, AREG25, AREG26, AREG27, AREG28, AREG29, AREG30, AREG31, AREG32, AREG33, AREG34, AREG35, AREG36, AREG37, AREG38, AREG39, AREG40, AREG41, AREG42, AREG43, AREG44, AREG45, AREG46, AREG47, AREG48, AREG49, AREG50, AREG51, AREG52, AREG53, AREG54, AREG55, AREG56, AREG57, AREG58, AREG59, AREG60, AREG61, AREG62, AREG63, AREG64, AREG65, AREG66, AREG67, AREG68, AREG69, AREG70, AREG71, AREG72, AREG73, AREG74, AREG75, AREG76, AREG77, AREG78, AREG79, AREG80, AREG81, AREG82, AREG83, AREG84, AREG85, AREG86, AREG87, AREG88, AREG89, AREG90, AREG91, AREG92, AREG93, AREG94, AREG95, AREG96, AREG97, AREG98, AREG99, AREG100	C0678222
Analysis	Mammary_Neoplasms	527	ABCB1, ABCC1, ABCG2, ABL1, ACHE, ACTA2, ACVR1, ADAM10, ADAM33, ADAMTS1, ADAR, AFP, AGR2, AHR, AKAP12, AKT1, AKT2, ALDOA, ALK, ALKBH8, ANGPTL4, ANKRD34A, APC2, APOBEC3A, APOBEC3B, APRT, AR, ARAF, AREG, AREG1, AREG2, AREG3, AREG4, AREG5, AREG6, AREG7, AREG8, AREG9, AREG10, AREG11, AREG12, AREG13, AREG14, AREG15, AREG16, AREG17, AREG18, AREG19, AREG20, AREG21, AREG22, AREG23, AREG24, AREG25, AREG26, AREG27, AREG28, AREG29, AREG30, AREG31, AREG32, AREG33, AREG34, AREG35, AREG36, AREG37, AREG38, AREG39, AREG40, AREG41, AREG42, AREG43, AREG44, AREG45, AREG46, AREG47, AREG48, AREG49, AREG50, AREG51, AREG52, AREG53, AREG54, AREG55, AREG56, AREG57, AREG58, AREG59, AREG60, AREG61, AREG62, AREG63, AREG64, AREG65, AREG66, AREG67, AREG68, AREG69, AREG70, AREG71, AREG72, AREG73, AREG74, AREG75, AREG76, AREG77, AREG78, AREG79, AREG80, AREG81, AREG82, AREG83, AREG84, AREG85, AREG86, AREG87, AREG88, AREG89, AREG90, AREG91, AREG92, AREG93, AREG94, AREG95, AREG96, AREG97, AREG98, AREG99, AREG100	C1458155
Analysis	Mammary_Neoplasms_Human	525	ABCB1, ABCC1, ABCG2, ABL1, ACHE, ACTA2, ACVR1, ADAM10, ADAM33, ADAMTS1, ADAR, AFP, AGR2, AHR, AKAP12, AKT1, AKT2, ALDOA, ALK, ALKBH8, ANGPTL4, ANKRD34A, APC2, APOBEC3A, APOBEC3B, APRT, AR, ARAF, AREG, AREG1, AREG2, AREG3, AREG4, AREG5, AREG6, AREG7, AREG8, AREG9, AREG10, AREG11, AREG12, AREG13, AREG14, AREG15, AREG16, AREG17, AREG18, AREG19, AREG20, AREG21, AREG22, AREG23, AREG24, AREG25, AREG26, AREG27, AREG28, AREG29, AREG30, AREG31, AREG32, AREG33, AREG34, AREG35, AREG36, AREG37, AREG38, AREG39, AREG40, AREG41, AREG42, AREG43, AREG44, AREG45, AREG46, AREG47, AREG48, AREG49, AREG50, AREG51, AREG52, AREG53, AREG54, AREG55, AREG56, AREG57, AREG58, AREG59, AREG60, AREG61, AREG62, AREG63, AREG64, AREG65, AREG66, AREG67, AREG68, AREG69, AREG70, AREG71, AREG72, AREG73, AREG74, AREG75, AREG76, AREG77, AREG78, AREG79, AREG80, AREG81, AREG82, AREG83, AREG84, AREG85, AREG86, AREG87, AREG88, AREG89, AREG90, AREG91, AREG92, AREG93, AREG94, AREG95, AREG96, AREG97, AREG98, AREG99, AREG100	C1257931





Enrichment of DisGeNET “Breast Carcinoma” associated genes



FoamTree

Binary Disease Relation Overlay

The screenshot displays the Reactome web interface with a binary disease relation overlay. The main content area shows a network diagram where two POMC peptide nodes, POMC(1-241) and POMC(138-176), are connected by a thick orange arrow. POMC(138-176) is highlighted with a blue border. Red lines radiate from POMC(138-176) to various disease nodes, including Obesity, Proopiomelanocortin Deficiency, Depressive disorder, Bipolar Disorder, Cholestasis, ACTH Syndrome Ectopic, Alcoholic Intoxication Chronic, Cushing Syndrome, Mental Depression, Diabetes Mellitus, Hypertensive disease, melanoma, Pain, Seizures, West Syndrome, and Pituitary dependent Cushing's disease. A blue box labeled 'PC1:calcium' is connected to West Syndrome. The diagram is set within a 'secretory granule lumen' environment. The interface includes a search bar, navigation tools, and a settings panel on the right.

reactome 3.7 79 Pathways for: Homo sapiens

Citation: Analysis: Tour: Layout:

Search for a term, e.g. pten ...

secretory granule lumen

POMC(1-241) 241

POMC(138-176) 241

Obesity

Proopiomelanocortin Deficiency

Depressive disorder

Bipolar Disorder

Cholestasis

ACTH Syndrome Ectopic

Alcoholic Intoxication Chronic

Cushing Syndrome

Mental Depression

Diabetes Mellitus

Hypertensive disease

melanoma

Pain

Seizures

West Syndrome

Pituitary dependent Cushing's disease

PC1:calcium

Settings

Data Overlays

Available data source:

- IntAct 24
- DisGeNet 301

PSICQUIC:

- APID Interactomes
- BAR
- Bhf-ucl
- BIND

Custom Resources:

- DisGeNet-2022-01 ...

+ Add a new resource

CGB3

DisGeNet (301) 0.4

Download as PNG or SVG



The screenshot shows the Reactome website interface. On the left is a sidebar with an 'Event Hierarchy' tree. The main area displays a pathway diagram titled 'GROWTH HORMONE RECEPTOR SIGNALING'. An 'Export diagram' dialog box is open in the center, showing a preview of the pathway and options for export format (SVG, PNG, JPG, GIF, PDF, SBGN) and resolution (Low, Medium, High). A red arrow points from the 'Download' icon in the top right of the main interface to the 'Export diagram' dialog box.

Export diagram

Get a snapshot

Export diagram

Export content

SVG Low Medium High PNG JPG GIF PDF SBGN

Overrepresentation analysis results for UNIPROT [Data: GBM Uniprot]

Pathway name	Entities found	Entities Total	Entities ratio	Entities pValue	Entities FDR	Reactions found	Reactions total
Signaling by SCF-KIT	15	45	0.004	5.88E-15	8.41E-13	36	36
Negative regulation of the PI3K/AKT network	21	122	0.011	7.99E-15	1.02E-12	4	4
Signaling by VEGF	20	108	0.009	9.44E-15	1.08E-12	42	42
PIP3 activates AKT signaling	29	276	0.024	1.45E-14	1.51E-12	31	31
VEGFA-VEGFR2 Pathway	18	98	0.009	2.47E-13	2.35E-11	39	39
PI5B, PP2A and IER3 Regulate PI3K/AKT Signaling	10	115	0.01	3.28E-13	2.89E-11	2	2

Download as pptx



PowerPoint File Edit View Insert Format Arrange Tools Slide Show Window Help [R-HSA-909733] Interferon alpha-beta signaling (1).pptx

Home Format Themes Tables Charts SmartArt Transitions Animations Slide Show Review

Slides Outline

Click to add notes

Pathway Analysis: PDF Export



overlay_1_0-3.pdf (page 3 of 37)

Q Search

2. Signaling by Receptor Tyrosine Kinases (R-HSA-9006934)

Receptor tyrosine kinases (RTKs) are a major class of cell surface proteins involved in Signal Transduction. Human cells contain ~60 RTKs, grouped into 20 subfamilies based on their domain architecture. All RTK subfamilies are characterized by an extracellular ligand-binding domain, a single transmembrane region and an intracellular region consisting of the tyrosine kinase domain and additional regulatory and protein interaction domains. In general, RTKs associate into dimers upon ligand binding and are activated by autophosphorylation on conserved intracellular tyrosine residues. Autophosphorylation increases the catalytic efficiency of

Reactome Icon Library

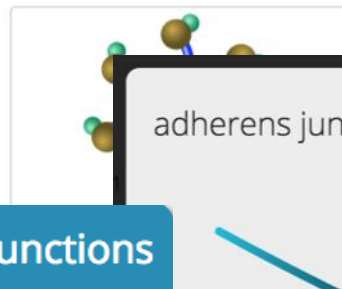
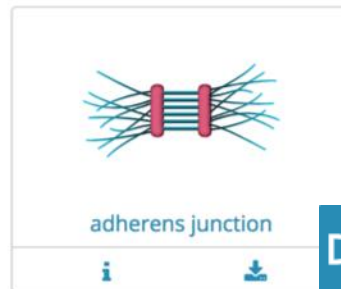


[Library home](#) > Cell elements

Cell elements (61 components)

e.g DNA, Microorganism, protein or person:jupe

Go!



Description: Adherens junctions are protein complexes that occur at cell-cell junctions in epithelial and endothelial tissues, usually more basal than tight junctions

Curator: [Steve Jupe](#)

Designer: [Cristoffer L Sevilla](#)

adherens junction

SVG
EMF
PNG

[i](#) [Download](#)

New: Backgrounds




e.g. P06241, liver, CFTR, protein


Go!

[Library home](#) > Background

 Background (13 components)



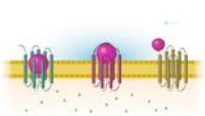
3D cell




4 cells



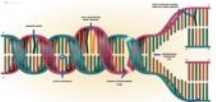
Cell cycle, Mitotic



Classes of GPCRs




Digestive system



DNA repair



ER to Golgi Anterograde Trans...



Homology Directed DNA Repair



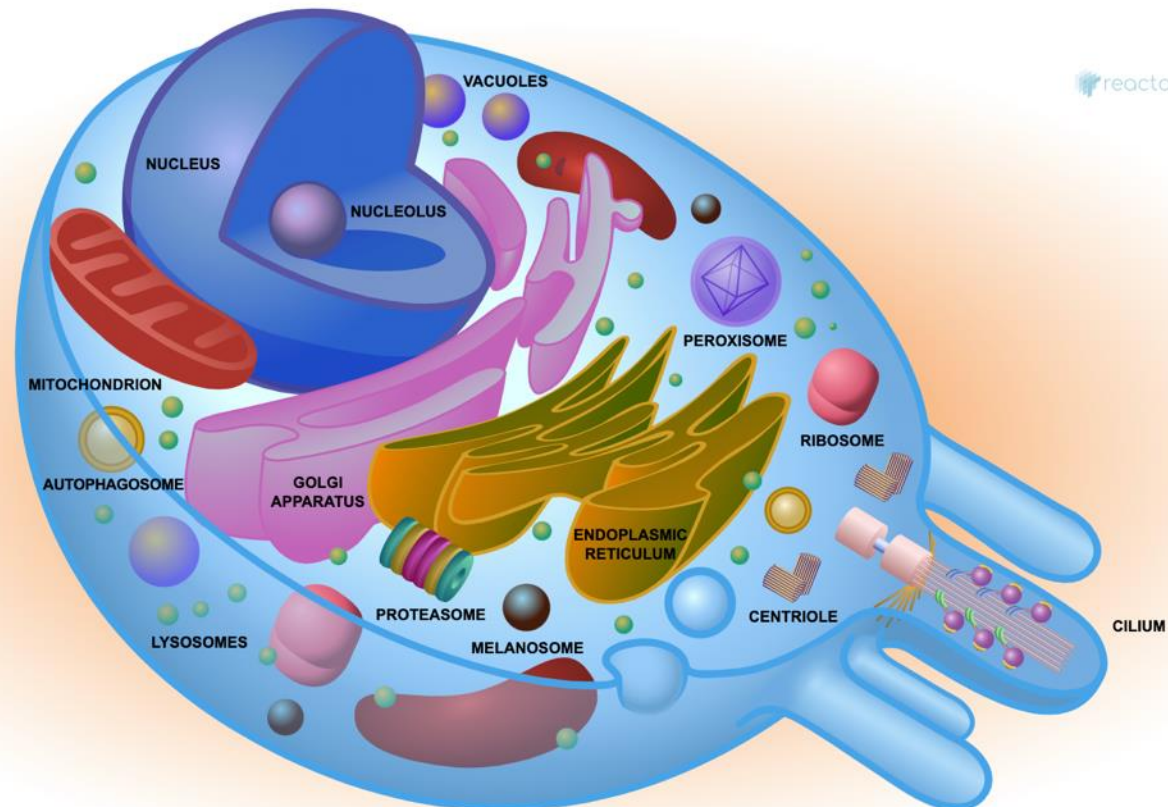
e.g. O95631, NTN1, signaling by EGFR, glucose, GO:0043293




Go!

3D cell

Categories	Background
Curator	Karen Rothfels
Designer	Cristoffer Sevilla

Icon preview



-  SVG
-  PNG
-  EMF



Reactome is Open and Documented

- Reactome is open source, open data, “open graphics”
- Most components CC-BY
- Recently released content under CC-0 for Wikidata integration



Reactome is Open and Documented

- Reactome is open source, open data, “open graphics”
- Most components CC-BY
- Recently released content under CC-0 for Wikidata integration
- Third parties can integrate Reactome components:
 - <http://www.reactome.org/pages/documentation/developer-guide/>

The screenshot shows the Reactome website's Developer's Zone. At the top, there is a navigation bar with the Reactome logo and links for About, Content, Docs, Tools, Community, and Download. Below the navigation bar is a search bar containing the text "e.g. O95631, NTN1, signaling by EGFR, glucose" and a "Go!" button. The main heading is "Developer's Zone" with the subtext "Explore our tools and web services and learn how to include them in your applications". Below this, there are six service tiles arranged in a 2x3 grid:

- Analysis Service**: Use the Analysis Service to analyse your data against Reactome's content.
- Content Service**: Use the Content Service to access all our knowledgebase content from your client.
- Graph Database**: Access to the Reactome knowledgebase content as an interconnected graph database.
- Pathways Overview**: Use this widget to include our pathways overview in your web application.
- Pathway Diagrams**: Use this widget to include our pathway diagrams in your web application.
- Reactome Partners**: Check out who is currently using Reactome web services and widgets.



Use of Reactome software by 3rd parties

Open Targets

For biomedical researchers who need to identify a biological target for a new therapy, Open Targets is a public-private initiative to generate evidence on the validity of therapeutic targets

- Analysis Service
- Widgets
- Graph Database

THE HUMAN PROTEIN ATLAS

Contains information for a large majority of all human proteins

- Analysis Service
- Widgets
- Graph Database

e!

Ensembl is a genome browser for vertebrate genomes that

BLUEPRINT epigenome

The BLUEPRINT consortium has been formed with the aim to

Tabloid Proteome

Tabloid Proteome is a database of protein association network generated using publicly available mass spectrometry based experiments in PRIDE. These associations represent a

- Analysis Service
- Widgets
- Graph Database

ILINCS

Integrative LINC is an integrative web platform for analysis of LINC data and signatures. The BD2K-LINC Data Coordination Integration Center is part of the Big Data to Knowledge

- Analysis Service
- Widgets
- Graph Database

Complex Portal

The Complex Portal is a manually curated, encyclopaedic resource of macromolecular complexes from a number of key model organisms. The majority of complexes are made up of

- Content Service
- Widgets
- Graph Database

ChEBI

Chemical Entities of Biological Interest (ChEBI) is a freely available dictionary of molecular entities focused on 'small' chemical compounds. The term 'molecular entity' refers to any constitutionally

- Analysis Service
- Widgets
- Graph Database

PepTracker: EPD

The Encyclopedia of Proteome Dynamics is a polyglot persistent database and web-application that provides open access to integrated proteomics data from published studies on human

- Analysis Service
- Widgets
- Graph Database

PRIDE

Proteomics IDentifications (PRIDE) database is a centralized, standards compliant, public data repository for proteomics data, including protein and peptide identifications, post-

- Analysis Service
- Widgets
- Graph Database



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PRODUCTS SERVICES TECHNOLOGY RESOURCES ABOUT

Simplifi
YOUR
DATA

SHOP
NOW

SIMPLIFI
Find the meaning in your data

What is ProtiFi?

ProtiFi, LLC was founded to understand life beyond genes. In contrast to static DNA, which is the same in every organ, the structures and machinery of life are dynamic and change with age or in conditions of health and disease. ProtiFi develops and provides innovative solutions to study proteins, metabolites, lipids and glycans. From sample



p-value < 0.05

log2 fold change > 0 up/down

≤ 25 % missing values

sensitivity ≥ 0 %

specificity ≥ 0 %

Text search

Only include favorite analytes

Found 782 of 5411 analytes.

Sort by p-value

Sort order Normal

Fold change format log2

Analytes Pathways

GO Terms Cell Markers

Volcano Plot Venn Diagram

Filters p-value < 0.05

Text search

Only show disease-associated pathways

R-HSA-6798695 2.1602e-69
Neutrophil degranulation 53 out of 480

R-HSA-6791226 4.7494e-47
Major pathway of rRNA processing in the nucleolus and cytosol 31 out of 183

R-HSA-381426 1.9134e-28
Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs) 19 out of 124

R-HSA-202733 3.5695e-26
Cell surface interactions at the vascular wall 20 out of 196

R-HSA-1268020 6.92e-26
Mitochondrial protein import 16 out of 83

R-HSA-8957275 5.4973e-24
Post-translational protein phosphorylation 16 out of 107

R-HSA-72764 8.351e-23
Eukaryotic Translation Termination 15 out of 97

R-HSA-198933 1.6406e-22
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell 20 out of 297

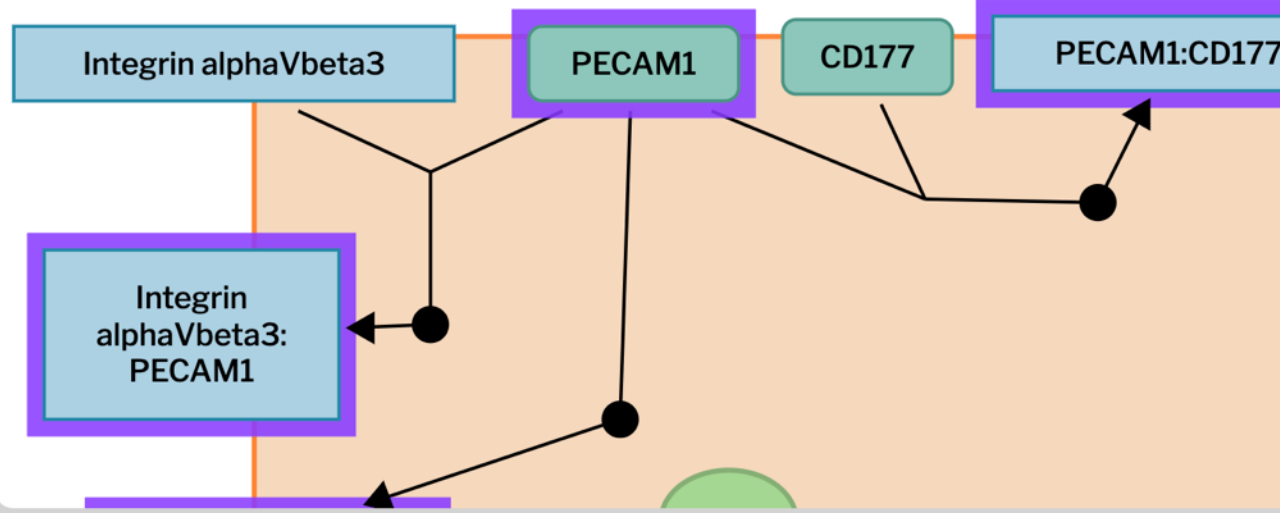
R-HSA-6790901 5.2134e-22
rRNA modification in the nucleus and cytosol 13 out of 60

R-HSA-202733

Cell surface interactions at the vascular wall

Found 20 of 196 analytes.
Hypergeometric p-value: 3.56

GSEA p=0 Score



New Bucket + ...

Contains 0 analytes.



Filter OFF

Acknowledgements

AlphaFold DB

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