Reactome

A database of human biological pathways

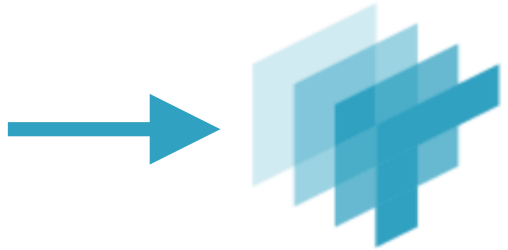
Contact: help@reactome.org

Rationale – Journal information

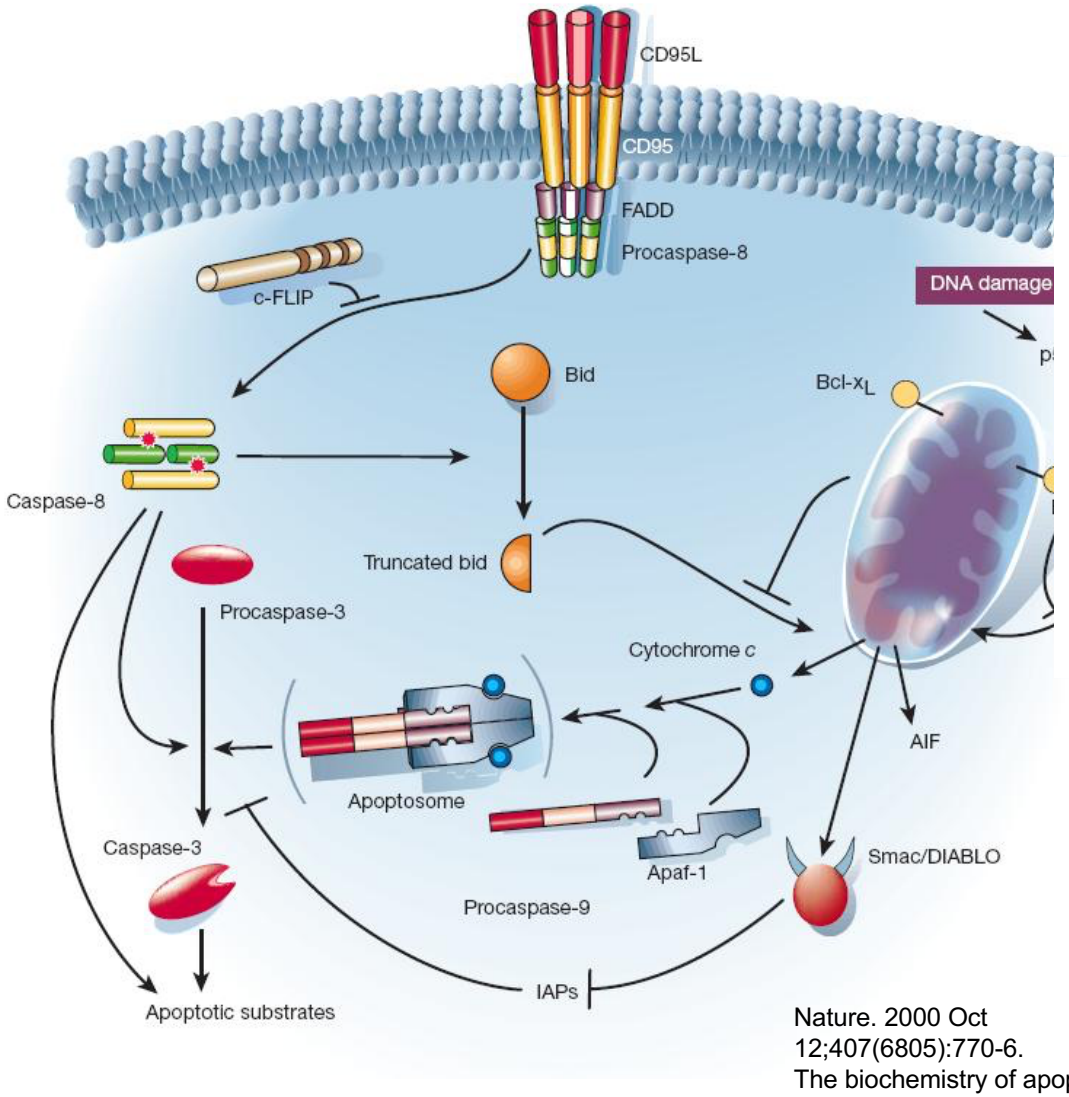
Nature 407(6805):770-6.The Biochemistry of Apoptosis.

"Caspase-8 is the key initiator caspase in the death-receptor pathway. Upon ligand binding, death receptors such as CD95 (Apo-1/Fas) aggregate and form membrane-bound signalling complexes (Box 3). These complexes then recruit, through adapter proteins, several molecules of procaspase-8, resulting in a high local concentration of zymogen. The induced proximity model posits that under these crowded conditions, the low intrinsic protease activity of procaspase-8 (ref. 20) is sufficient to allow the various proenzyme molecules to mutually cleave and activate each other (Box 2). A similar mechanism of action has been proposed to mediate the activation of several other caspases, including caspase-2 and the nematode caspase CED-3 (ref. 21)."

How can I access the pathway described here and reuse it?



Rationale - Figures

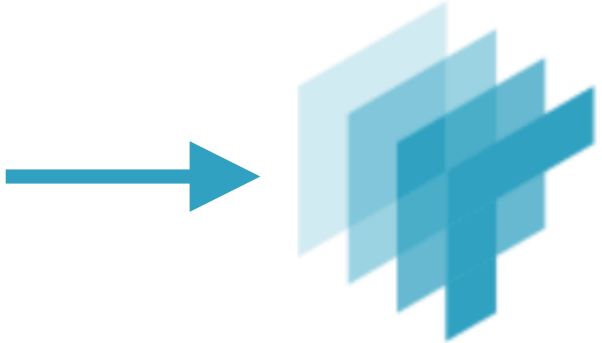


Nature. 2000 Oct 12;407(6805):770-6.
The biochemistry of apoptosis.

A picture paints a thousand words…

but….

- Just pixels
- Omits key details
- Assumes
- Fact or Hypothesis?

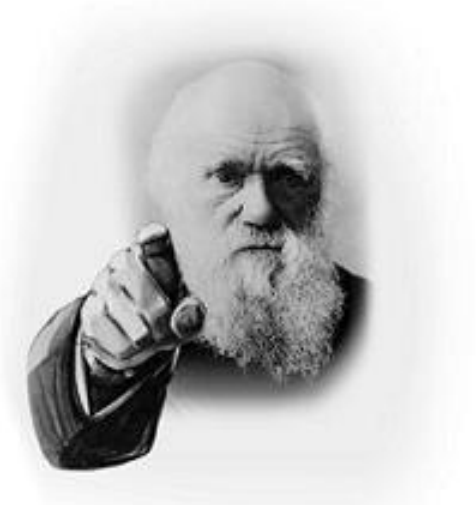


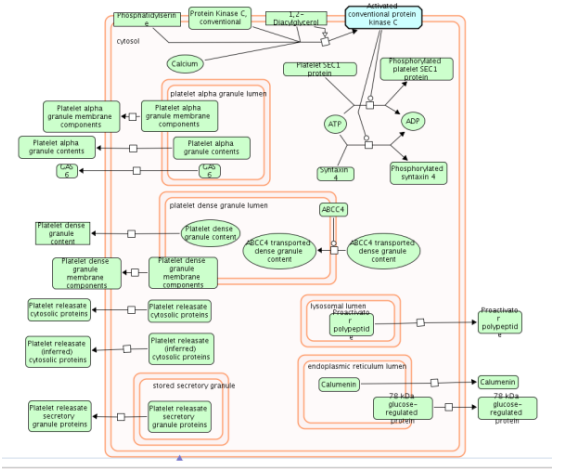
Reactome is…

Free, online, open-source curated database of pathways and reactions in human biology

Authored by expert biologists, maintained by Reactome editorial staff (curators)

Mapped to cellular compartment





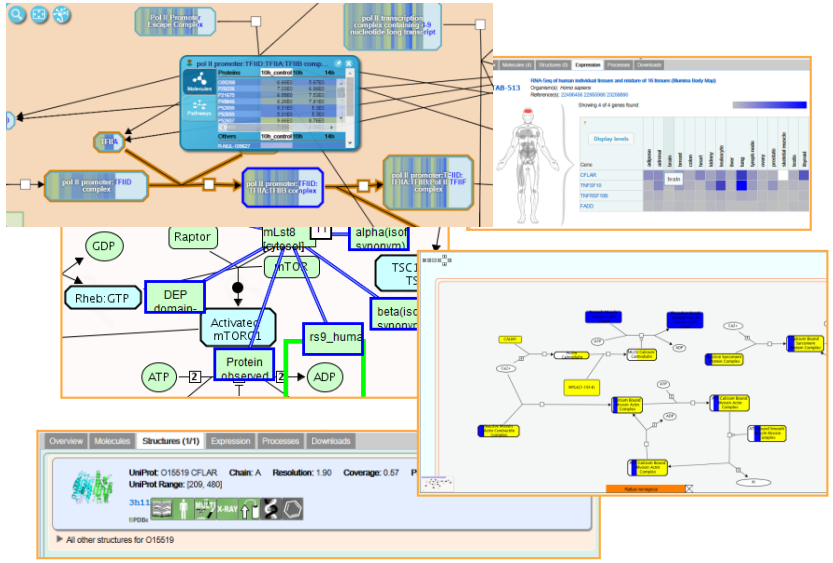
Reactome is…

Extensively cross-referenced

Entrez Gene

UniProt ChEBI PubMed e!Ensembl the Gene Ontology

Tools for data analysis – Pathway Analysis, Expression Overlay, Species Comparison

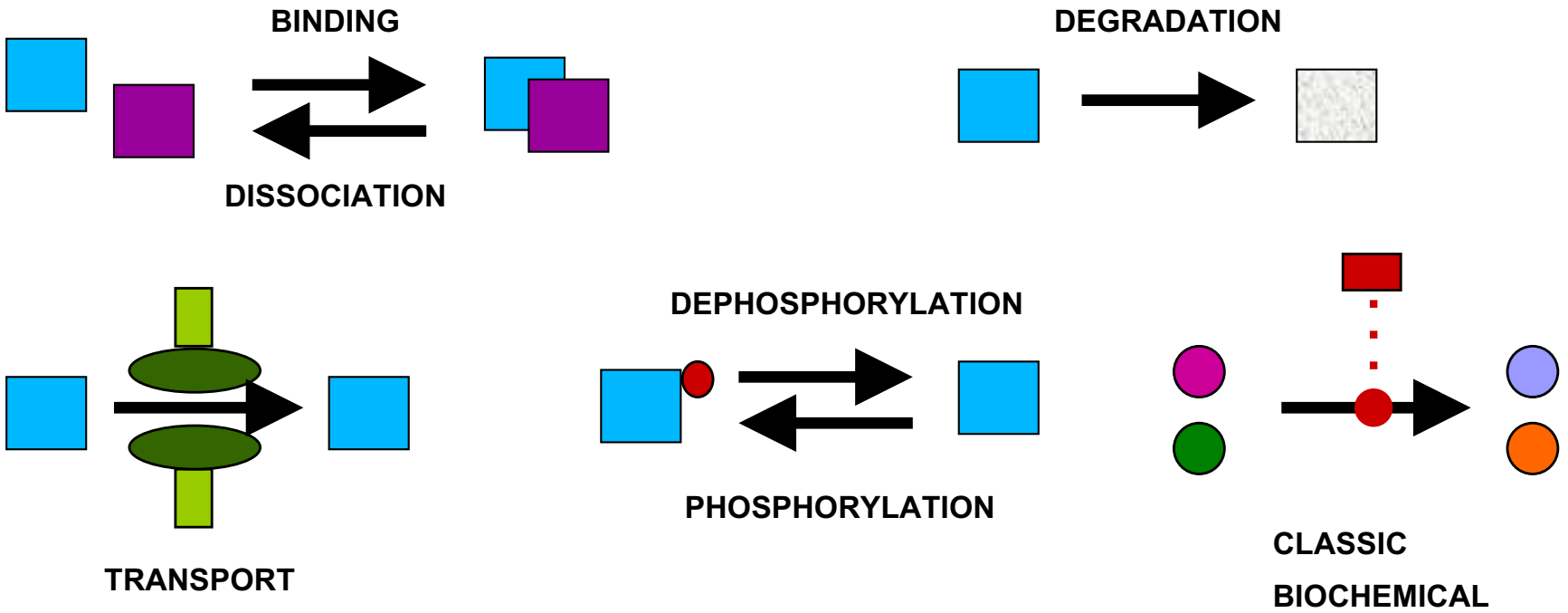


Used to infer orthologous events in 17 other species

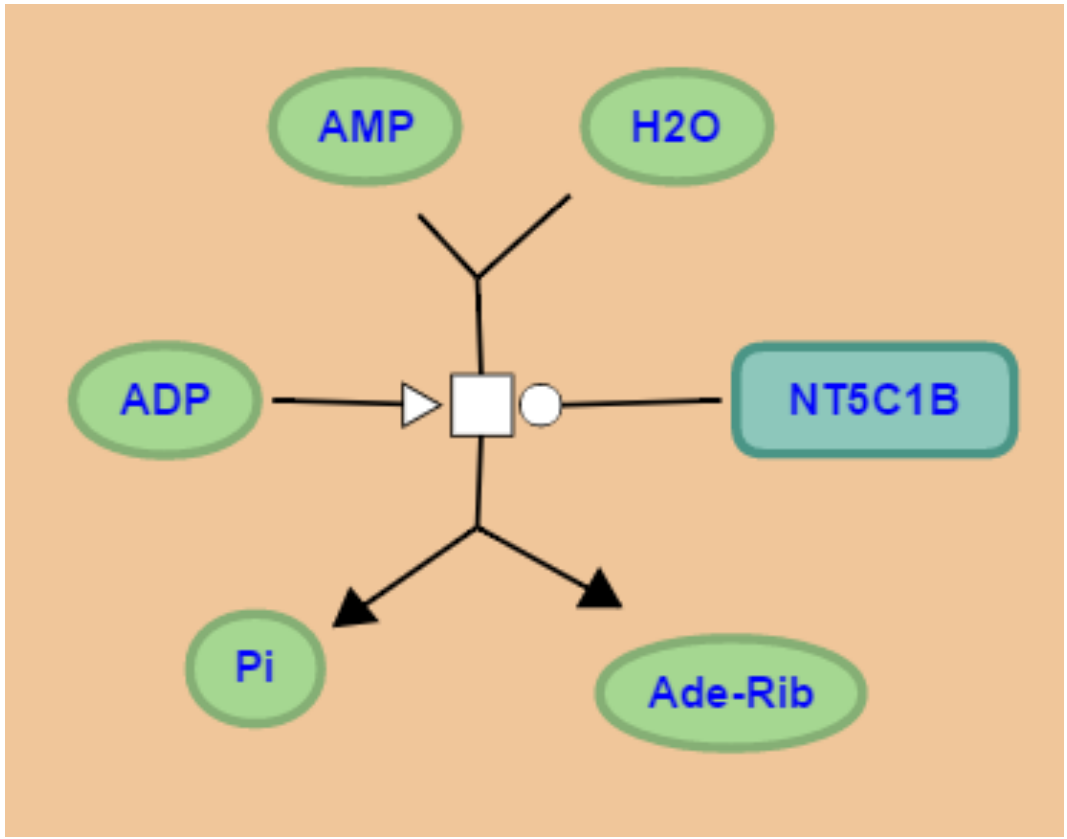
Theory - Reactions

Pathway steps = the “units” of Reactome

= events in biology

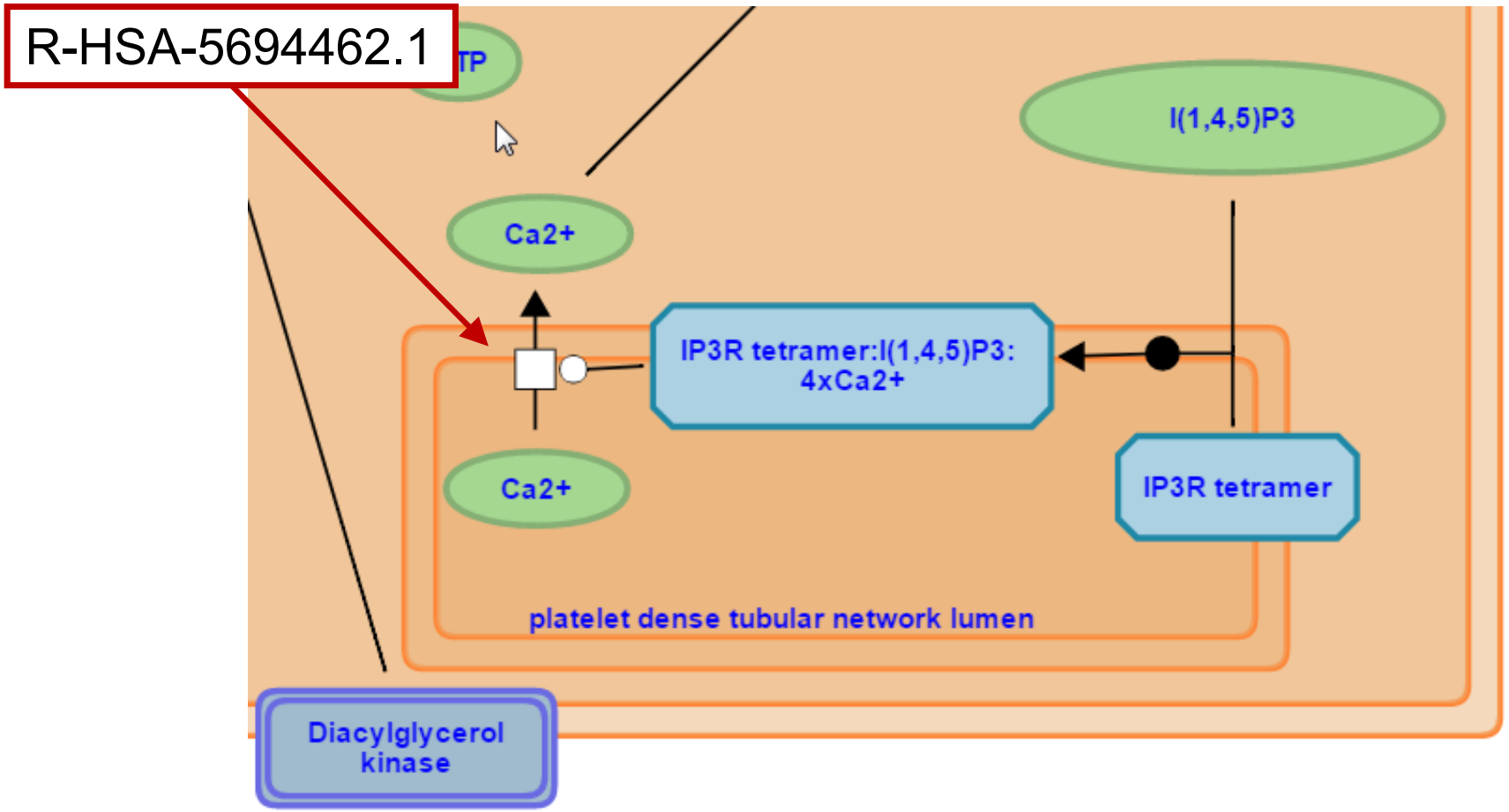


Reaction example 1: Enzymatic



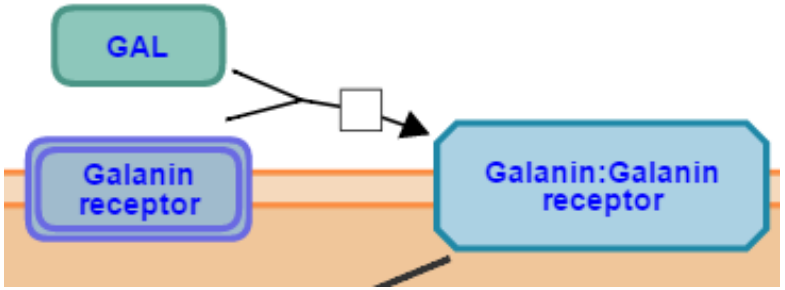
Reaction example 2: Transport

Transport of Ca++ from platelet dense tubular system to cytoplasm

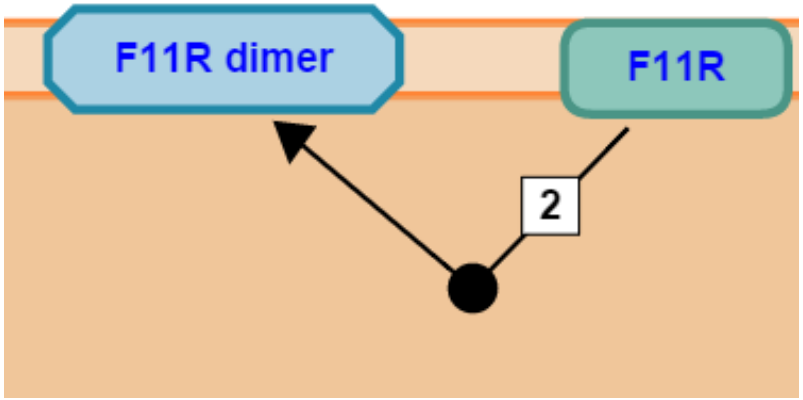


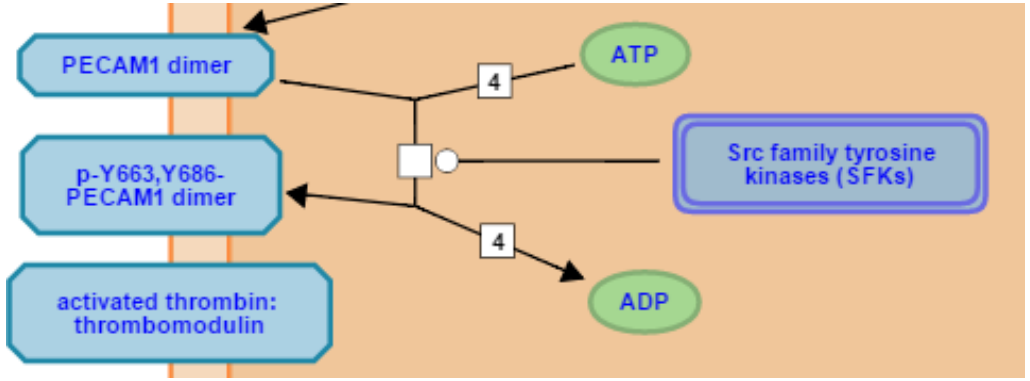
Other reaction examples

Binding



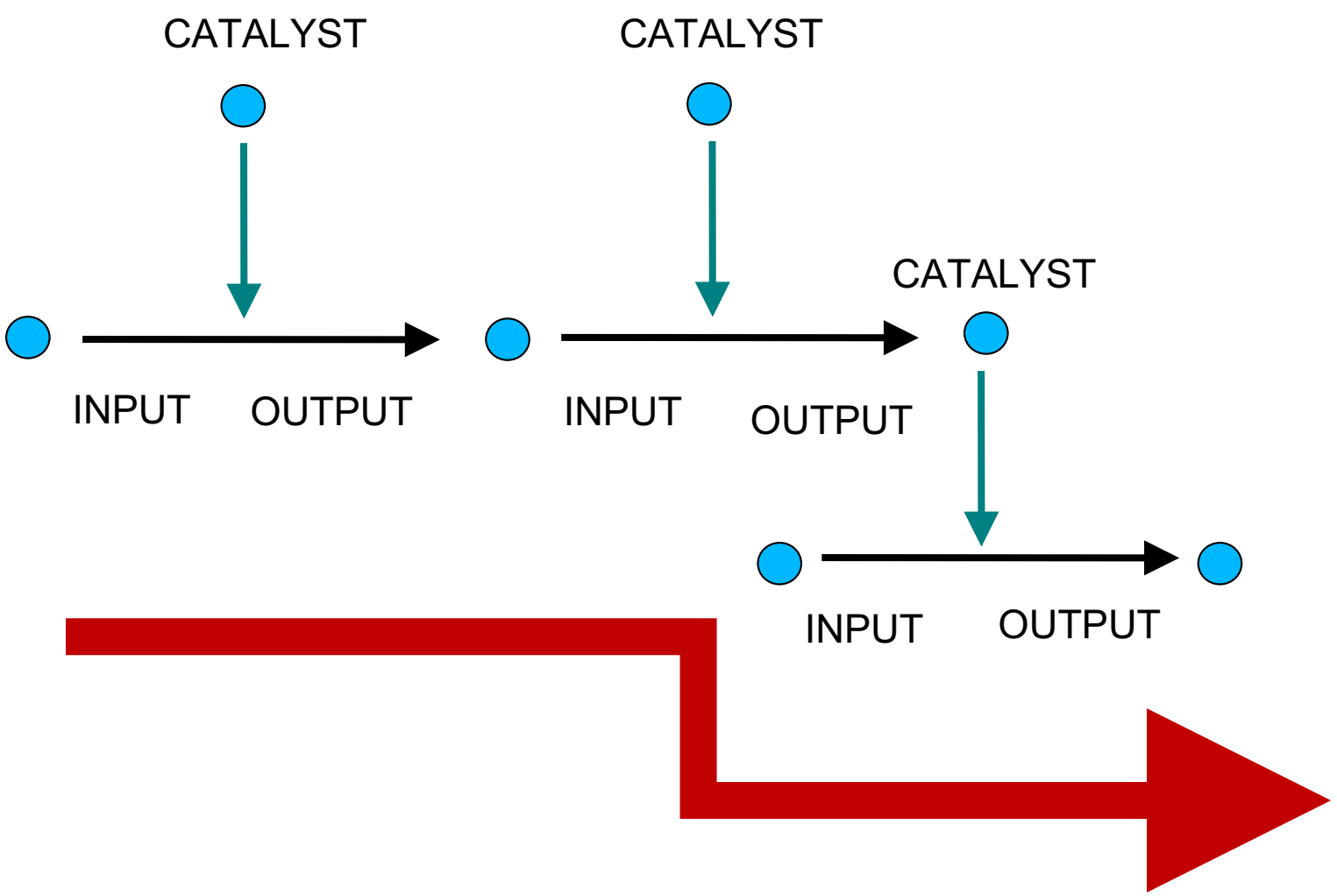
Dimerization



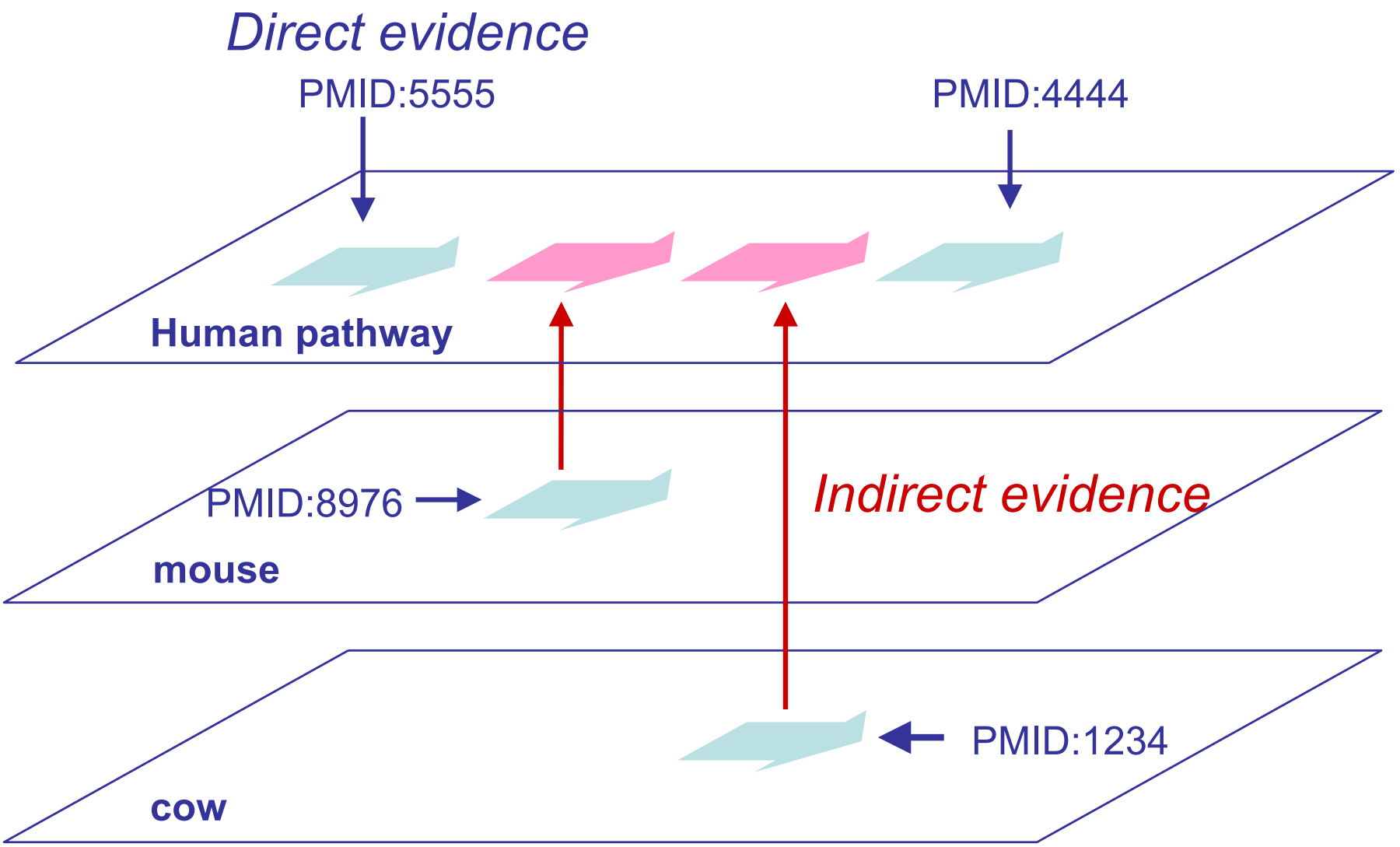


Phosphorylation

Reactions connect into Pathways



Evidence – Inferred Reactions



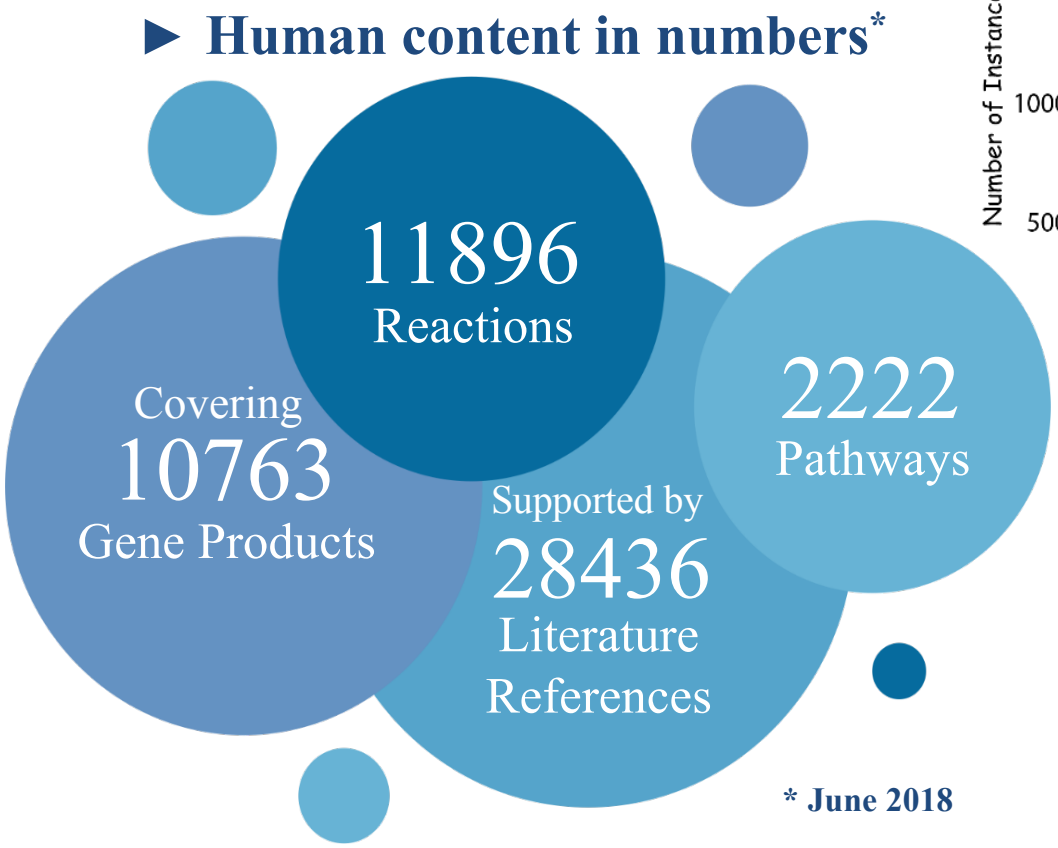
Primary external sources

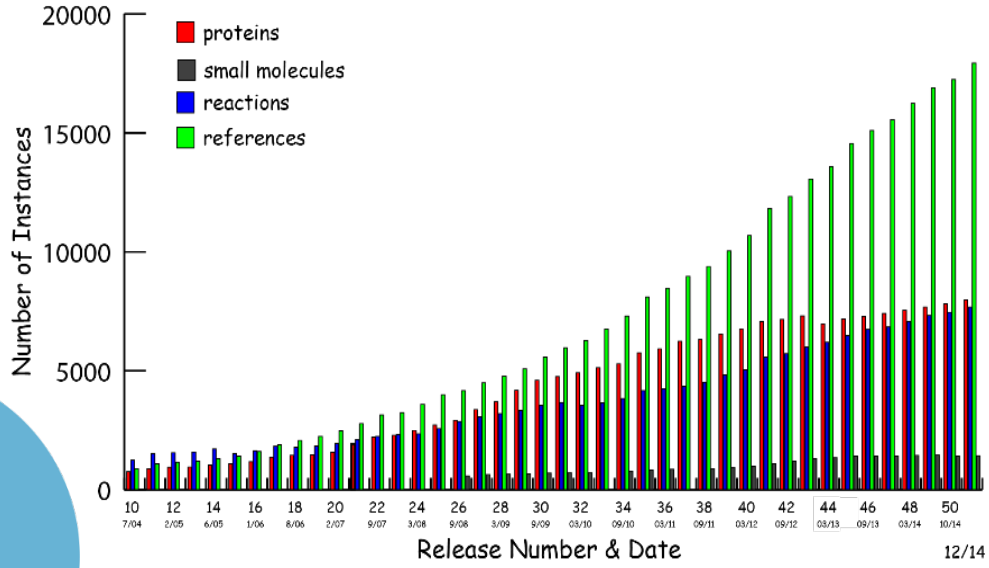
- Gene Ontology
  - Molecular Function
  - Compartment
  - Biological Process

- ChEBI – small molecules
- UniProt – proteins
- Ensembl – genes and transcripts
- PubMed – literature evidence for events

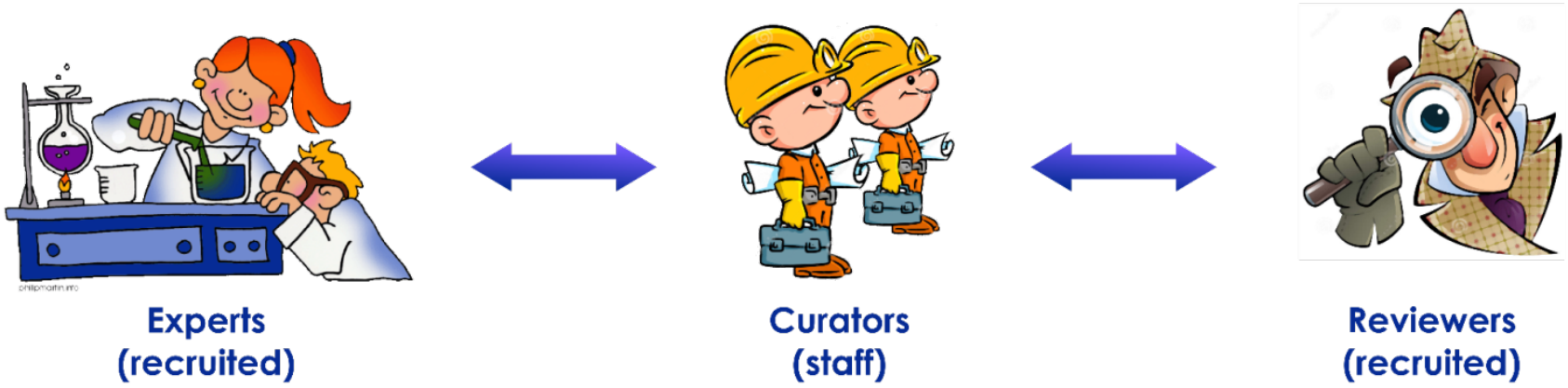
Curation

- 52.6% of the 20,296 predicted human protein-coding genes





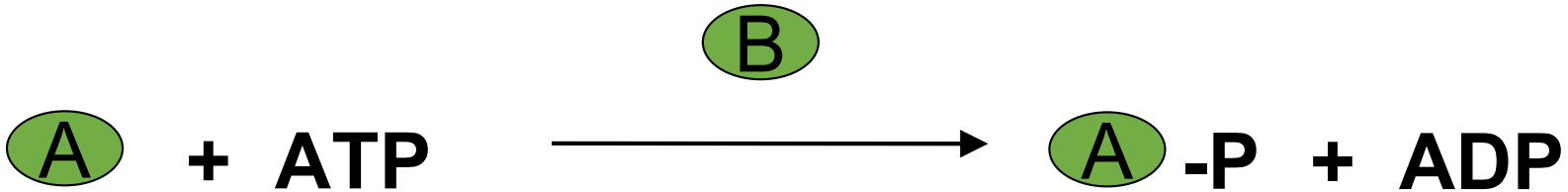
Data Curation Process



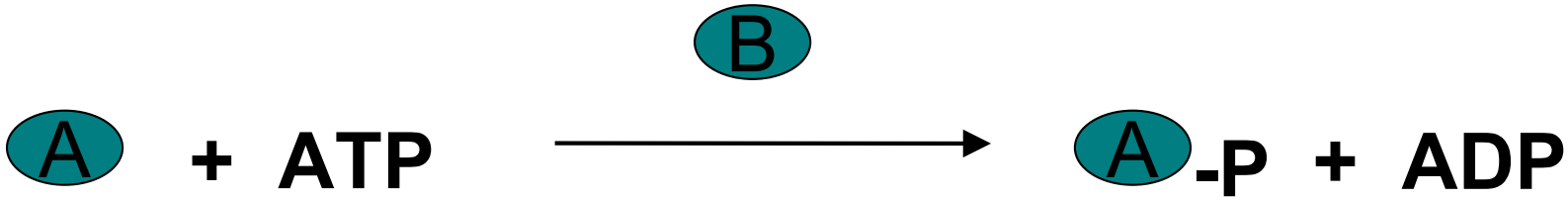
- Pathways authored and reviewed by expert biologists
- Curator works with Author to represent knowledge in Reactome data structure
- All new pathways are internally reviewed within Reactome
- New pathways sent for Review by another expert
- New data release every 3 months
- Regular Pathway updates.
- ORCID and doi ed as attributions for Reactome content
  - For visibility of expert contributions (authors, reviewers and curators).

Data Expansion – Projecting to Other Species

Human



Mouse

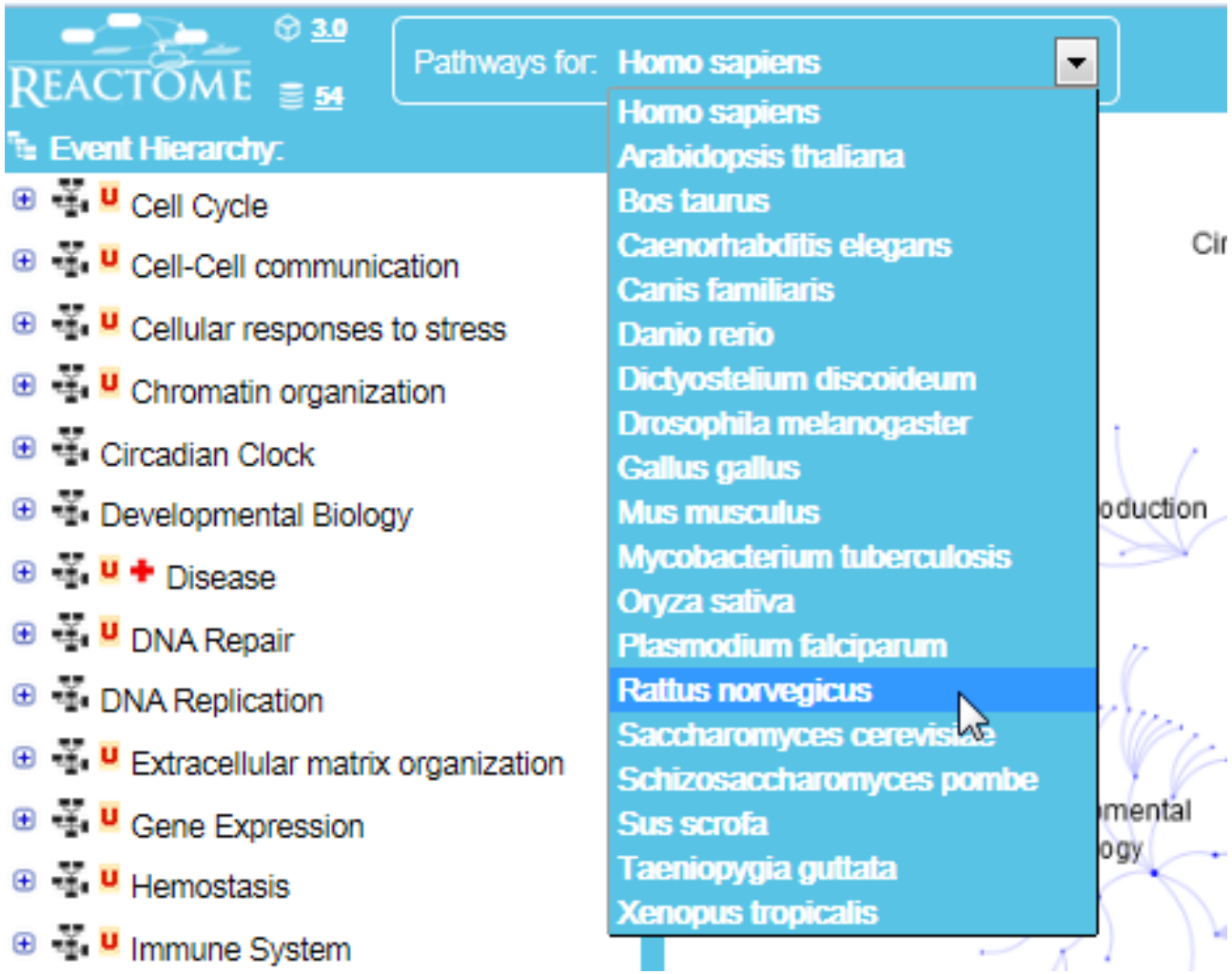


Drosophila

Reaction not projected

No orthologue - Protein not projected

Species Selection



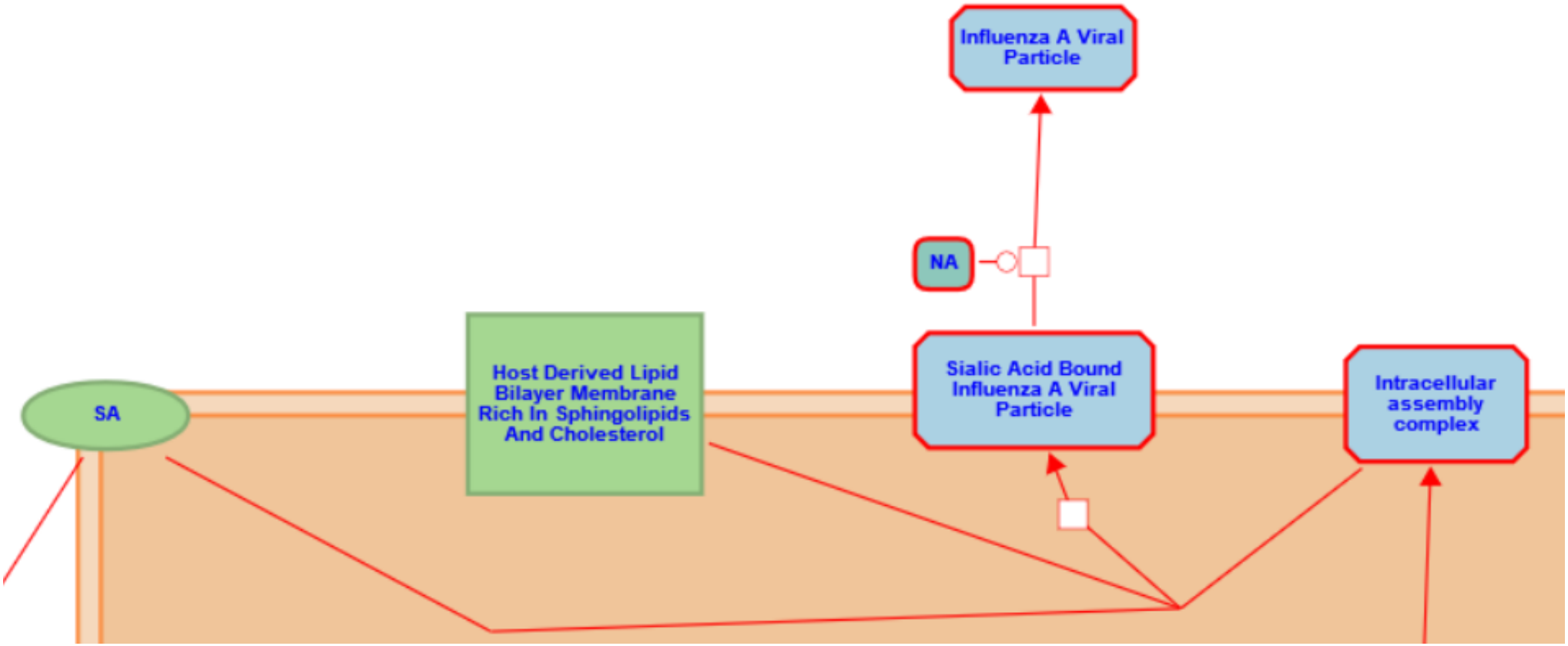
Disease annotation in Reactome

Three main areas:

- Infection (eg. HIV, influenza, botulism)
  - microbially-expressed proteins
- Cancer (eg. EGFR, FGFR and NOTCH signalling)
  - altered protein functions
- Metabolic diseases (eg. mucopolysaccharidoses, phenylketonuria, vitamin metabolism abnormalities)
  - altered expression of proteins

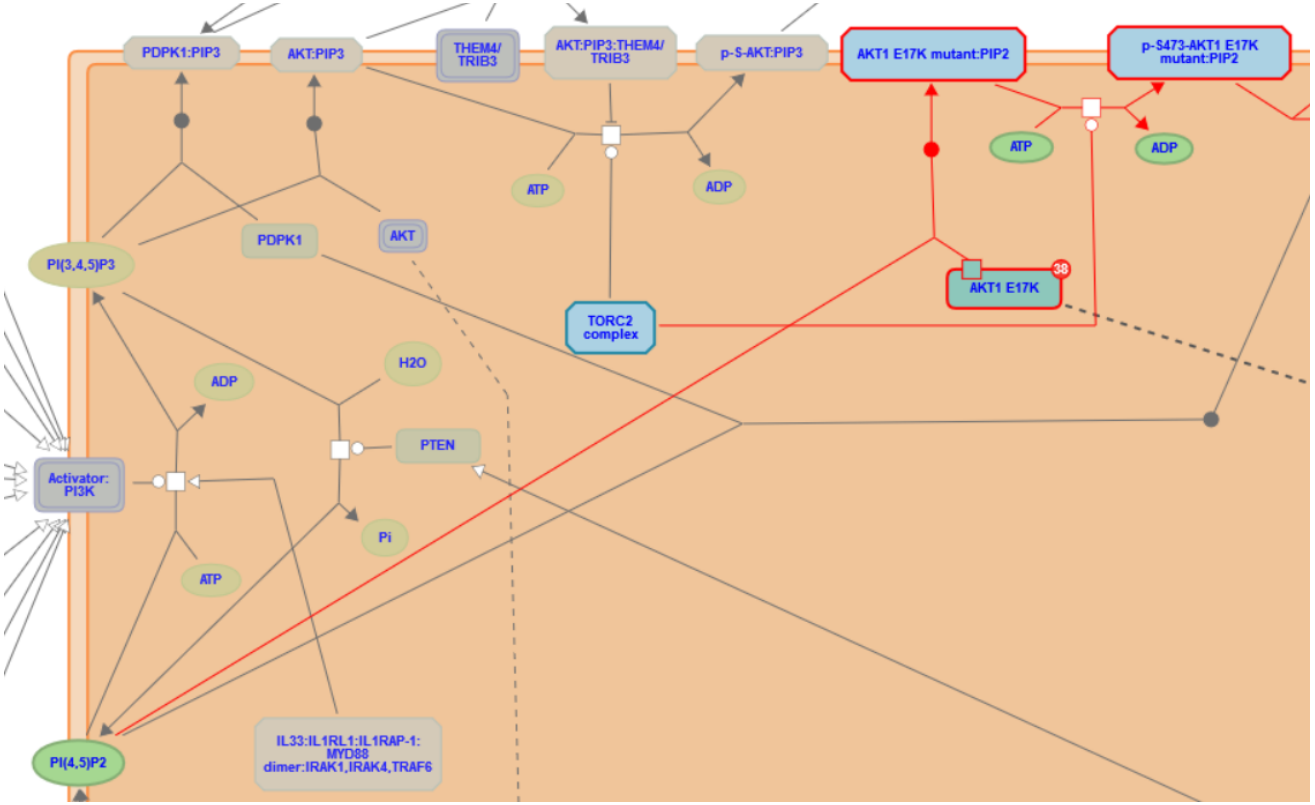
Disease display in Reactome - Infection

Influenza virus life cycle: budding



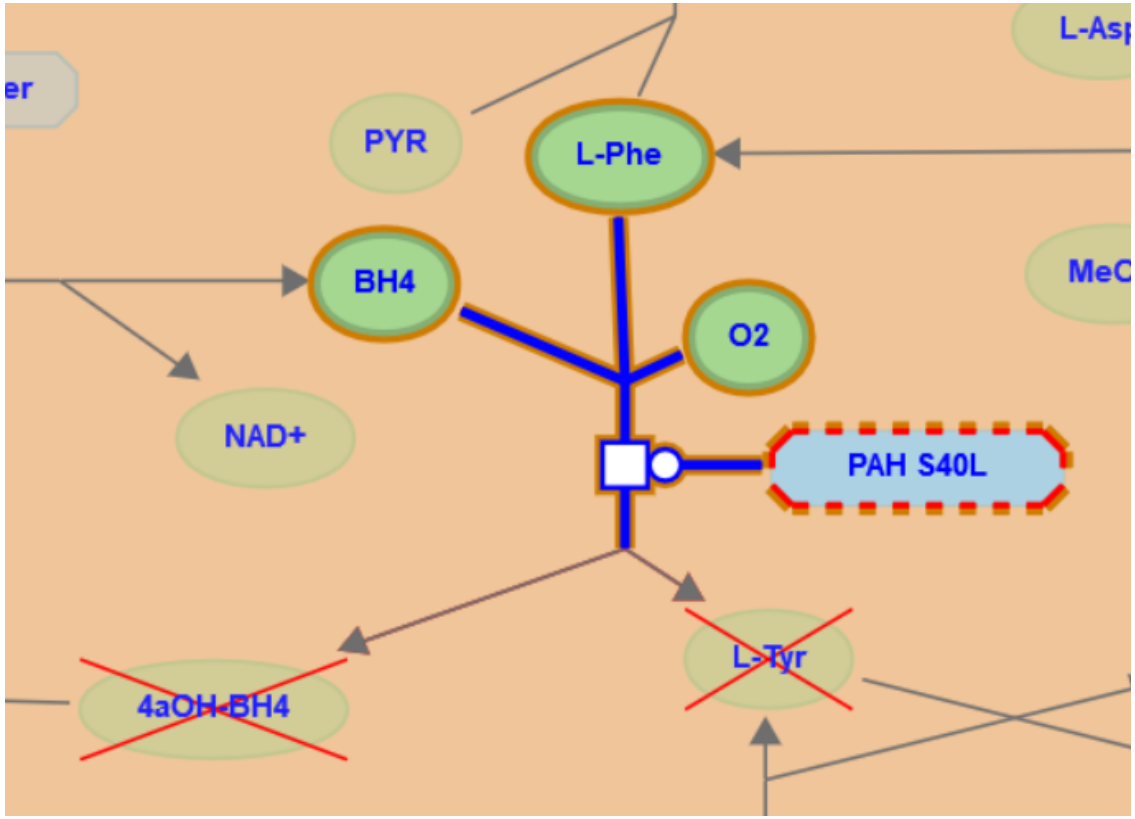
Disease display in Reactome – Altered protein function in Cancer

Constitutive Signaling by AKT1 E17K in Cancer



Disease display in Reactome – Loss of function in metabolism

Phenylketonuria



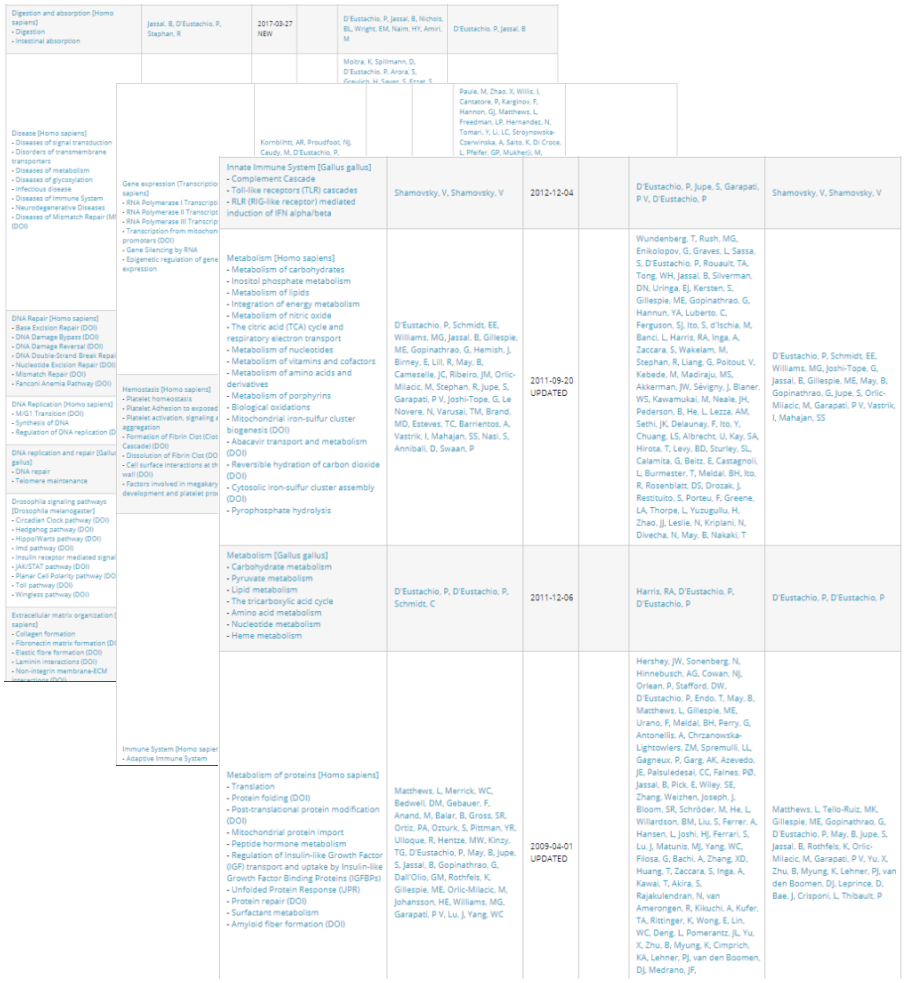
Downloads

- Small(ish) sections from Pathway Browser as text, PDF, etc.
- Entire database content (and software) from Downloads page (linked to Homepage).
- Reusable standard formats BioPAX & SBML
- Illustrations and icon library
- UniProt to Pathways
- GO annotations
- Protein-Protein interaction pairs - Interactions between proteins in the same complex, reaction, or adjoining reaction

Coverage – Content, TOC

Topic	Authors	Released	Revised	Reviewers	Editors
Cell Cycle [Homo sapiens] - Cell Cycle Checkpoints - Cell Cycle, Mitotic - Chromosome Maintenance - Meiosis	Hoffmann, I, Khanna, KK, Walworth, N, Yen, TJ, O'Donnell, M, Bosco, G, Matthews, L, Orlic-Milacic, M, Gillespie, ME, May, B, Blackburn, EH, Seidel, J, D'Eustachio, P, Borowiec, JA, Pagano, M, Davey, MJ, Tye, BK, Lorca, T, Castro, A, Roger, PP, Gopinathrao, G, Tom, S, Bambara, RA, Lee, KS, Gallie, BL, Sanchez, Y, Nasi, S, Annibali, D, Joshi-Tope, G, Jupe, S, Watanabe, N, Hunter, T	2011-12-06 UPDATED		Sanchez, Y, Knudsen, E, Hardwick, KG, Manfredi, J, MacPherson, D, Grana, X, Bolcun-Filas, E, Cohen, PE, Holloway, JK, Lyndaker, A, Schimenti, JC, Strong, E, Price, C, Bird, AW, Peters, JM, Coqueret, O, Zhang, N, Watanabe, Y, Tanno, Y, Lorca, T, Almouzni-Pettinotti, G, Dunleavy, EM, Foltz, DR, Borowiec, JA, Zaccara, S, Inga, A, Weil, R, Bruinsma, W, Merdes, A, Chen, H, Maxwell, CA, Grant, R, Lindon, C, Shah, K, Wang, Y, Colanzi, A, Malhotra, V, Longworth, MS, Mochida, S, Burgess, A, Gorjánácz, M, Mattaj, IW, Cheeseman, IM, Bosco, G, Samarajiwa, S, Roger, PP, D'Eustachio, P, Greene, LA, Pires, IM, Janssens, V, Avruch, J, Antonin, W, Dixit, VM, Herlihy, A	Matthews, L, Gopinathrao, G, Joshi-Tope, G, May, B, Orlic-Milacic, M, D'Eustachio, P, Gillespie, ME, Jupe, S, D'Eustachio, P
Cell-Cell communication [Homo sapiens] - Cell junction organization (DOI) - Signal regulatory protein family interactions (DOI) - Nephrin family interactions (DOI)	Garapati, P V, de Bono, B, Matthews, L, Jassal, B	2011-09-20 UPDATED		Barclay, AN, Huber, TB, Grahammer, Florian, Ebnet, K, Wu, C, Sonnenberg, A, Honig, B, Sanes, JR, D'Eustachio, P	Garapati, P V, Matthews, L, Jupe, S, Jassal, B, Wu, C
Cellular responses to external stimuli [Homo sapiens] - Response to metal ions (DOI) - Macroautophagy (DOI) - Cellular responses to stress	D'Eustachio, P, May, B, Jupe, S, Matthews, L, Shamovsky, V, Orlic-Milacic, M, Jassal, B, Vastrik, I, Stephan, R, Luo, F, Khanna, KK, Pagano, M, Nasi, S, Annibali, D	2017-03-27 NEW		Atrian, S, D'Eustachio, P, Klionsky, DJ, Tooze, SA, Ford, D, Wang, Q, Kavdia, M, Pani, B, Samarajiwa, S, Rothfels, K, Echeverria, PC, Picard, D, Brown, DR, Rantanen, K, Inga, A, Zaccara, S, Warner, D, Roger, PP, Gillespie, ME, Gay, NJ, Borowiec, JA, Du, F, Sun, Y, Sanchez, Y, Coqueret, O, Greene, LA, Maltepe, E	D'Eustachio, P, May, B, Jupe, S, Matthews, L, Shamovsky, V, D'Eustachio, P, Jassal, B, Vastrik, I, Orlic-Milacic, M
Chromatin organization [Homo sapiens] - Chromatin modifying enzymes (DOI)	May, B, Jupe, S, Jassal, B, Orlic-Milacic, M, Walport, J, Hopkinson, J	2013-12-04		Karagiannis, T, Yang, XJ, Schofield, CJ, Walport, J, Hopkinson, J, Motamedi, M, Guccione, E, Fischle, W, Meldal, BH, D'Eustachio, P, Mandal, M, Cheng, X, Falnes, PØ	May, B, Jupe, S, Jassal, B, Orlic-Milacic, M, Duenas, C, Shamovsky, V
Circadian Clock [Homo sapiens] (DOI) - BMAL1:CLOCK,NPAS2 activates circadian gene expression - RORA activates gene expression - NR1D1 (REV-ERBA) represses gene expression	May, B	2010-12-14		D'Eustachio, P, Albrecht, U, Kay, SA, Hirota, T, Delaunay, F, Kersten, S, Lezza, AM, Jain, MK	May, B
Developmental Biology [Homo sapiens] - Axon guidance (DOI) - Myogenesis (DOI) - Regulation of beta-cell development (DOI) - Signaling by NODAL (DOI) - Transcriptional regulation of white adipocyte differentiation - Transcriptional regulation of pluripotent stem cells (DOI) - Activation of HOX genes during	Garapati, P V, Ferrer, J, Tello-Ruiz, MK, May, B, Jupe, S, Orlic-Milacic, M, Jassal, B, Heldin, CH, Moustakas, A, Huminiecki, L, Rezsohazy, R, Nasi, S, Annibali, D, Charalambous, M, Akkerman, JW	2011-09-20 UPDATED		Maness, PF, Krauss, RS, Walmod, PS, Jensen, J, Peng, C, D'Eustachio, P, Sethi, JK, Wang, J, Blasi, F, Rezsohazy, R, Meijer, D, Blumenberg, M, Kumanogoh, A, Kikutani, H, Cooper, HM, Kidd, T, Jaworski, A, Ip, NY, Morales, D, Luo, W, Heldin, CH, Huang, T, Chen, YG, May, B, Kersten, S,	Matthews, L, Garapati, P V, D'Eustachio, P, May, B, Gopinathrao, G, Jupe, S, Orlic-Milacic, M, Jassal, B, Schmidt, EE

And many more...



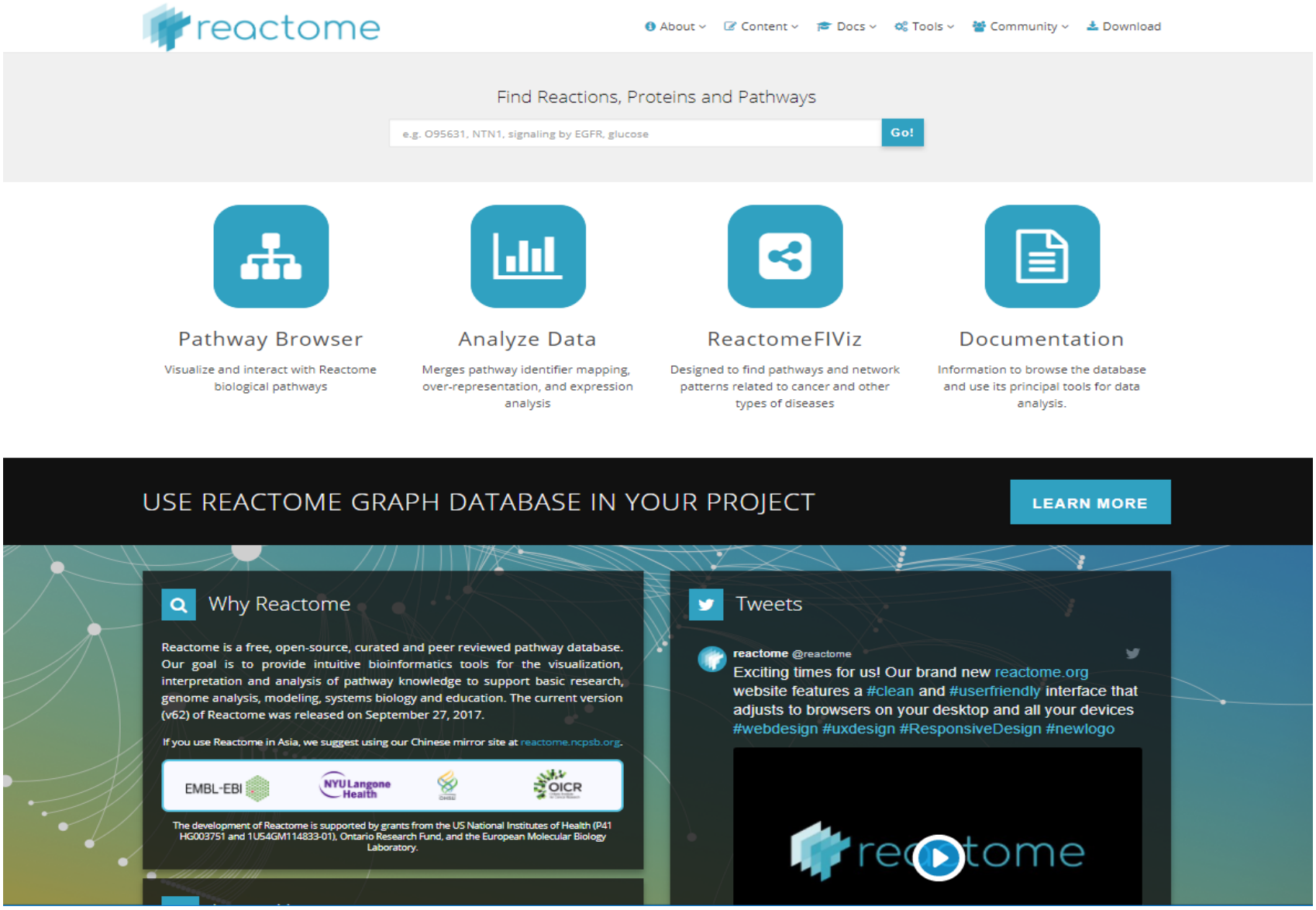
Reactome Tools

- Interactive Pathway Browser

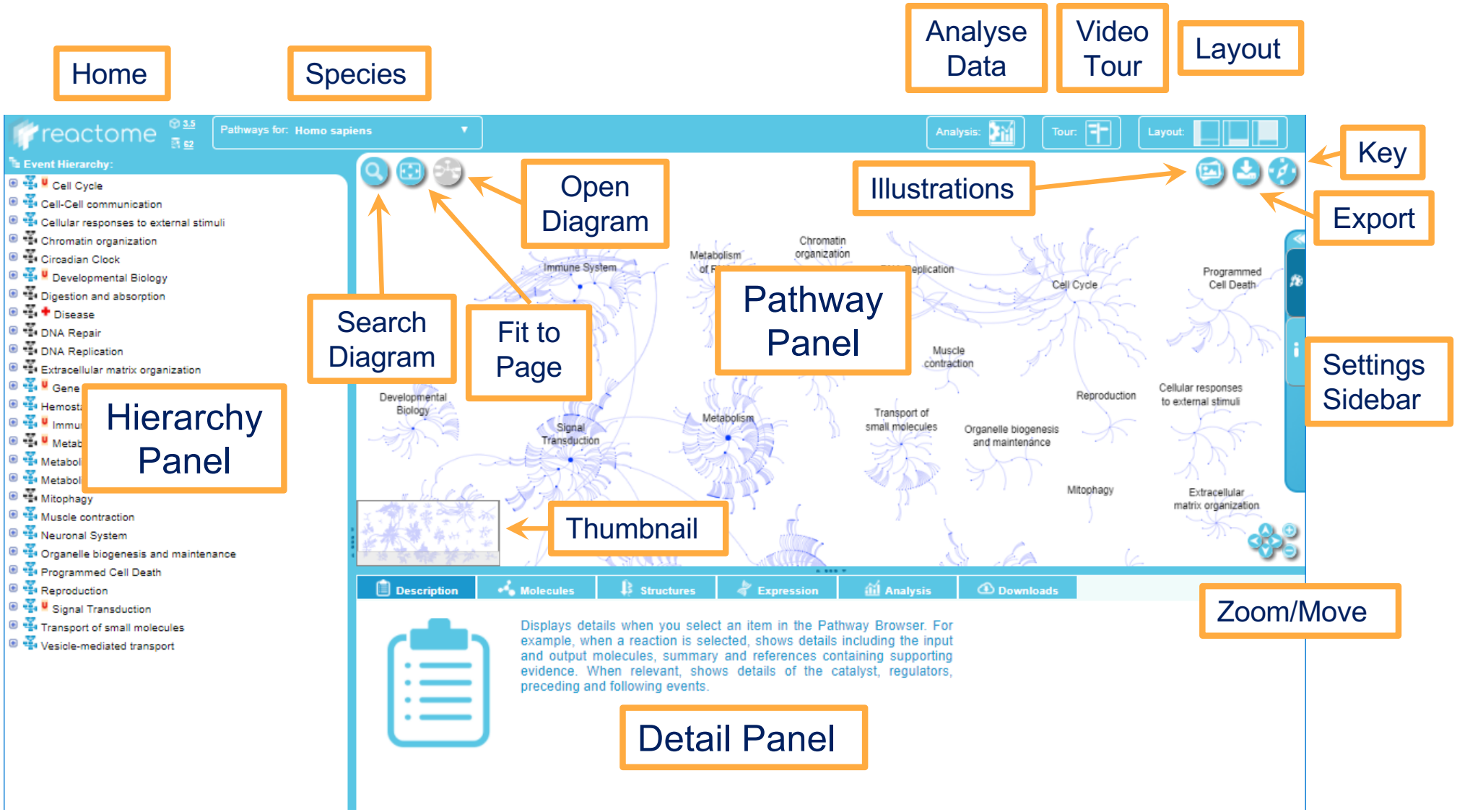
- Analysis
  - Over-representation
  - Pathway topology
  - Expression overlay

- Molecular Interaction overlay
- Species Comparison

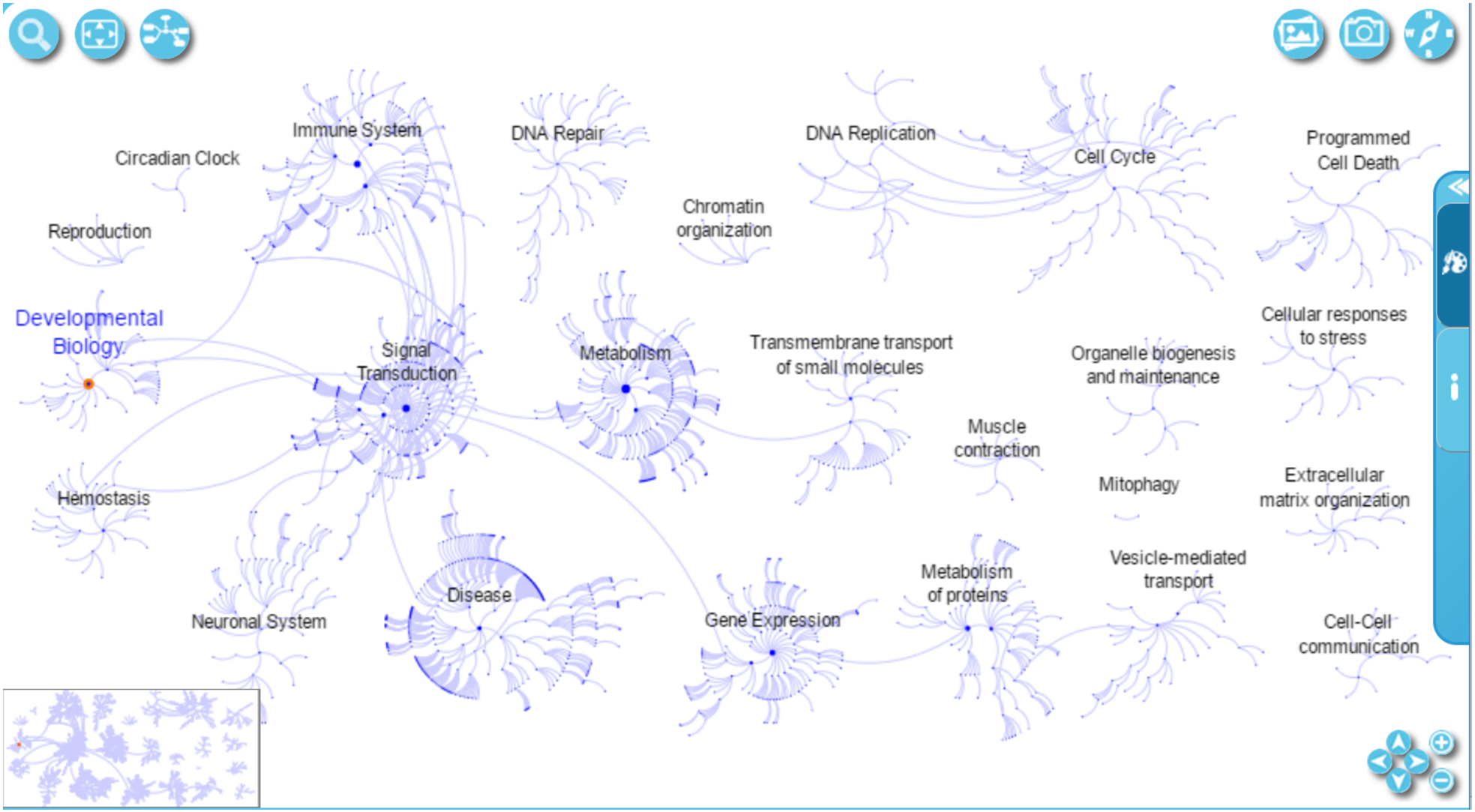
Front Page http://www.reactome.org



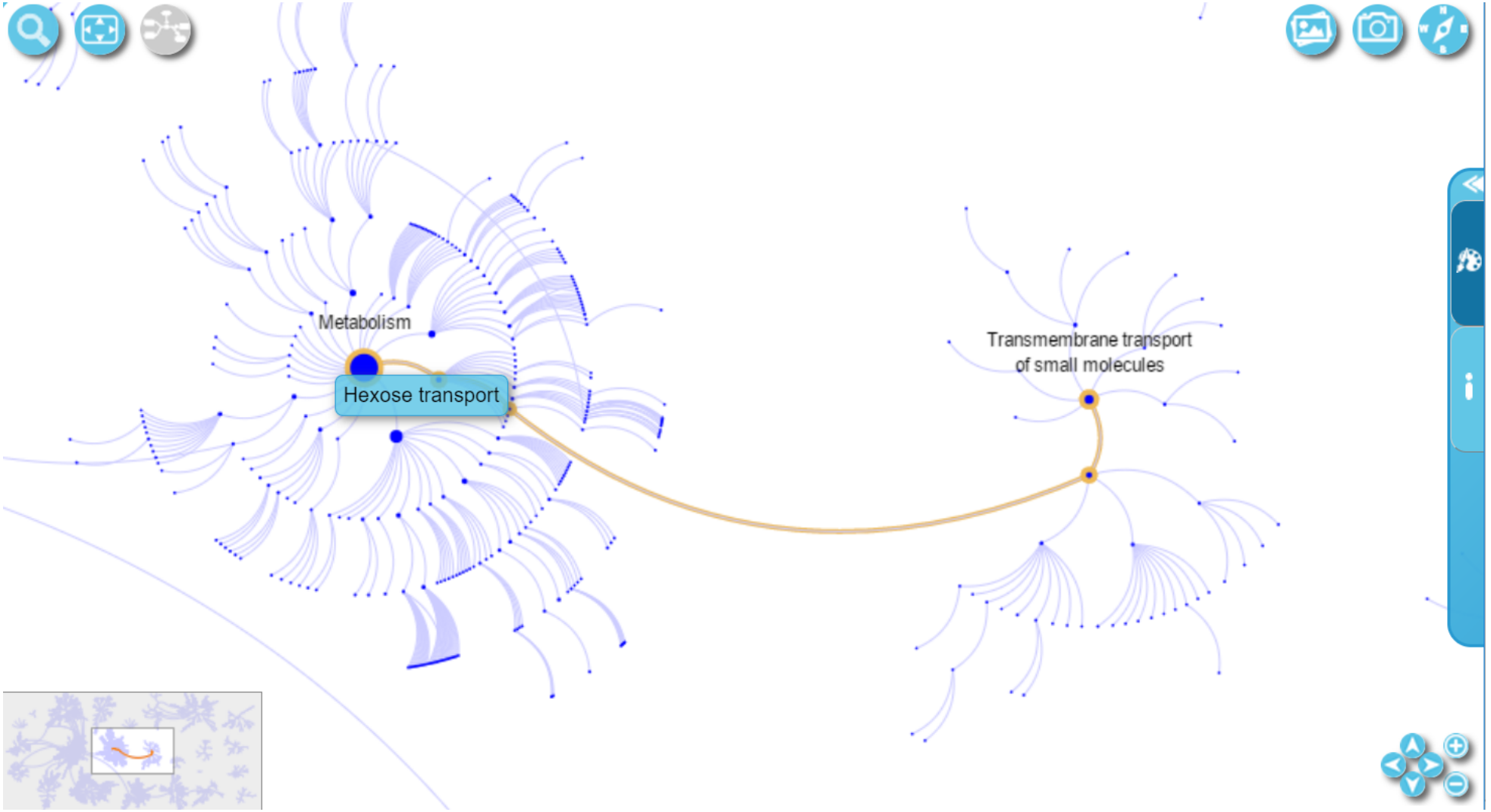
The Pathway Browser



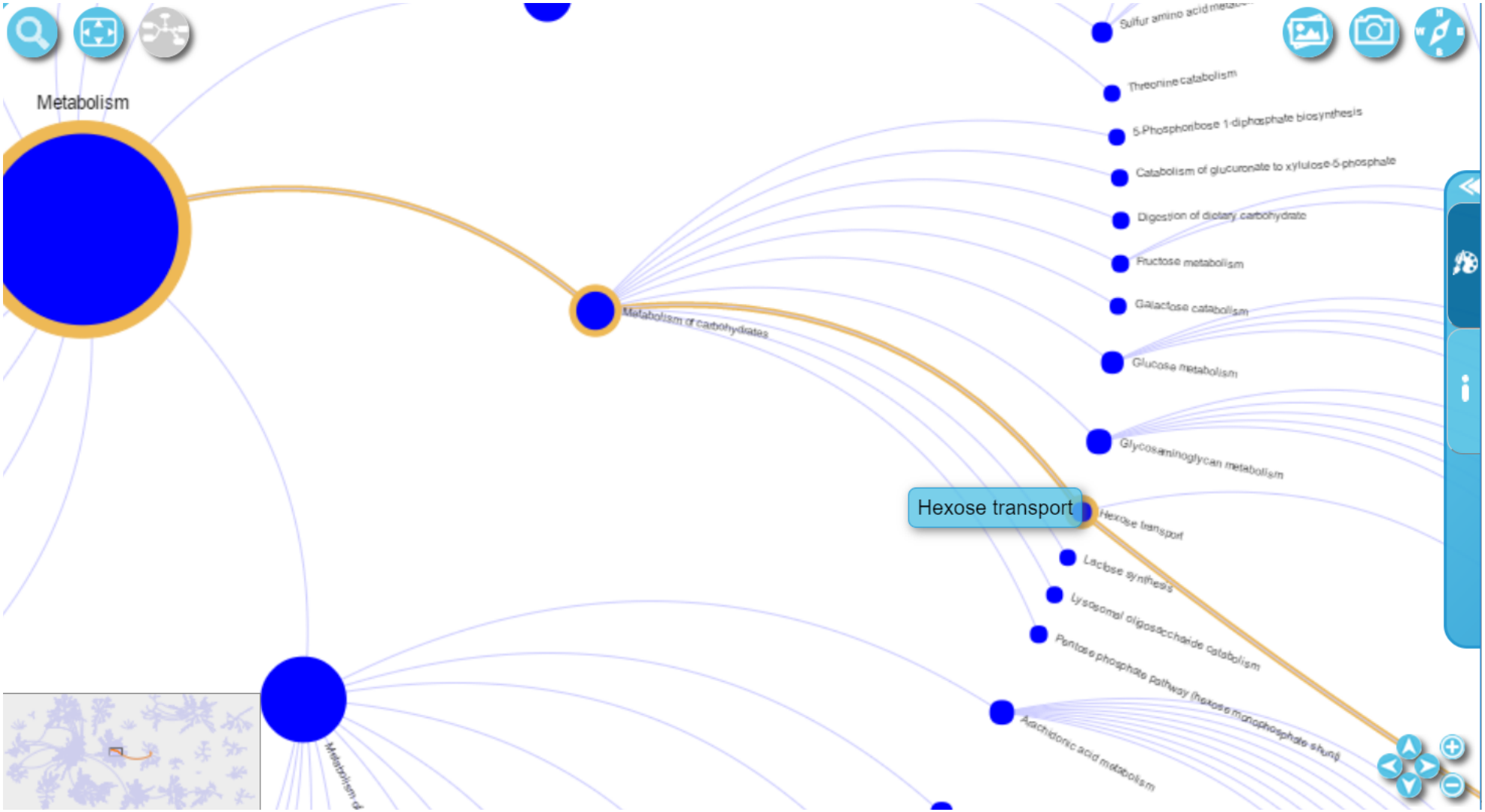
Pathway Overview



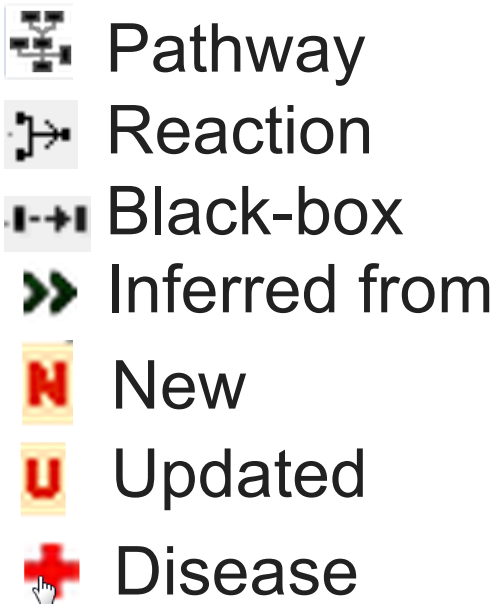
Edges = shared pathways



Zoom in for pathway names

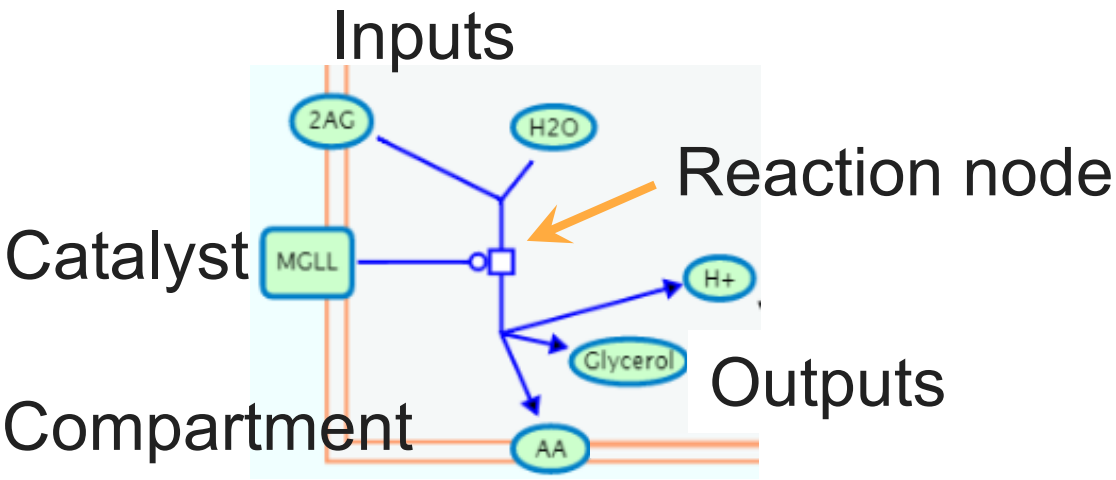


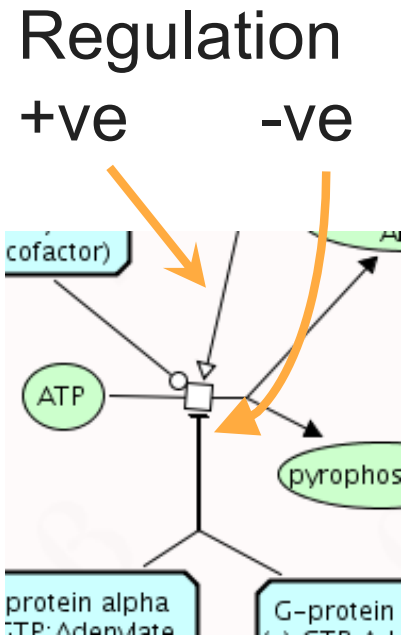
Hierarchy Panel

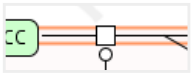


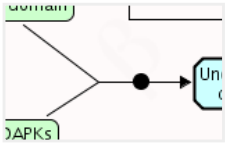
The Pathway Browser - Pathway Diagrams

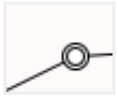
Ovals are small molecules (or sets of)
Green boxes are proteins,
Blue are complexes,
Blue with double-boundary are sets

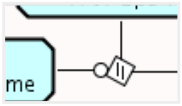





Transition


Binding

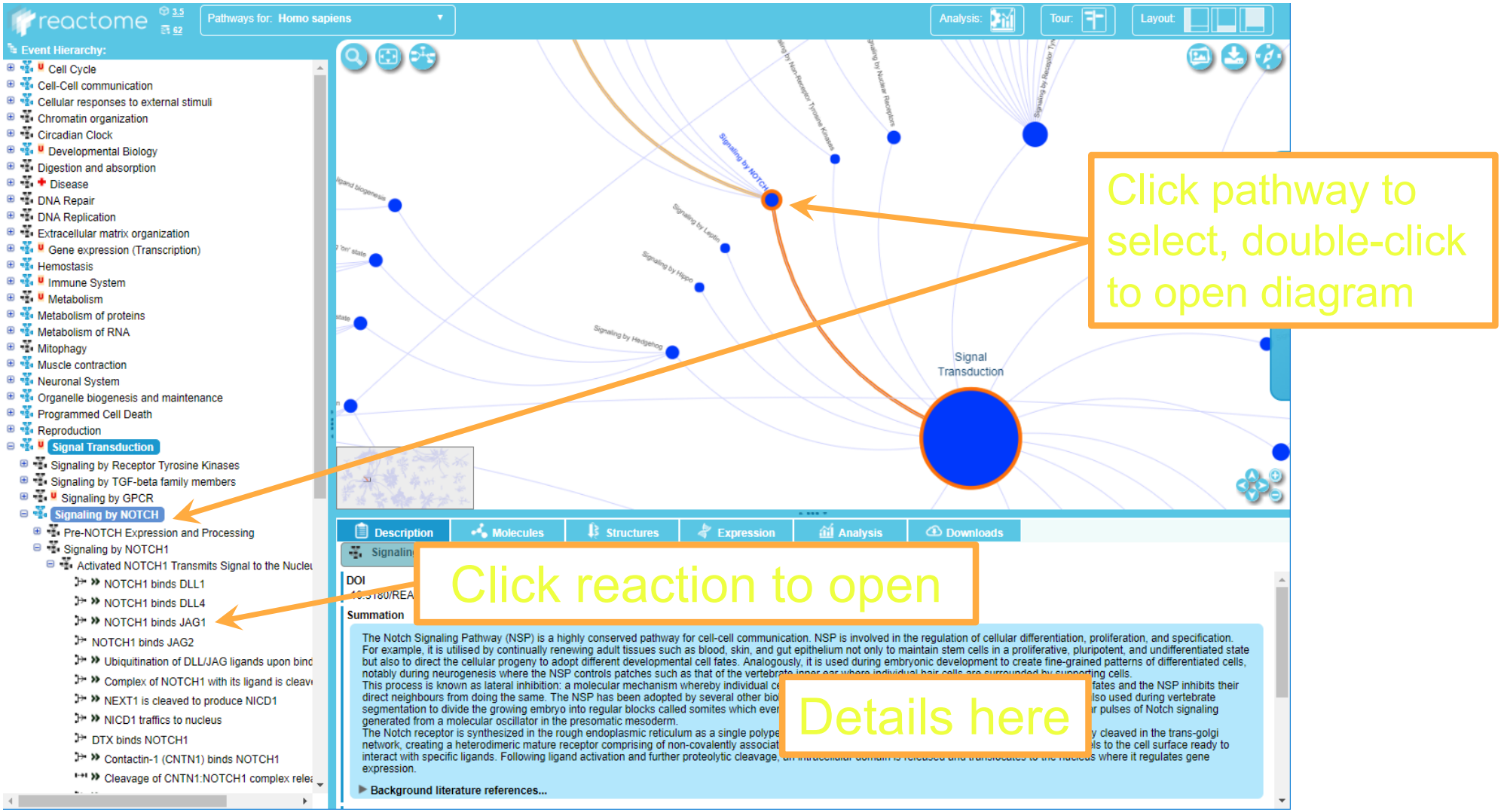

Dissociation


Omitted

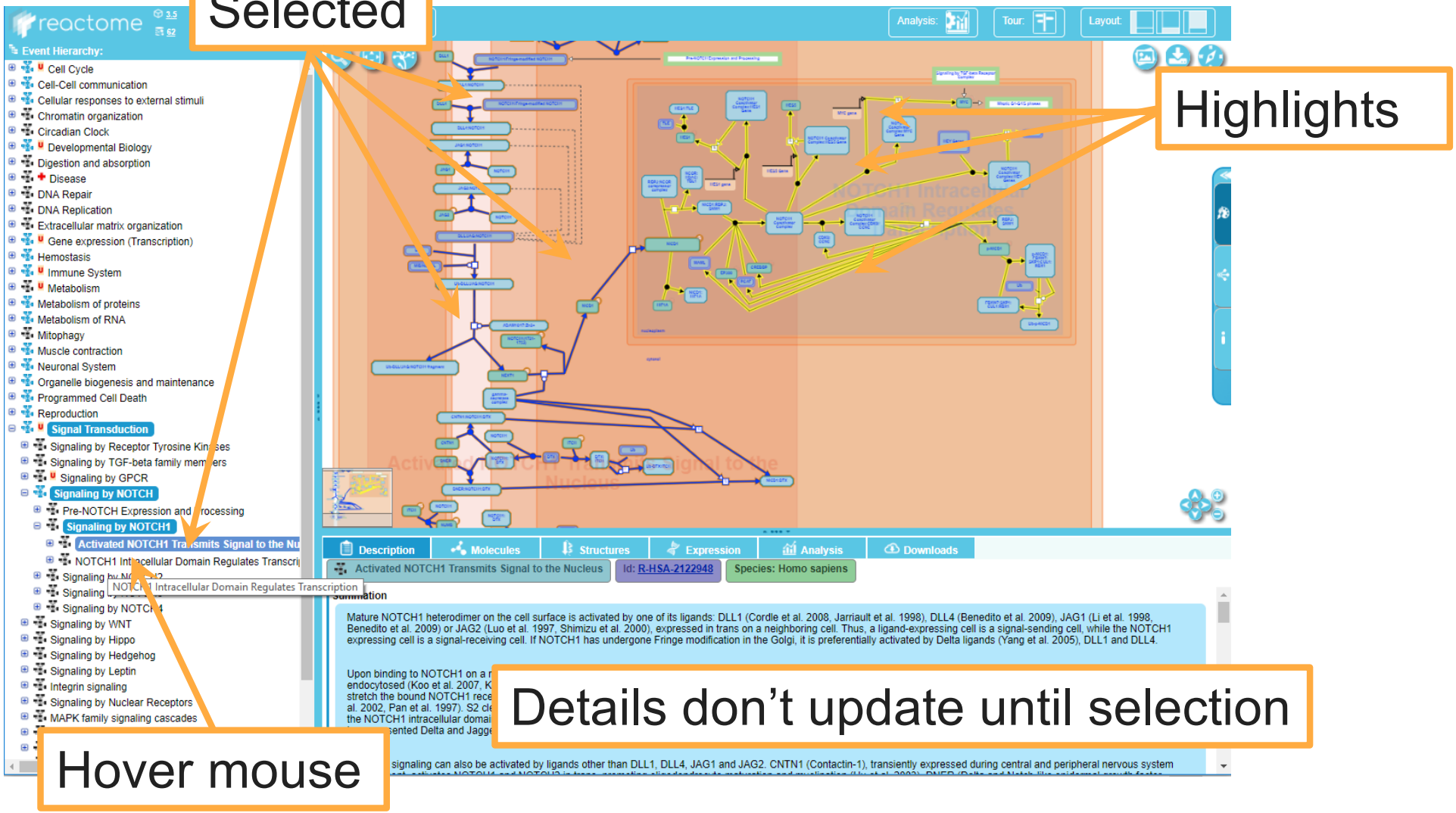

Uncertain

Navigating in the Pathway Browser

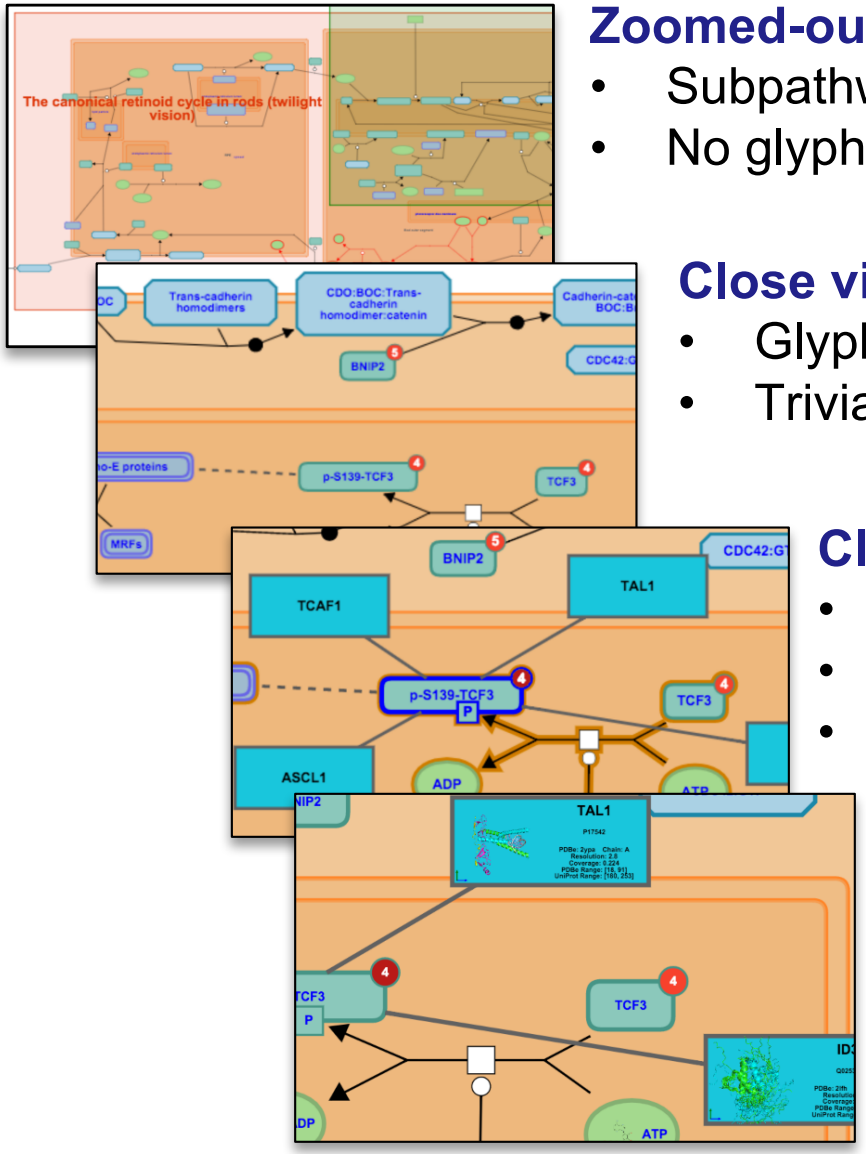
Home button



Navigating in the Pathway Browser



Pathway Diagram Viewer



Zoomed-out view

- Subpathway boxes
- No glyph labels, No trivial molecules

Close view

- Glyph labels
- Trivial molecules and interactor summary appear

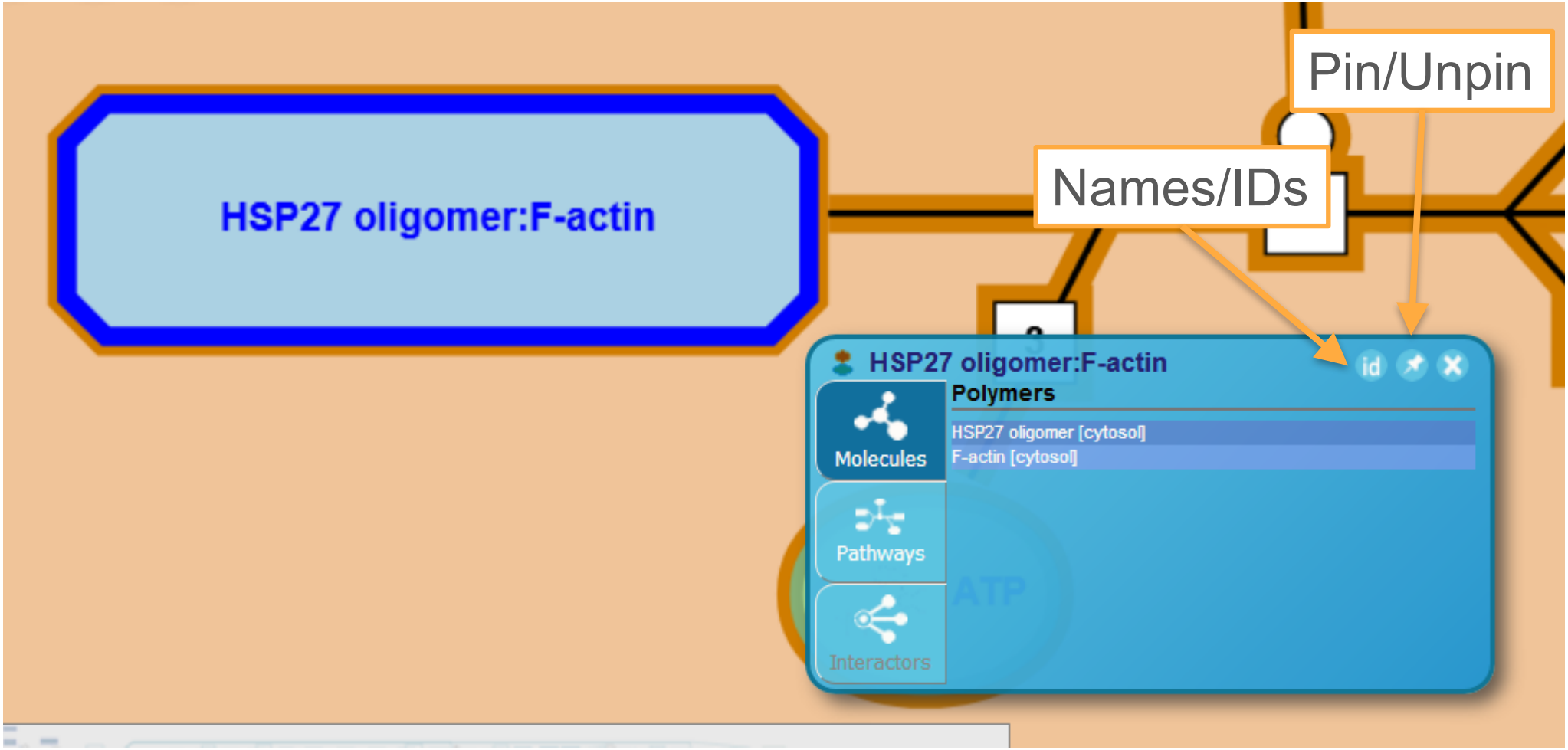
Closer view

- Stoichiometry shown
- Node attachments appear
- Interactors show gene or chemical name

Zoomed-in view

- Interactors show structures and details
- Diagram proteins, chemicals extra info

Contextual Information Panel



Colour Profiles

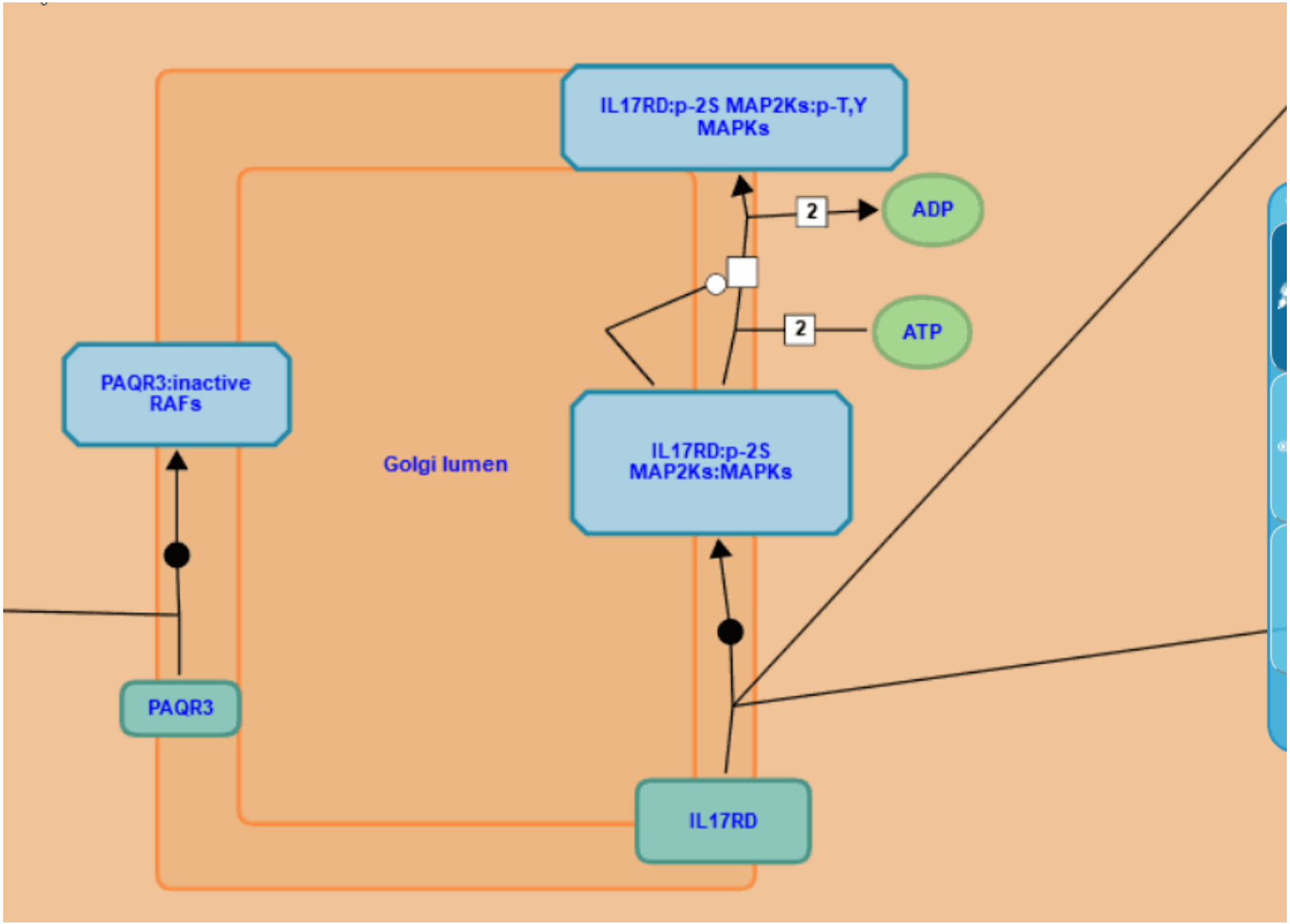
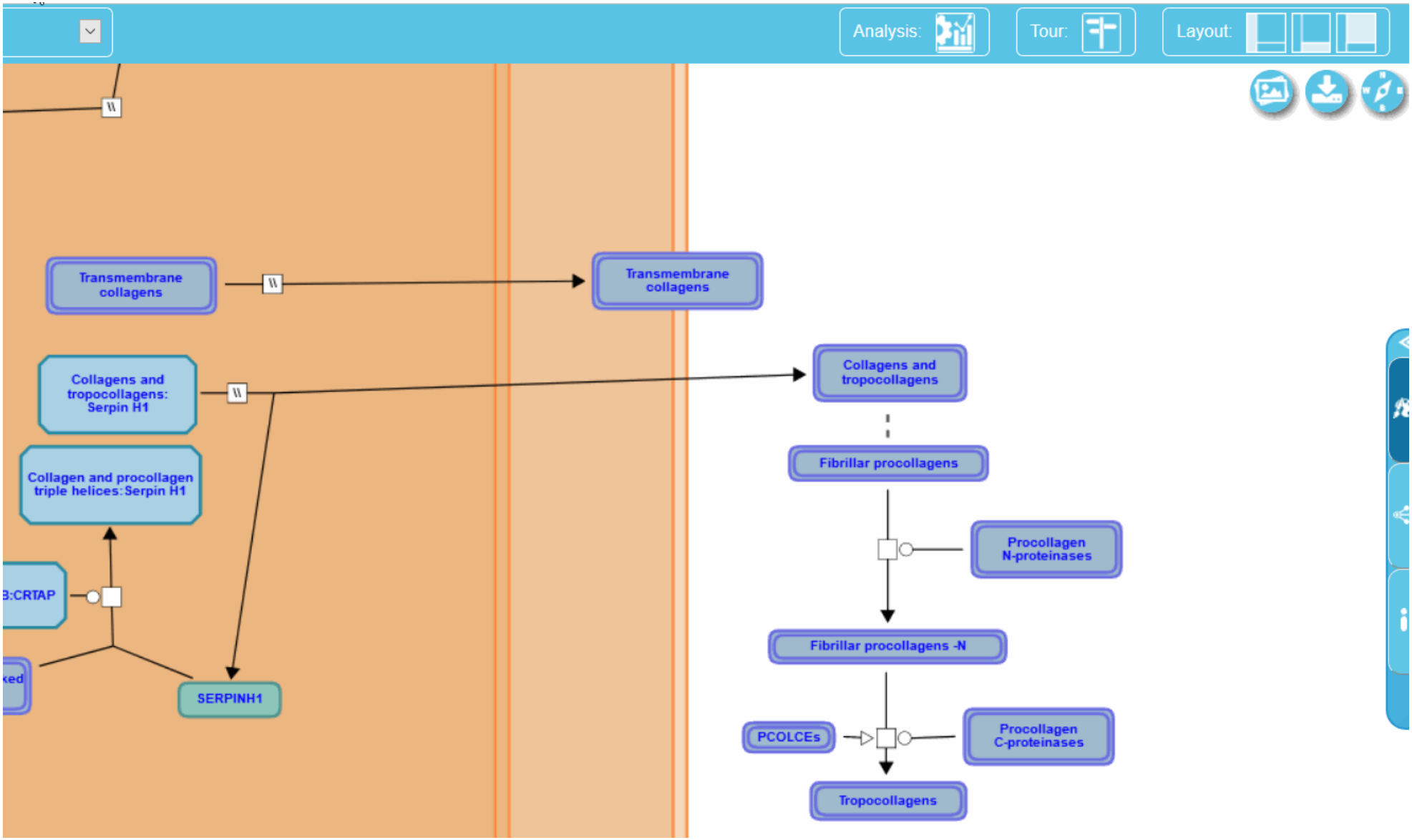
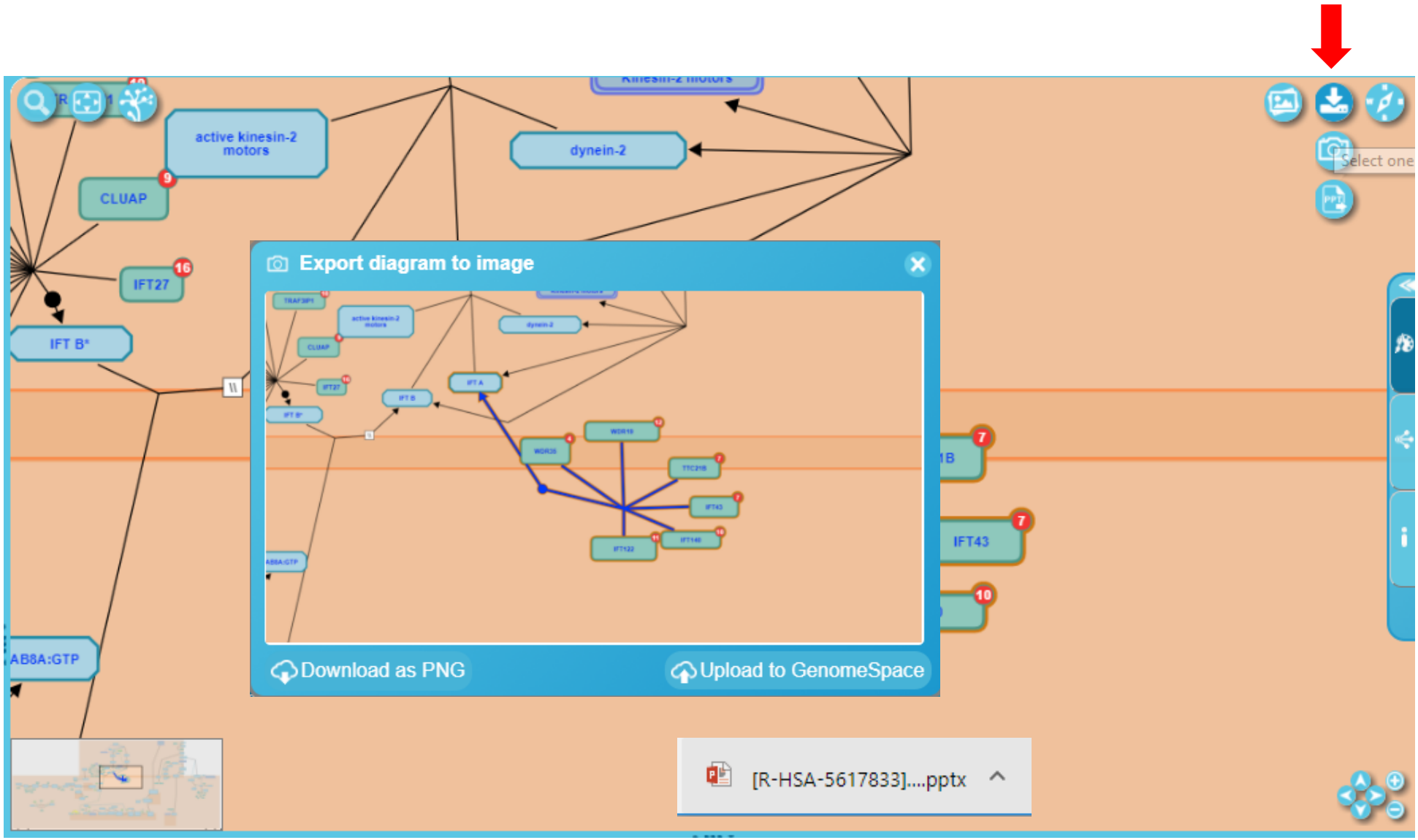


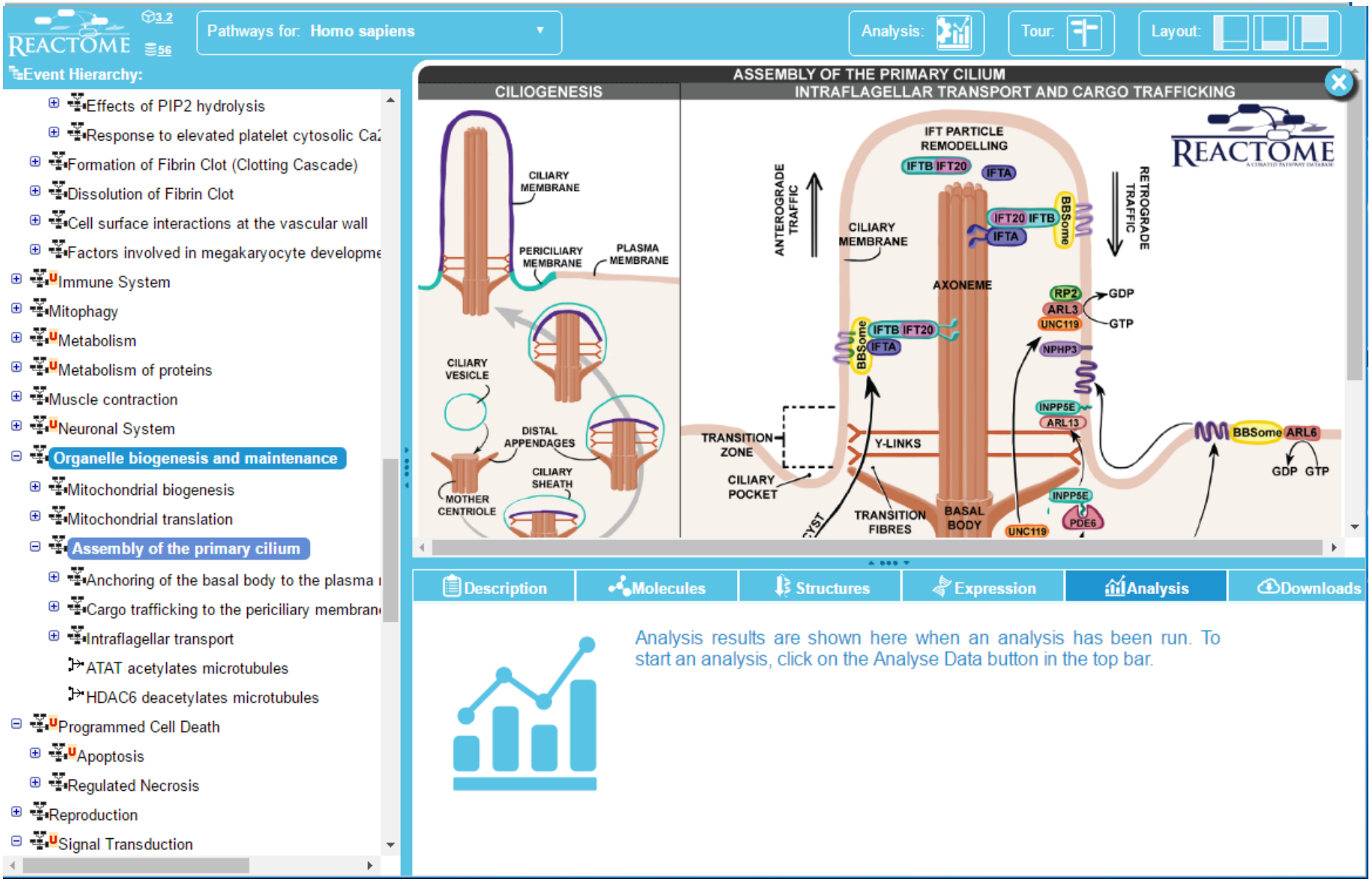
Diagram Key


Analysis:
Tour:
Layout:
Transmembrane collagens
Transmembrane collagens
Collagens and tropocollagens: Serpin H1
Collagen and procollagen triple helices:Serpin H1
:CRTAP
SERPINH1
Collagens and tropocollagens
Fibrillar procollagens
Procollagen N-proteinases
Fibrillar procollagens -N
PCOLCEs
Procollagen C-proteinases
Tropocollagens

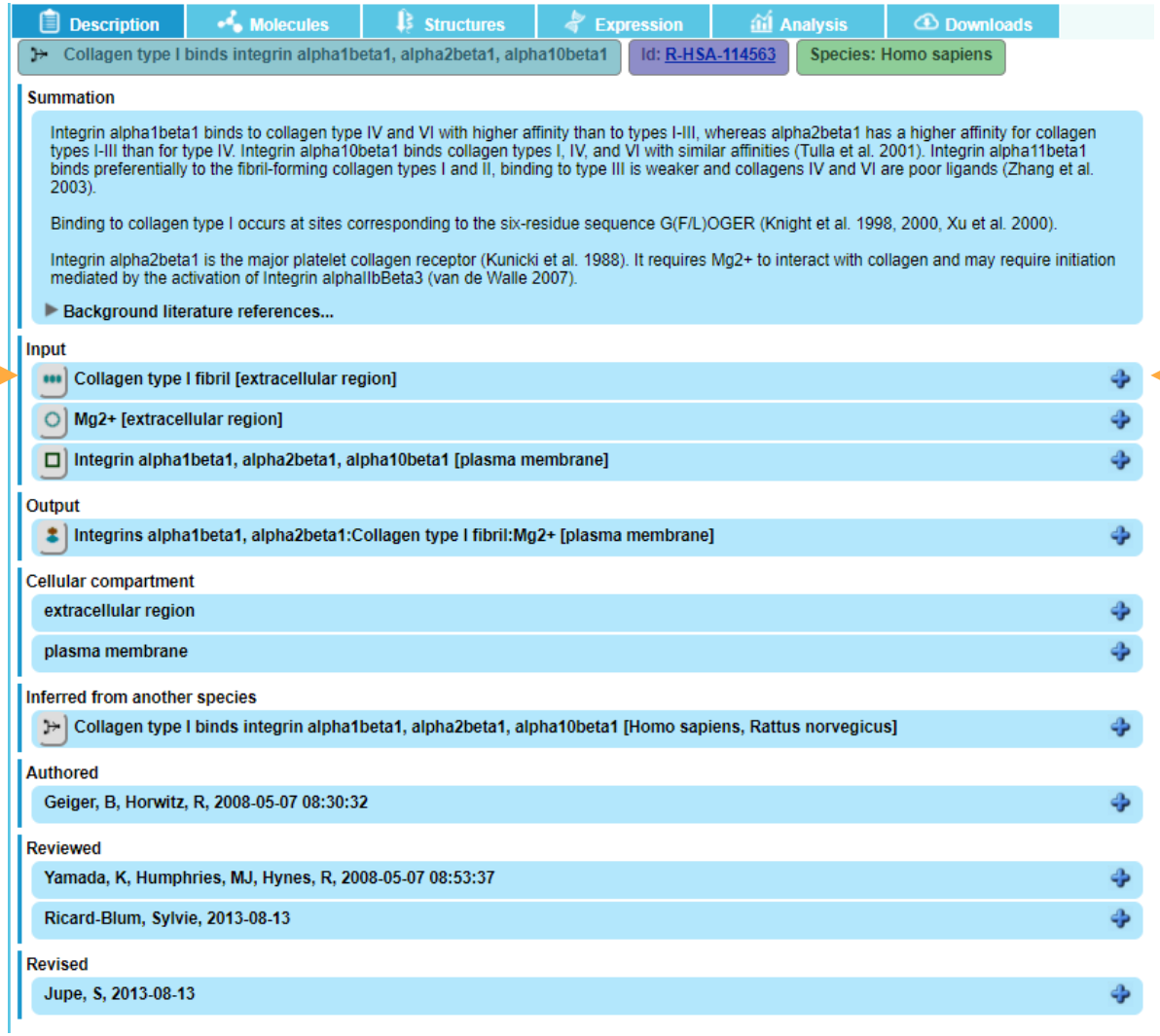
Export Diagram



Show Illustration



The Details Panel - Overview



Background

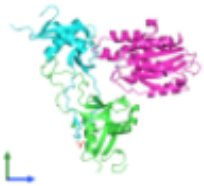
Select

Orthologues

Key literature

Reveal Details

Description | Molecules | Structures 5/6 | Expression | Analysis | Downloads

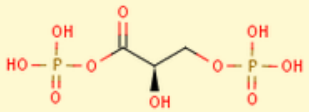


UniProt: P17301 ITGA2 **Chain:** C **Resolution:** 1.9 **Coverage:** 0.174 **PDB Range:** [1, 200]
UniProt Range: [167, 366]

1v7p PDBe

▶ All other structures for P17301

▶ All other struct

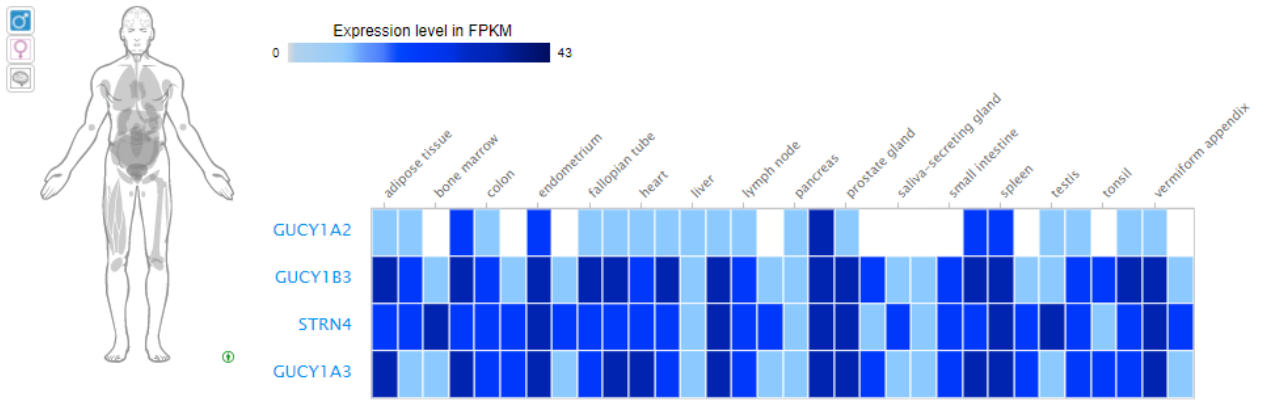


ChEBI Name	3-phospho-D-glyceroyl dihydrogen phosphate
ChEBI ID	CHEBI:16001
Definition	The (R)-enantiomer of 3-phosphoglyceroyl dihydrogen phosphate.
Stars	★★★
Secondary ChEBI IDs	CHEBI:1658, CHEBI:11881, CHEBI:20189

RNA-seq of coding RNA from tissue samples of 122 human individuals representing 32 different tissues

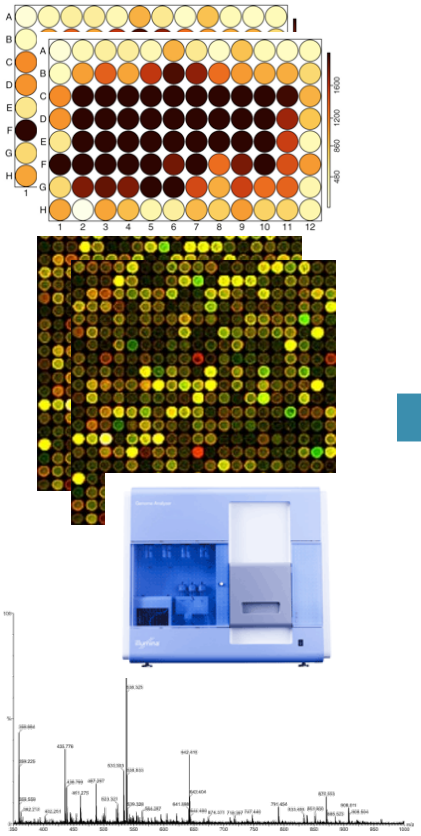
Showing 4 genes:

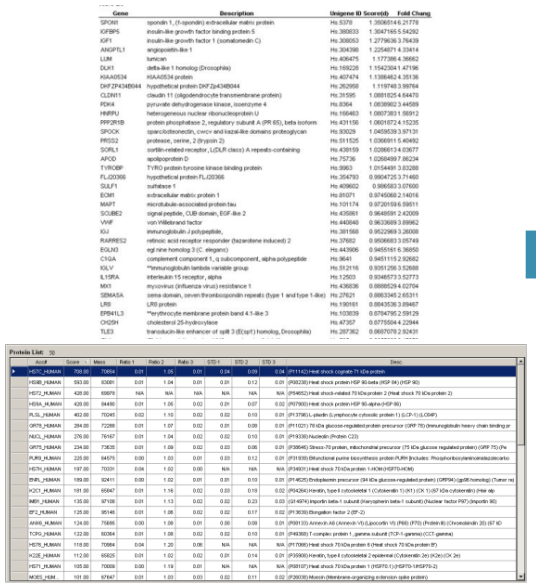
Select genome browser to view tracks | Download

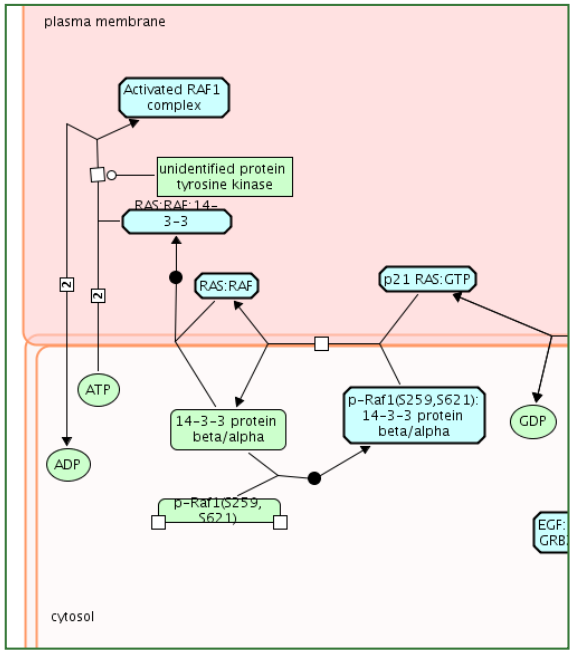


See more expression data at Expression Atlas.
This expression view is provided by Expression Atlas.
Please send any queries or feedback to arrayexpress-atlas@ebi.ac.uk.

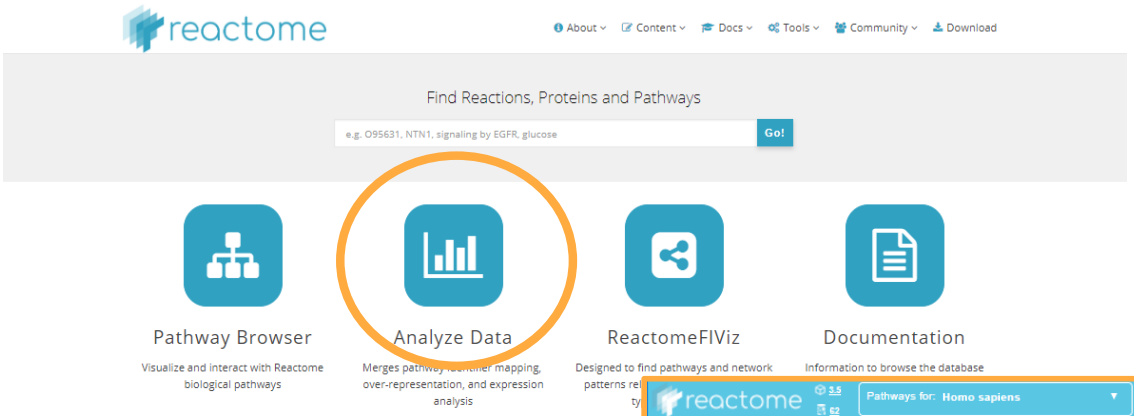
Understanding gene lists…Reactome Tools







Analysis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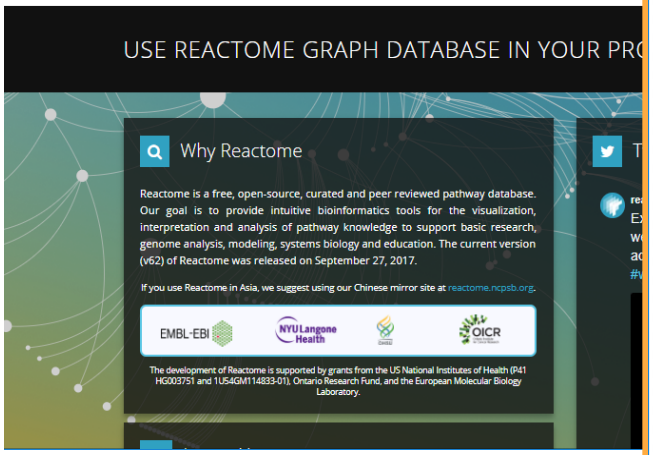
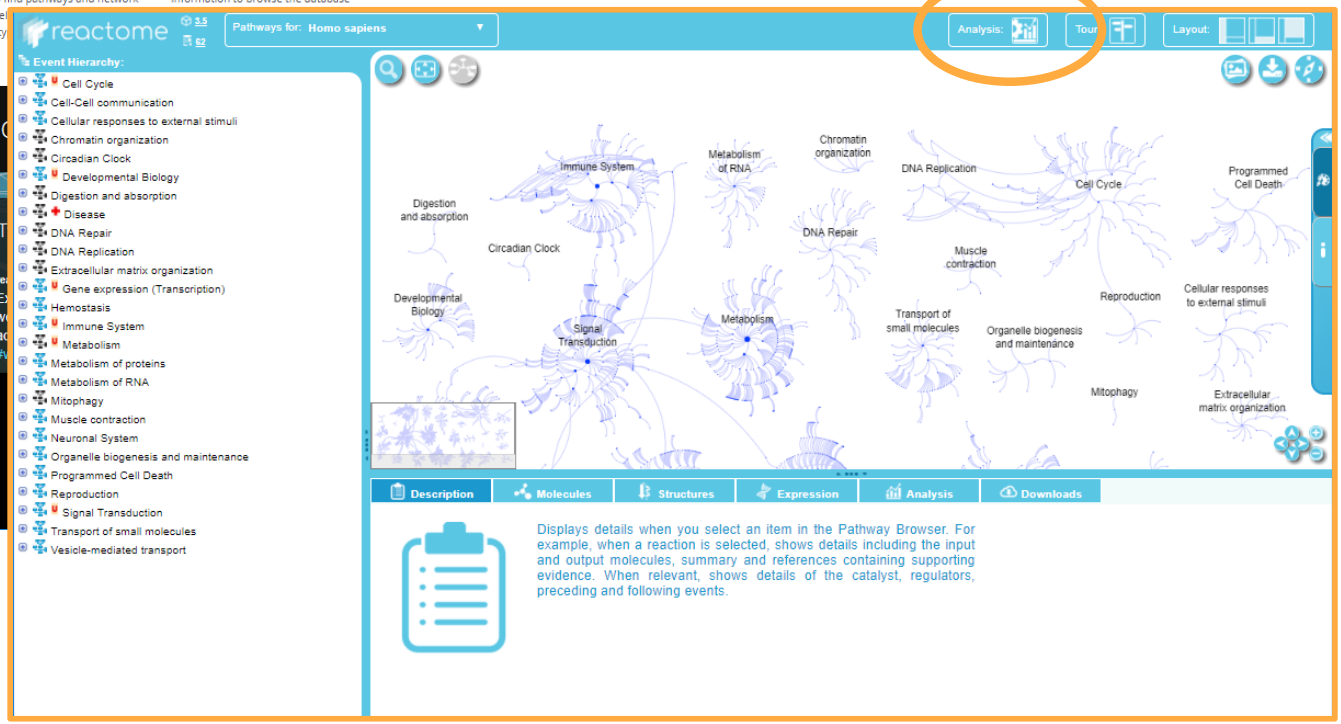
Find Reactions, Proteins and Pathways
e.g. O95631, NTN1, signaling by EGFR, glucose
Go!
Pathway Browser
Visualize and interact with Reactome biological pathways
Analyze Data
Merges pathway/container mapping, over-representation, and expression analysis
ReactomeFIViz
Designed to find pathways and network
Documentation
Information to browse the database


USE REACTOME GRAPH DATABASE IN YOUR PR
Why Reactome
Reactome is a free, open-source, curated and peer reviewed pathway database. Our goal is to provide intuitive bioinformatics tools for the visualization, interpretation and analysis of pathway knowledge to support basic research, genome analysis, modeling, systems biology and education. The current version (v62) of Reactome was released on September 27, 2017.
If you use Reactome in Asia, we suggest using our Chinese mirror site at reactome.ncpsb.org.
EMBL-EBI
NYU Langone Health
OICR
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751 and 1U54GM114833-01), Ontario Research Fund, and the European Molecular Biology Laboratory.


reactome
Pathways for: Homo sapiens
Analysis:
Tour
Layout:
Event Hierarchy:
Cell Cycle
Cell-Cell communication
Cellular responses to external stimuli
Chromatin organization
Circadian Clock
Developmental Biology
Digestion and absorption
Disease
DNA Repair
DNA Replication
Extracellular matrix organization
Gene expression (Transcription)
Hemostasis
Immune System
Metabolism
Metabolism of proteins
Metabolism of RNA
Mitophagy
Muscle contraction
Neuronal System
Organelle biogenesis and maintenance
Programmed Cell Death
Reproduction
Signal Transduction
Transport of small molecules
Vesicle-mediated transport
Immune System
Metabolism of RNA
Chromatin organization
DNA Replication
Cell Cycle
Programmed Cell Death
Digestion and absorption
Circadian Clock
DNA Repair
Muscle contraction
Developmental Biology
Signal Transduction
Metabolism
Transport of small molecules
Organelle biogenesis and maintenance
Reproduction
Cellular responses to external stimuli
Mitophagy
Extracellular matrix organization
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Molecules
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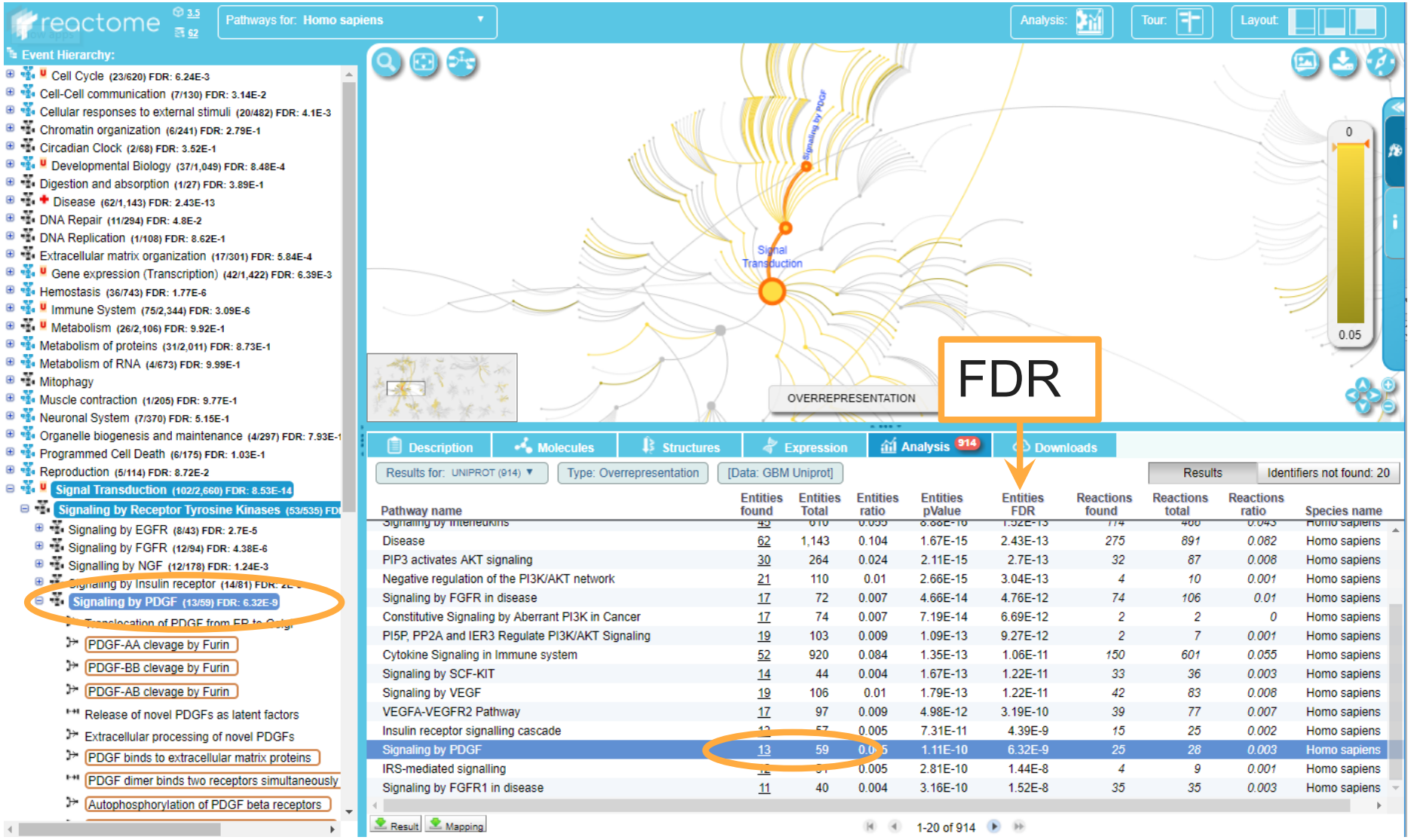
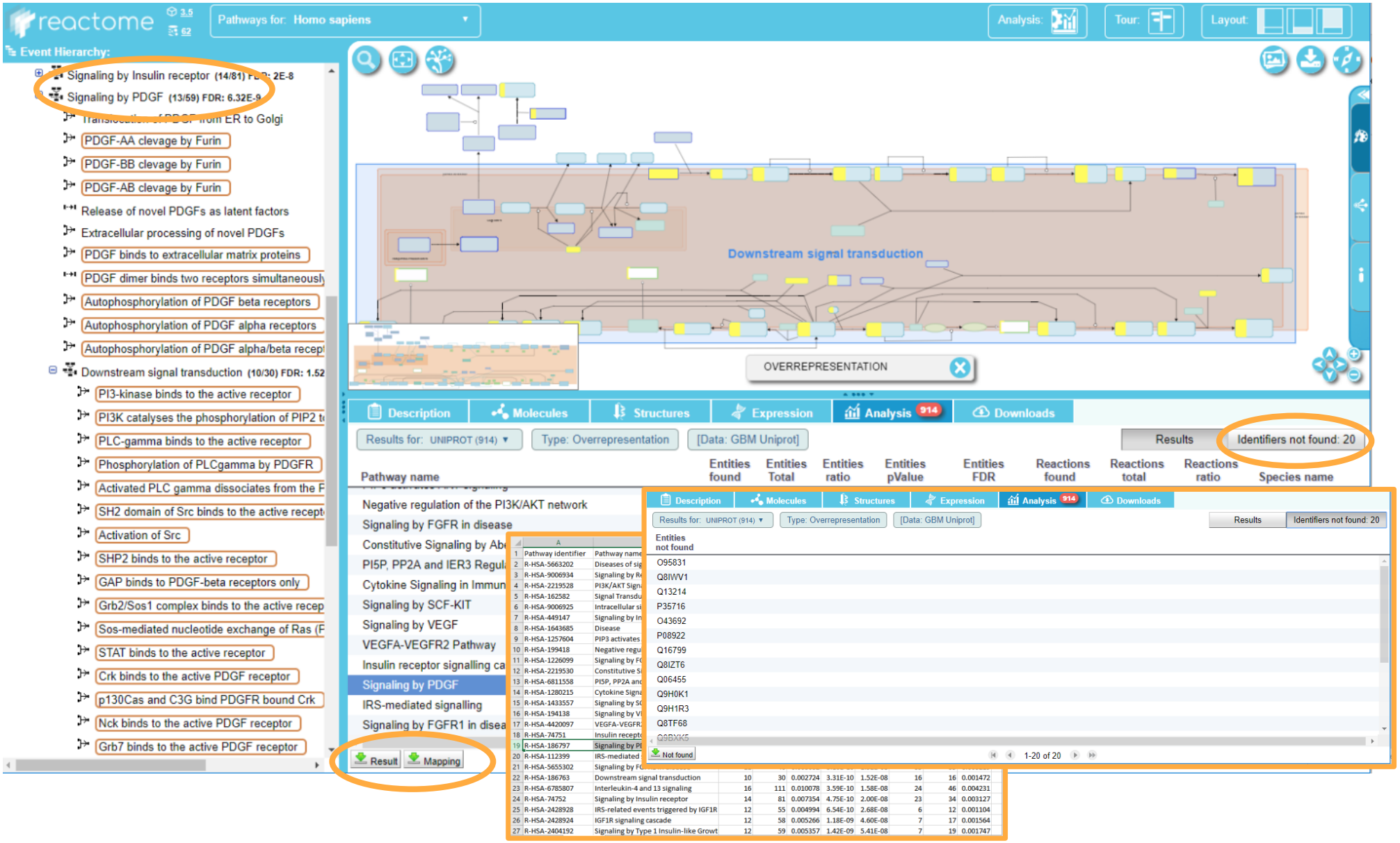
Expression
Analysis
Downloads
Displays details when you select an item in the Pathway Browser. For example, when a reaction is selected, shows details including the input and output molecules, summary and references containing supporting evidence. When relevant, shows details of the catalyst, regulators, preceding and following events.

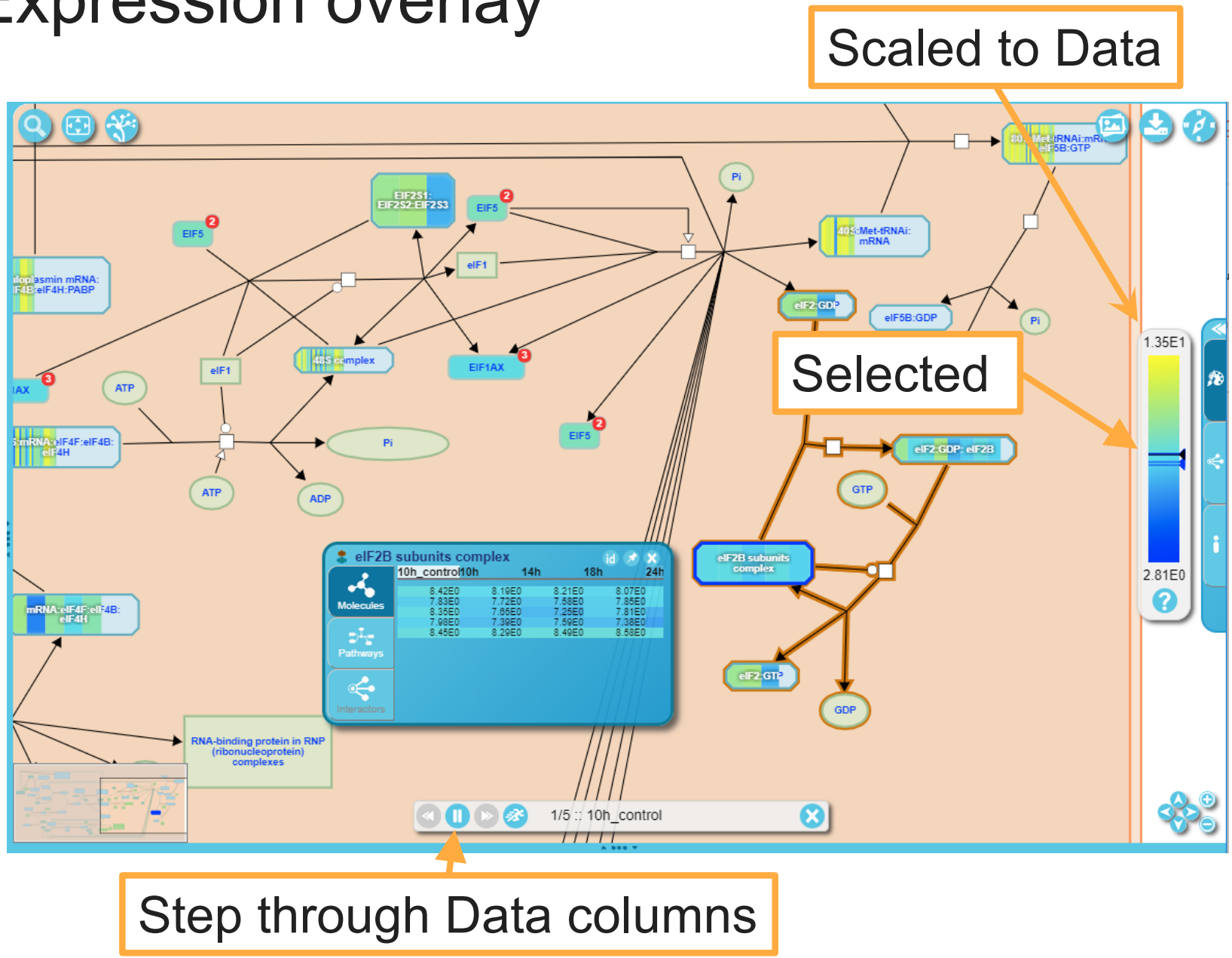
Analysis Result – Over-representation



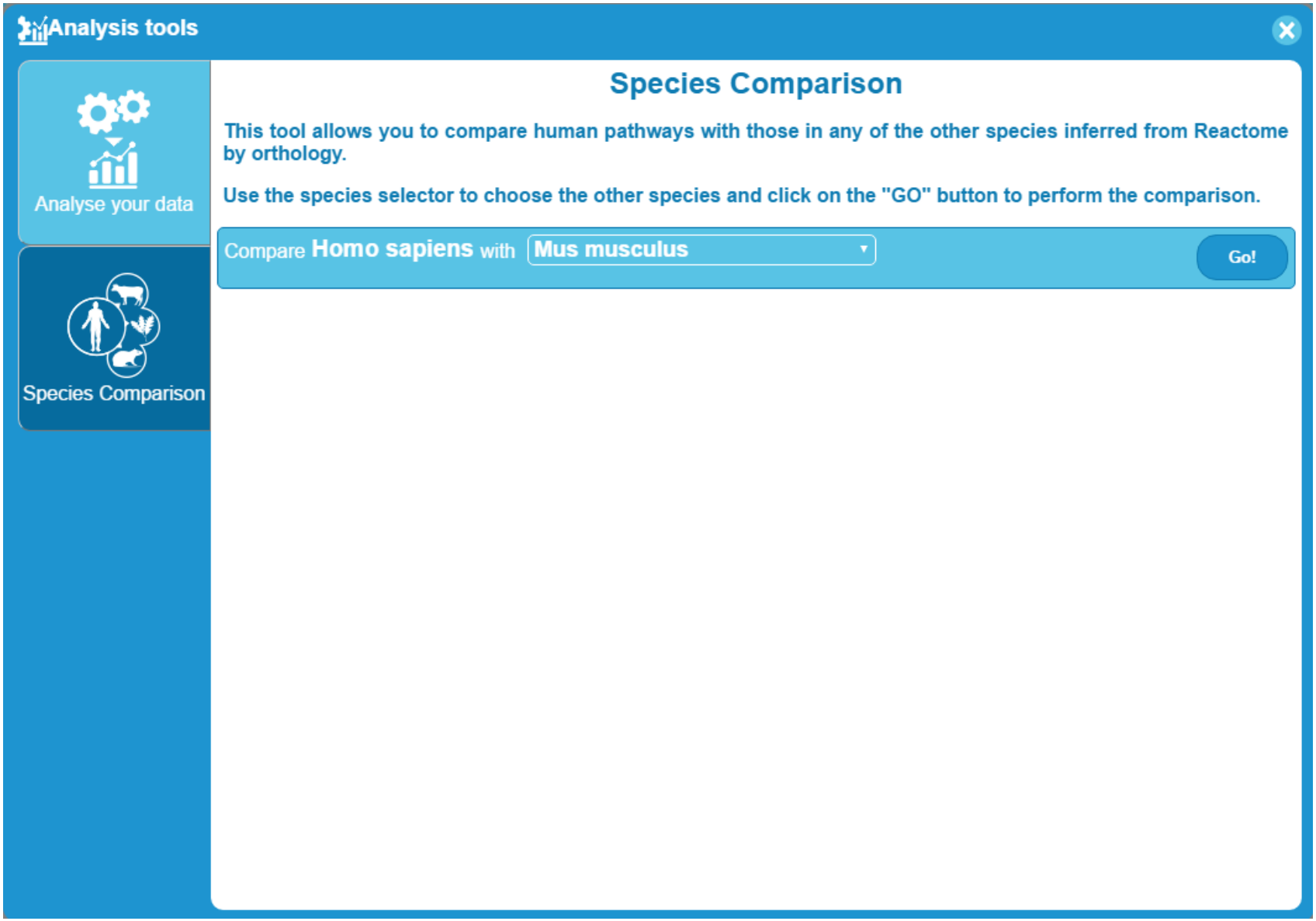
Analysis - Pathway topology matching



Expression overlay

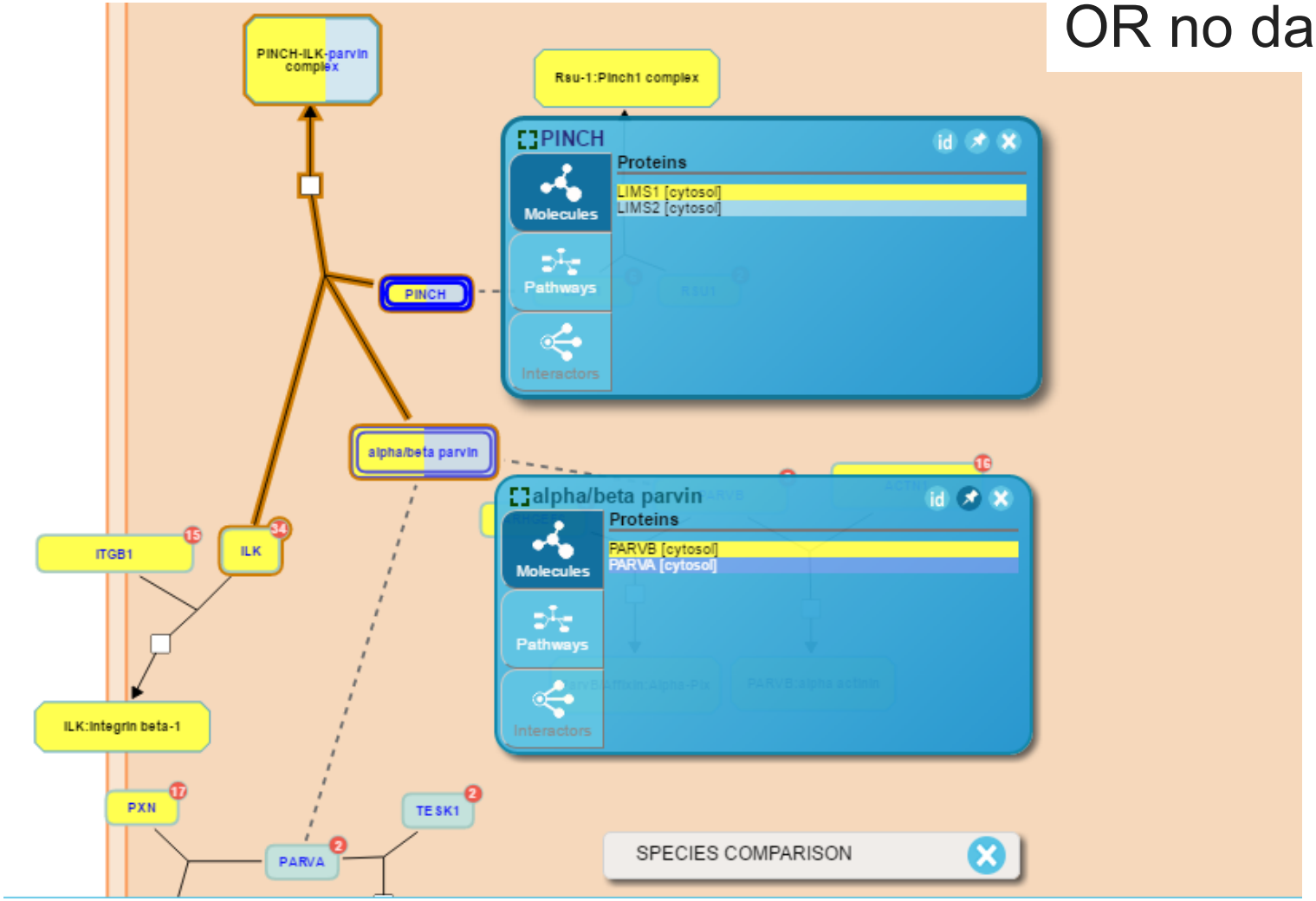


Species Comparison I

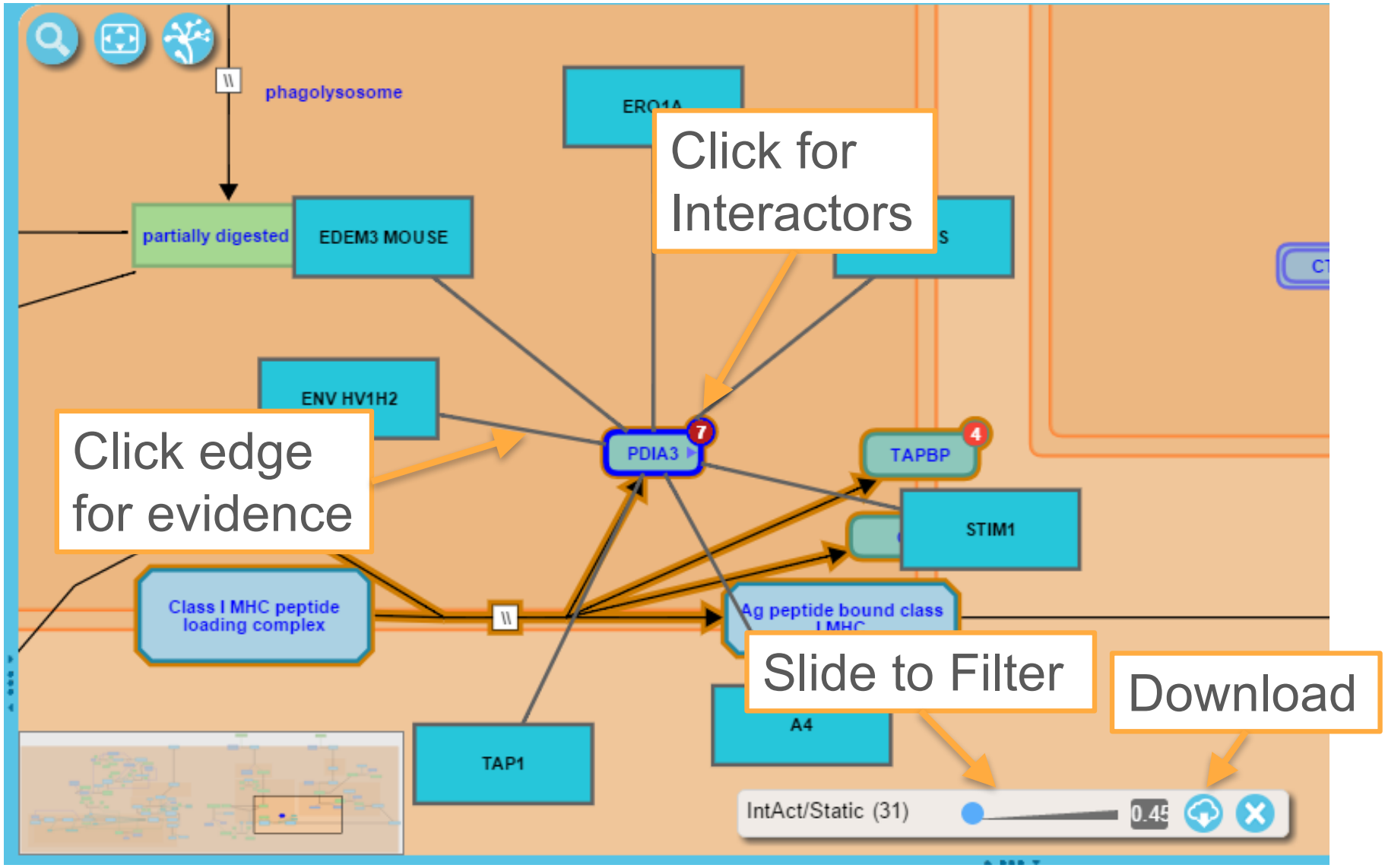


Species Comparison II

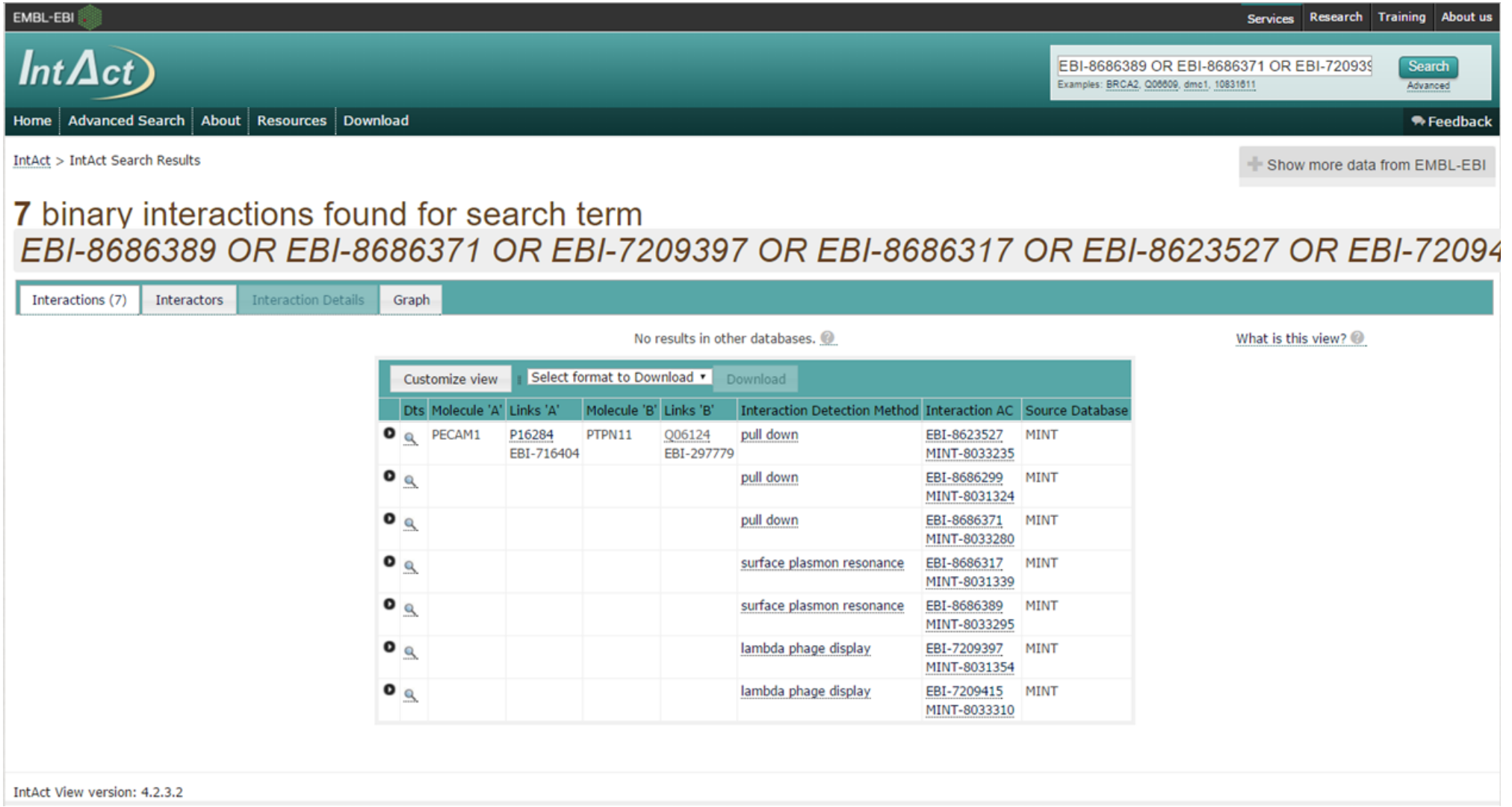
Yellow = orthologue
No colour = not found
OR no data



Interactors

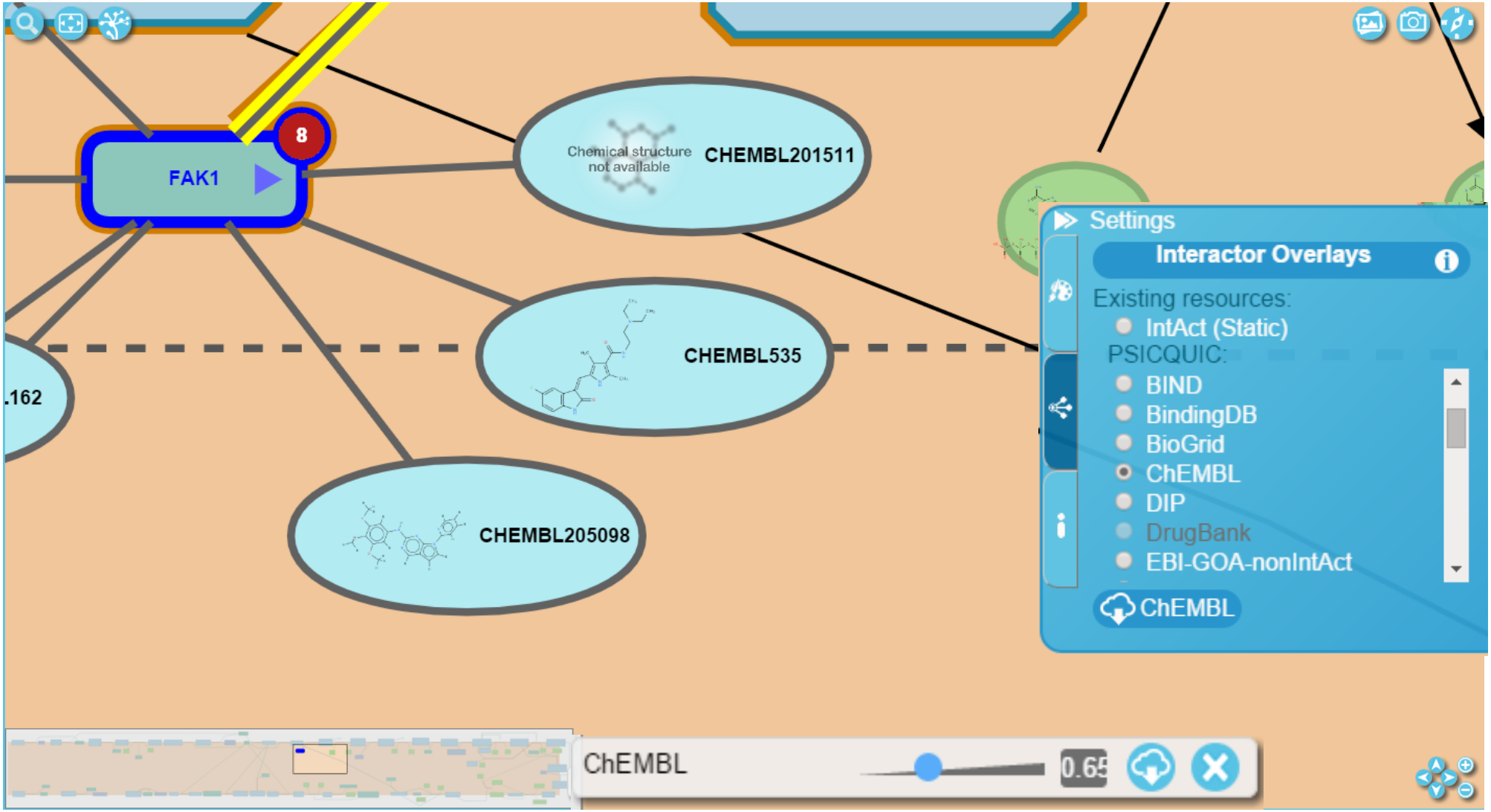


Molecular Interaction Overlay - Data

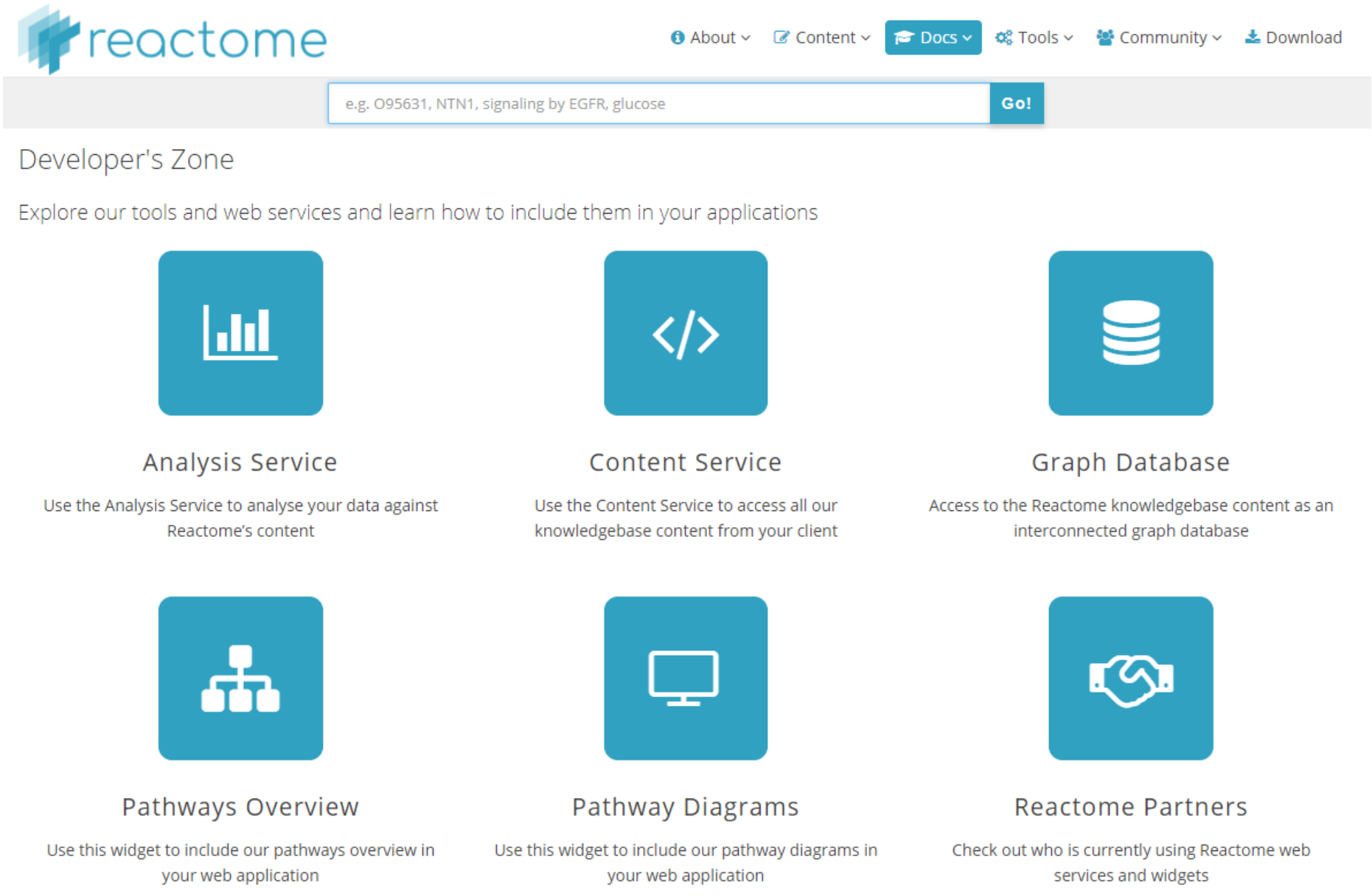


Dts	Molecule 'A'	Links 'A'	Molecule 'B'	Links 'B'	Interaction Detection Method	Interaction AC	Source Database
	PECAM1	P16284 EBI-716404	PTPN11	Q06124 EBI-297779	pull down	EBI-8623527 MINT-8033235	MINT
					pull down	EBI-8686299 MINT-8031324	MINT
					pull down	EBI-8686371 MINT-8033280	MINT
					surface plasmon resonance	EBI-8686317 MINT-8031339	MINT
					surface plasmon resonance	EBI-8686389 MINT-8033295	MINT
					lambda phage display	EBI-7209397 MINT-8031354	MINT
					lambda phage display	EBI-7209415 MINT-8033310	MINT

Molecular Interaction Overlay – Set source



Developer’s Zone



Extracting participating molecules using the Graph Database and Cypher

Breaking down complexes and sets to get their participants

The components of a complex, which are also physical entities, are stored in the "hasComponent" slot. Let's use the complex "**Ag-substrate:E3:E2:Ub**" with identifier **R-HSA-983126** as example in this case:

```
//First level components for the complex with stable identifier R-HSA-983126
MATCH (Complex{stId:"R-HSA-983126"})-[:hasComponent]->(pe:PhysicalEntity)
RETURN pe.stId AS component_stId, pe.displayName AS component
```

The result of the query is

component_stId	component
R-NUL-983035	antigenic substrate [cytosol]
R-HSA-976075	E3 ligases in proteasomal degradation [cytosol]
R-HSA-976165	Ubiquitin:E2 conjugating enzymes [cytosol]

Partners


BLUEPRINT
The BLUEPRINT consortium has been formed with the aim to further the understanding of how genes are activated or repressed in both healthy and diseased human cells.
Analysis Service
Widgets
Graph Database
BLUEPRINT
THE HUMAN PROTEIN ATLAS
Contains information for a large majority of all human protein-coding genes regarding the expression and localization of the corresponding proteins based on both RNA and protein data.
Analysis Service
Widgets
Graph Database
The Human Protein Atlas
PRIDE
compliant, public data repository for proteomics data, including protein and peptide identifications, post-translational modifications and supporting spectral evidence.
Analysis Service
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Graph Database
PRIDE
Integrative LINCS is an integrative web platform for analysis of LINCS data and signatures.The BD2K-LINCS Data Coordination and Integration Center is part of the Big Data to Knowledge
Analysis Service
Widgets
Graph Database
iLINCS
COPaKB
The COPa Knowledgebase (COPaKB) has been created as a unique resource to facilitate the discovery of novel biological insights from proteomic datasets. COPaKB was developed under the
Analysis Service
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Graph Database
COPaKB
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
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Open Targets
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
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ChEBI
The Scripps Research Institute
PINT, the Proteomics INTegrator, is an online experiment repository for final results coming from different qualitative and/or quantitative proteomics assays. PINT is a new
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PINT
Integrated Proteomics Applications provides a comprehensive proteomic data analysis solution, the Integrated Proteomics Pipeline (IP2), which allows researchers to identify,
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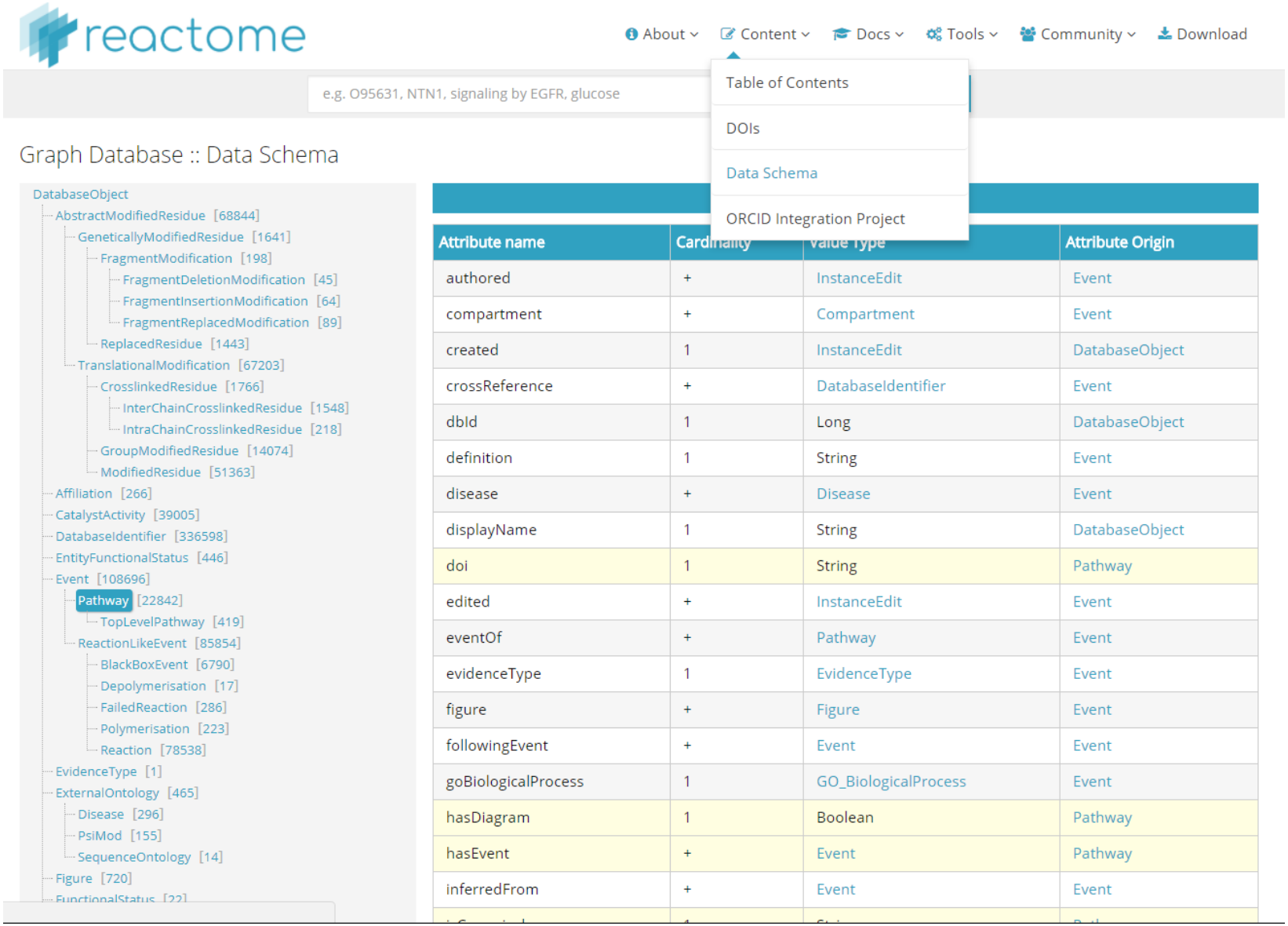
Graph Database
Tabloid Proteome is a database of protein association network generated using publicly available mass spectrometry based experiments in PRIDE. These associations represent
Analysis Service
Widgets
Graph Database

Schema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dbId 1 Long DatabaseObject
definition 1 String Event
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displayName 1 String DatabaseObject
doi 1 String Pathway
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hasDiagram 1 Boolean Pathway
hasEvent + Event Pathway
inferredFrom + Event Event

More Information

- From the Reactome Homepage
  - Reactome User Guide

  - help@reactome.org
  - Tour

- Train Online - https://www.ebi.ac.uk/training/online/

Acknowledgements

- **OICR**
  - Lincoln Stein
  - Justin Cook
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  - Veronica Shamovsky
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  - US NIH BD2K 1U54GM114833-01
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