

The background of the slide features a complex, abstract network diagram. It consists of numerous small, semi-transparent blue dots representing nodes, connected by thin, curved blue lines representing edges. These lines form a dense web of paths that radiate from several central, larger dark blue dots. The overall effect is one of a complex biological or chemical pathway system.

# Reactome

A database of human biological pathways

Contact: [help@reactome.org](mailto:help@reactome.org)



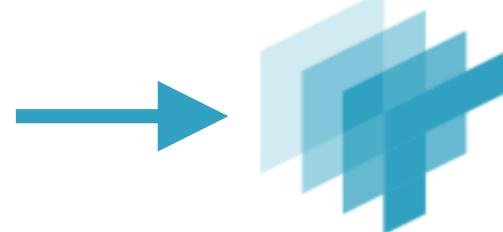
reactome

# Rationale – Journal information

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

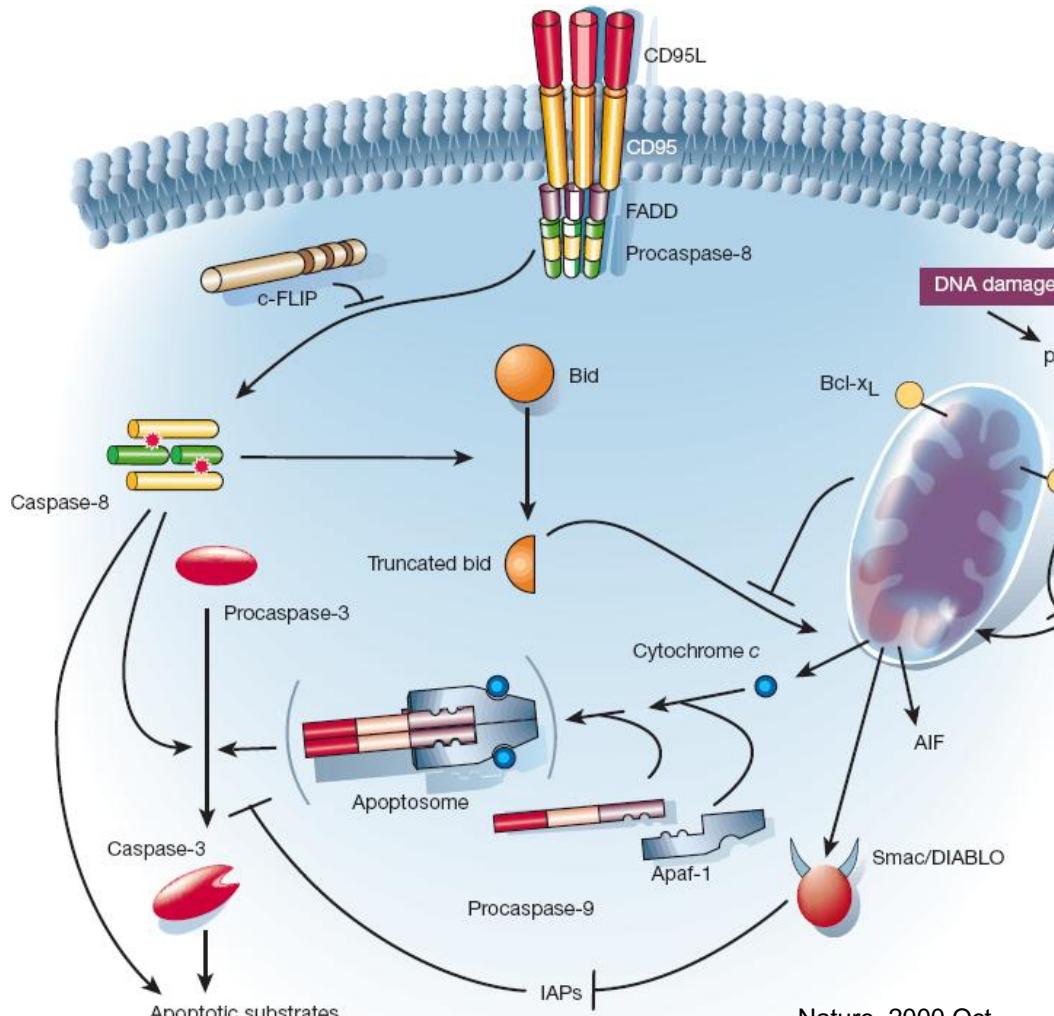
“Caspase-8 is the key initiator caspase in the death-receptor pathway. Upon ligand binding, death receptors such as CD95 (Apo-1/Fas) aggregate and form membrane-bound signalling complexes (Box 3). These complexes then recruit, through adapter proteins, several molecules of procaspase-8, resulting in 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

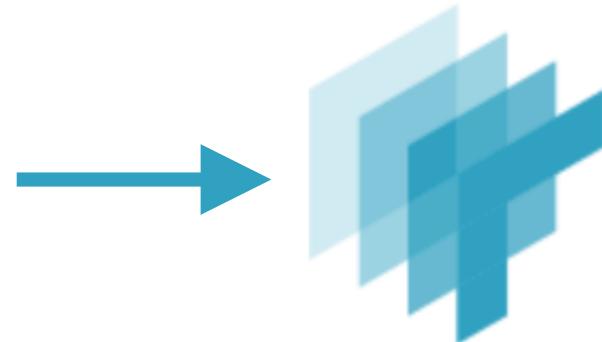
A picture paints a thousand words...



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

but....

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

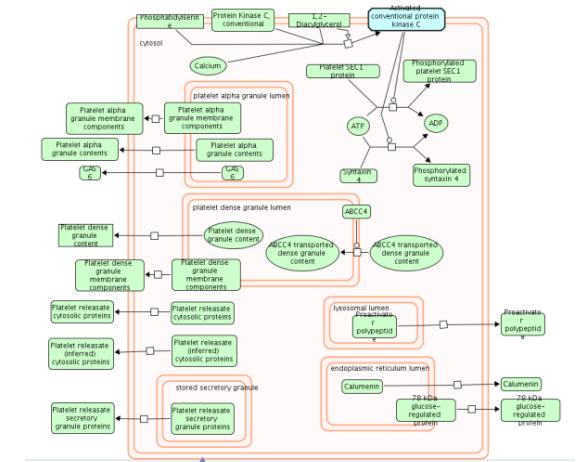
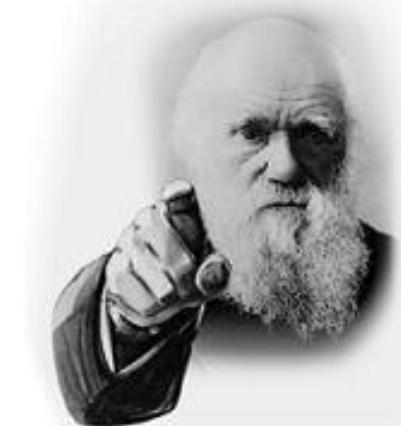


# Reactome is...

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

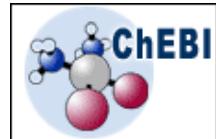
Authored by expert biologists,  
maintained by Reactome editorial  
staff (curators)

Mapped to cellular compartment



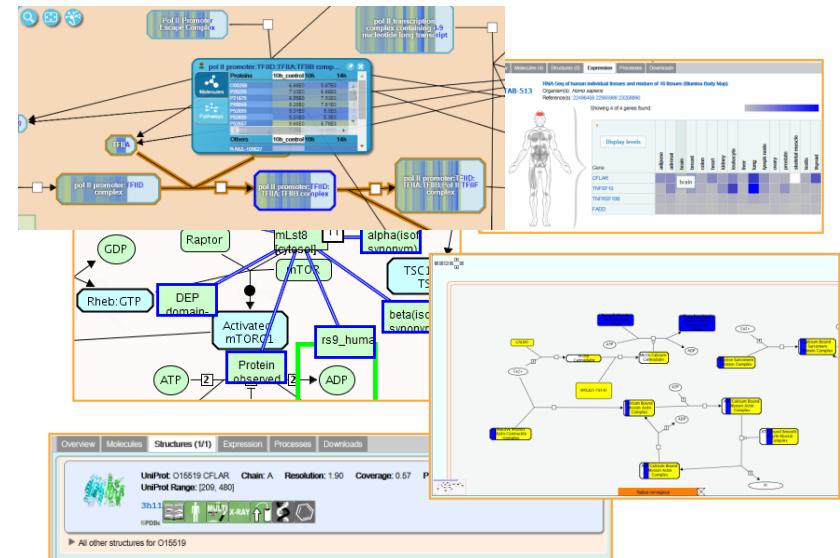
# Reactome is...

Extensively cross-referenced



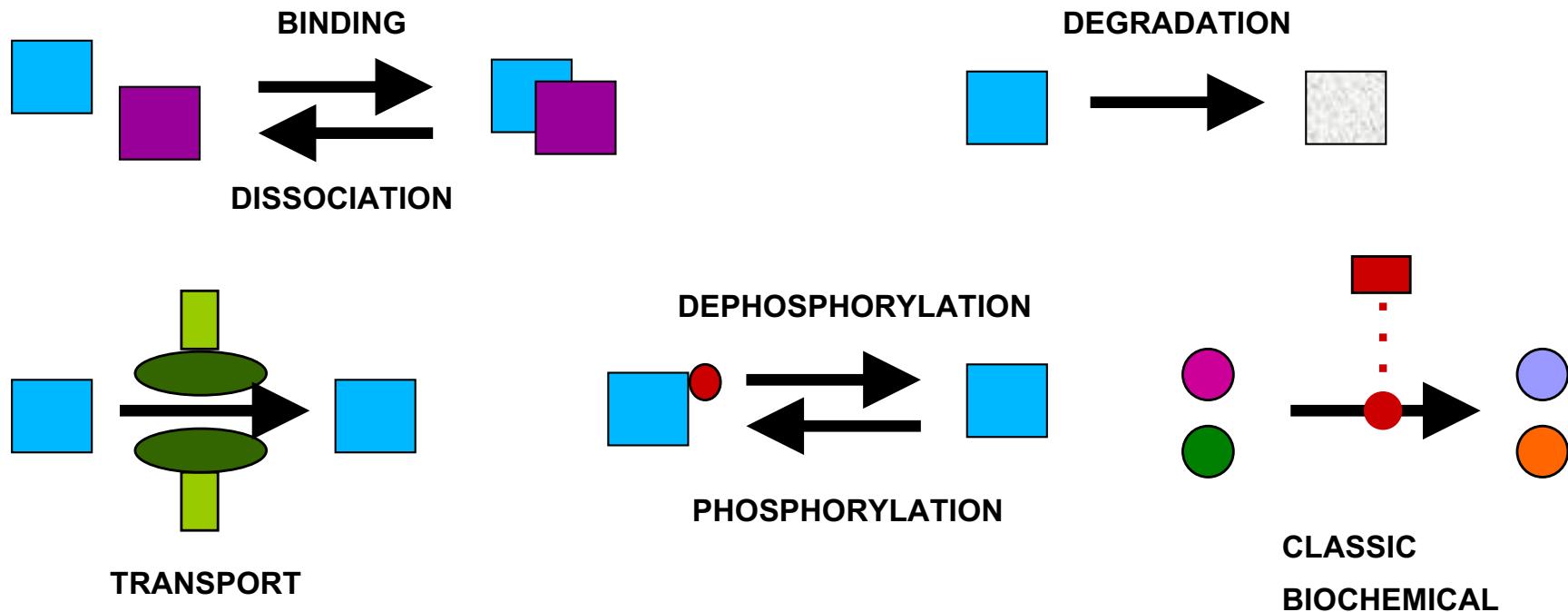
Tools for data analysis –  
Pathway Analysis,  
Expression Overlay, Species  
Comparison

Used to infer orthologous  
events in 17 other species

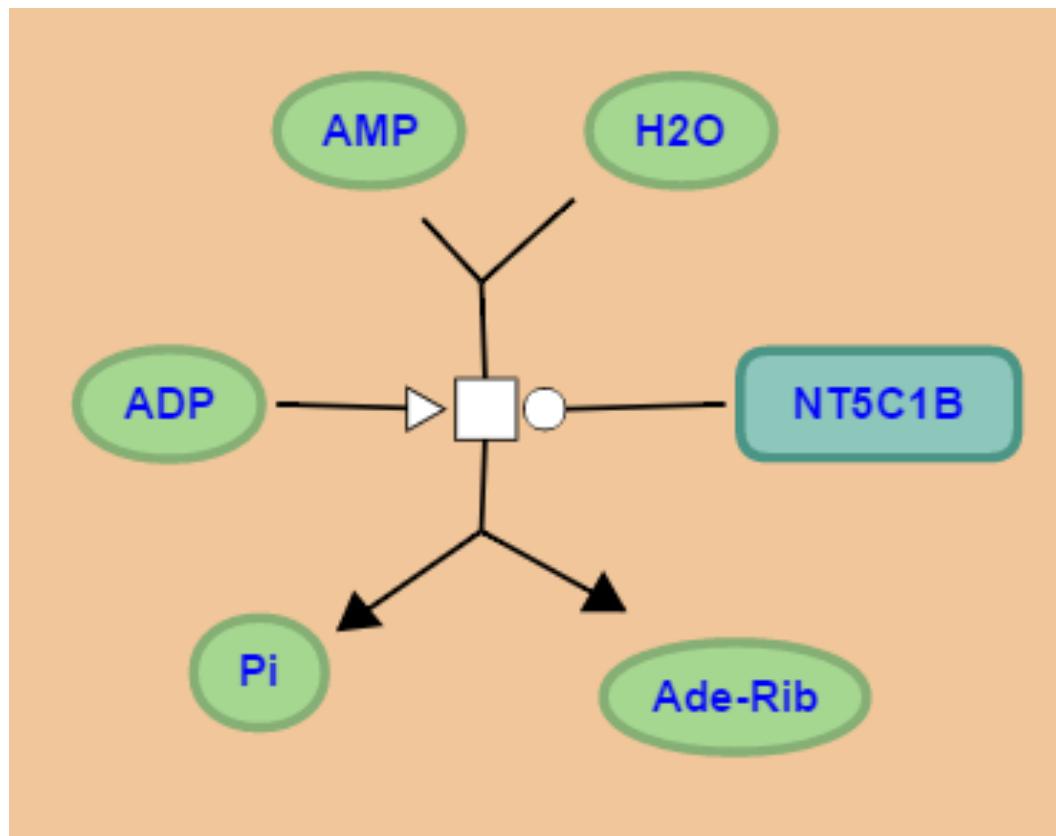


# Theory - Reactions

Pathway steps = the “units” of Reactome  
= events in biology

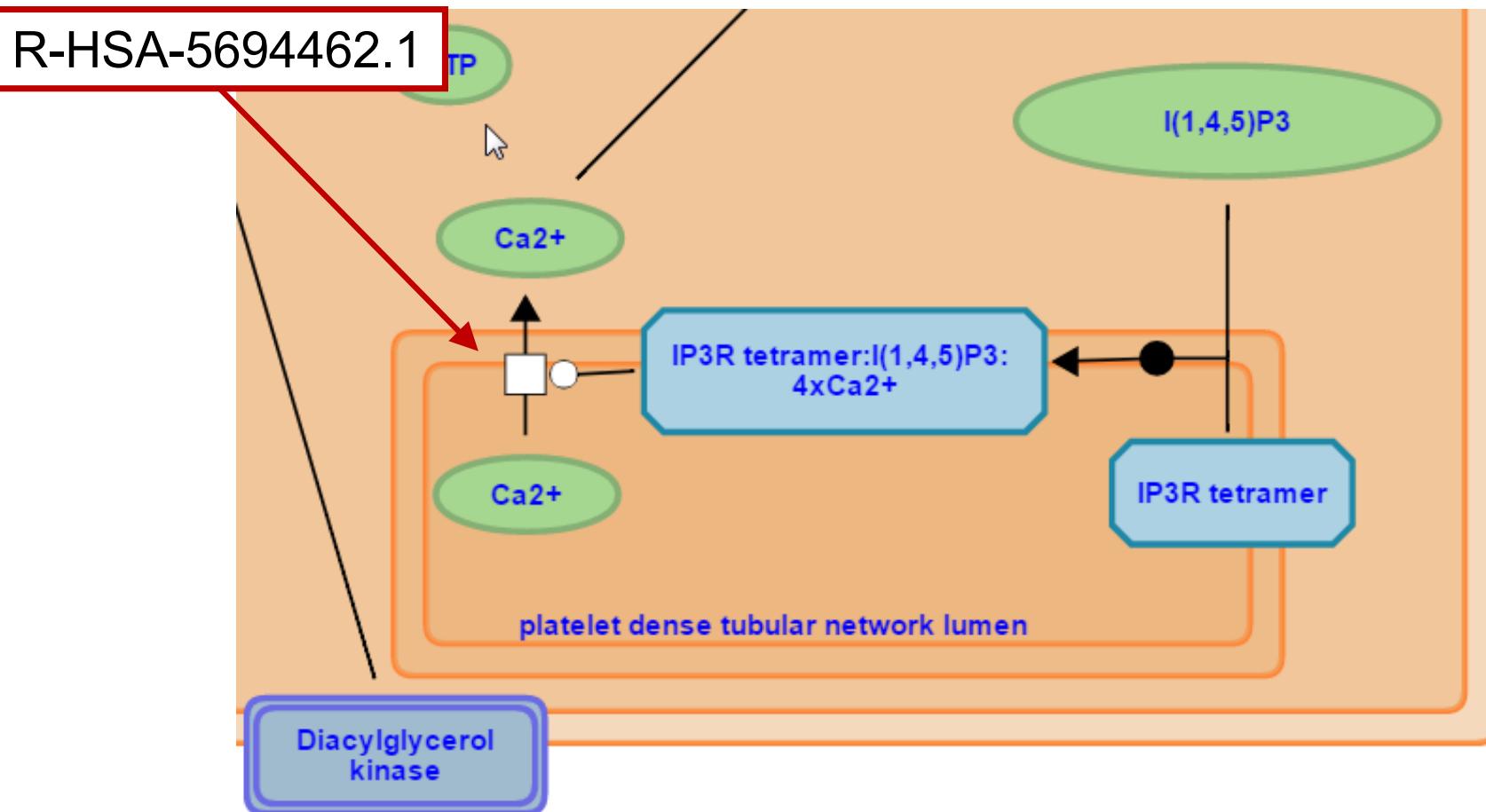


# Reaction example 1: Enzymatic



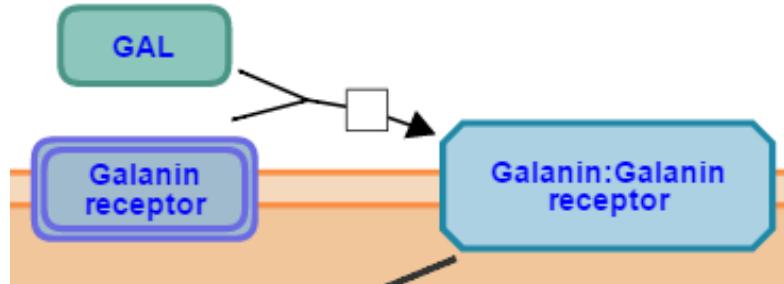
# Reaction example 2: Transport

Transport of Ca<sup>++</sup> from platelet dense tubular system to cytoplasm

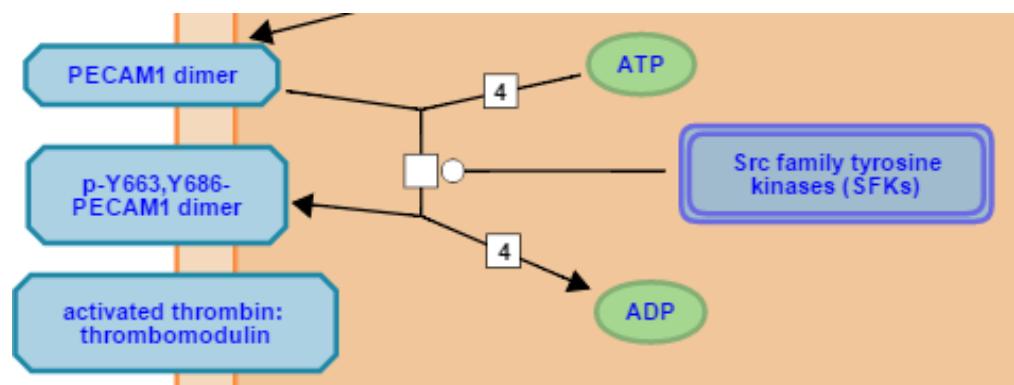
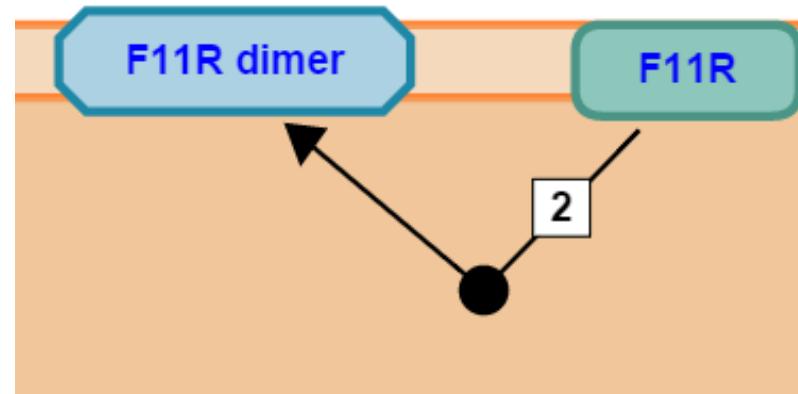


# Other reaction examples

## Binding

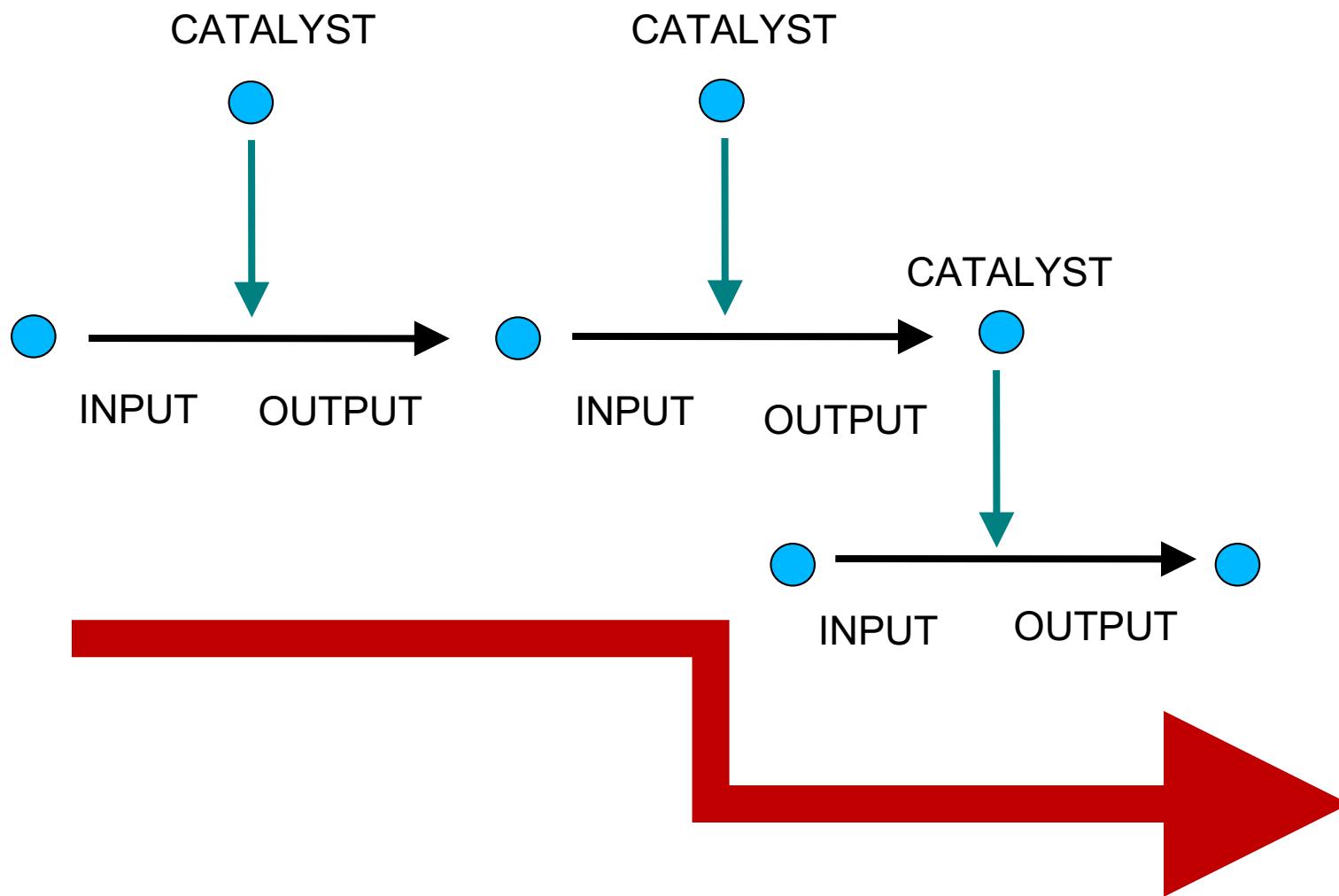


## Dimerization



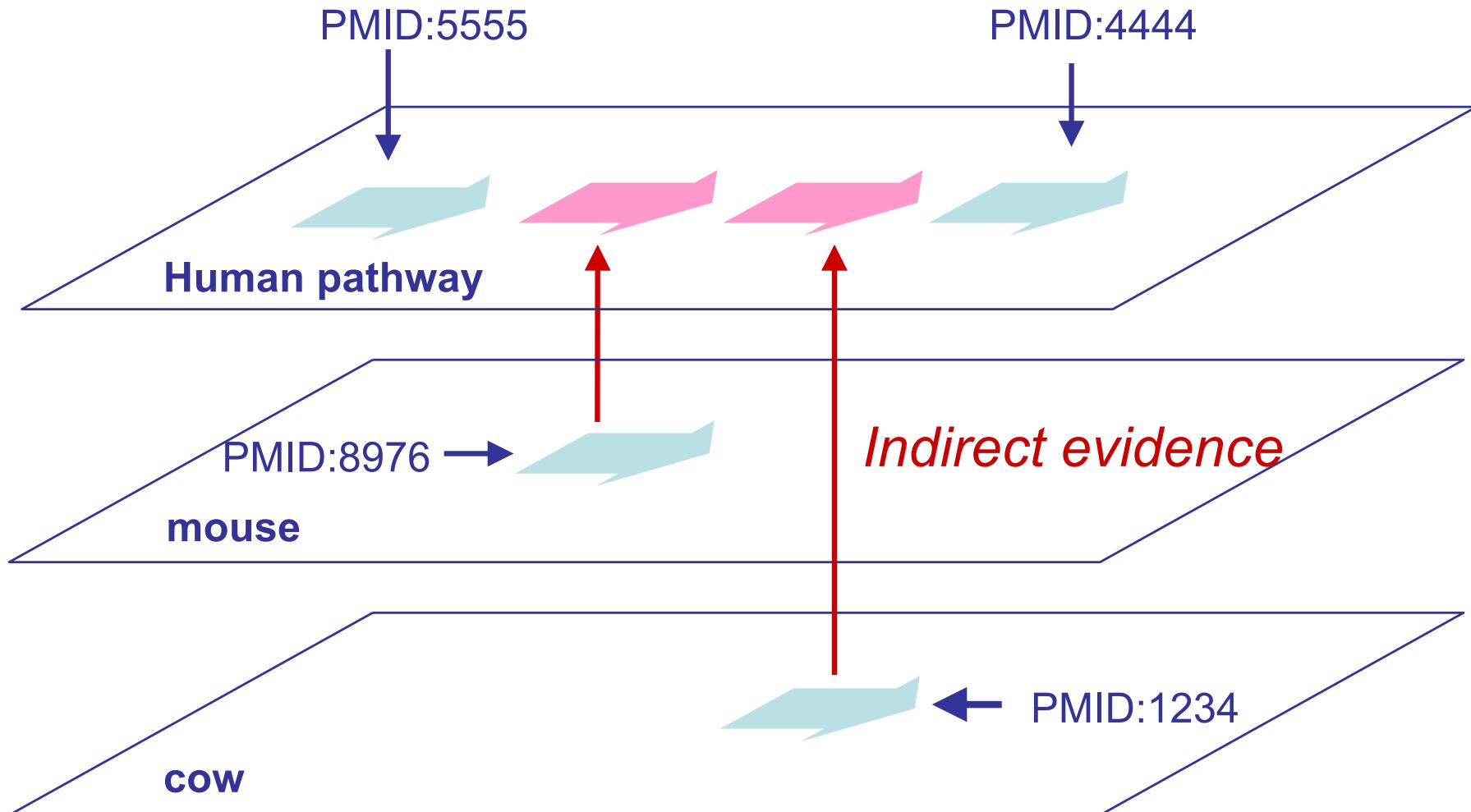
## Phosphorylation

# Reactions connect into Pathways



# Evidence – Inferred Reactions

*Direct evidence*

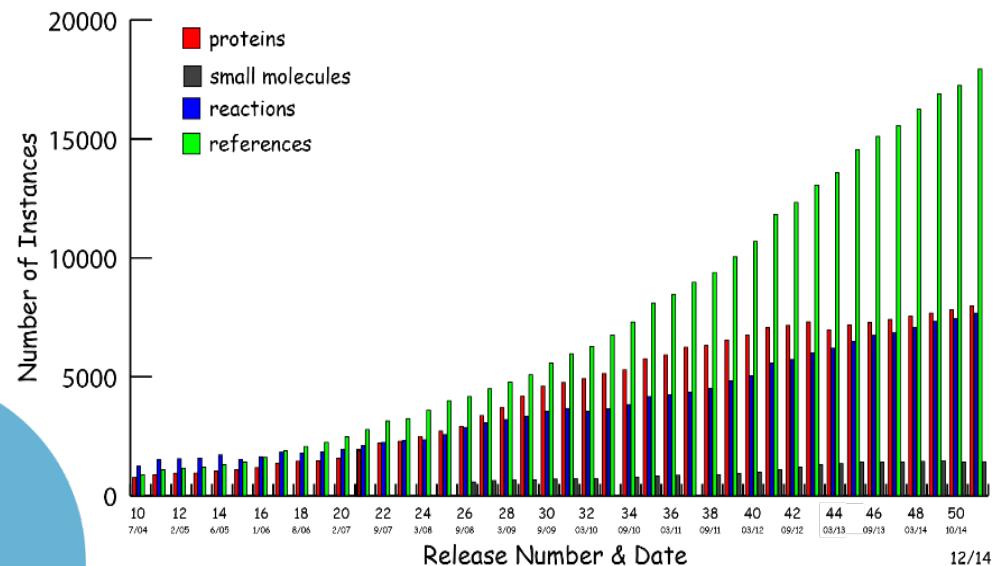
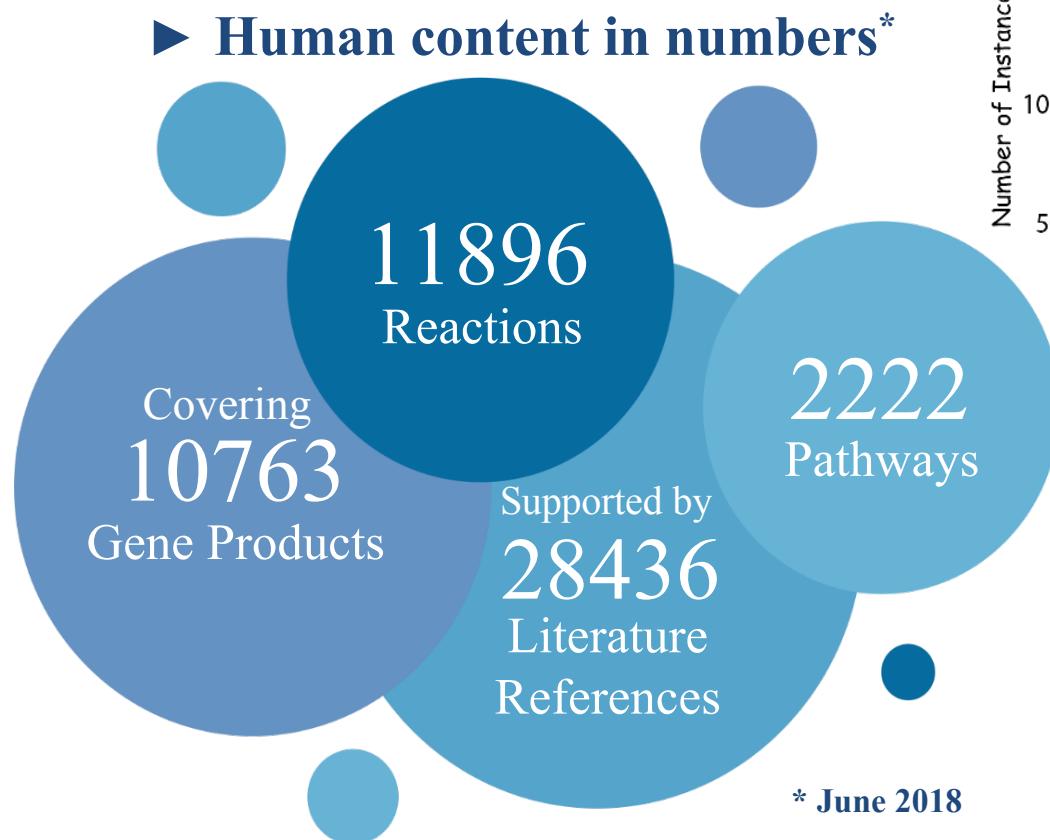


# Primary external sources

- 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



Experts  
(recruited)



Curators  
(staff)

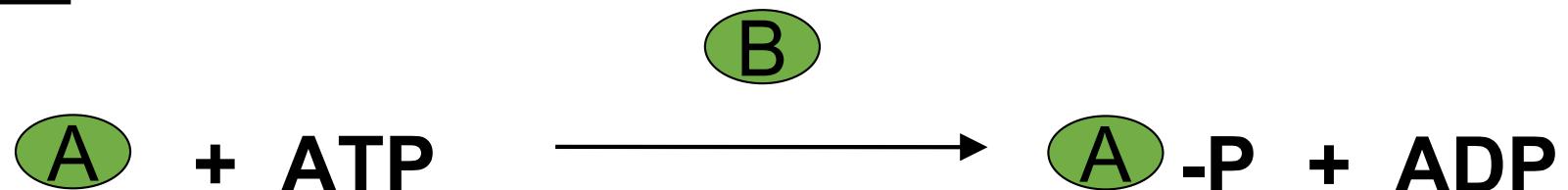


Reviewers  
(recruited)

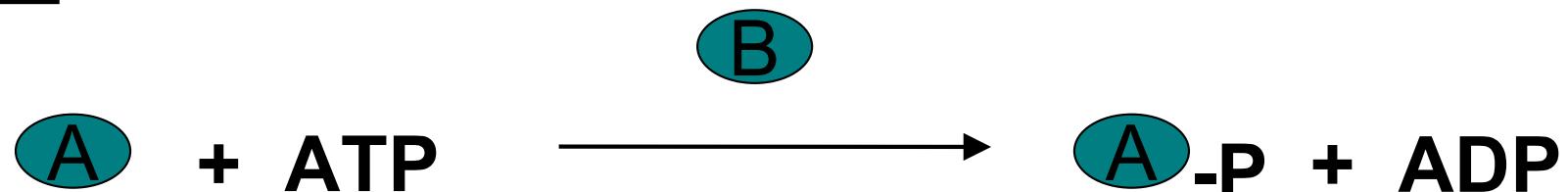
- Pathways authored and reviewed by expert biologists
- Curator works with Author to represent knowledge in Reactome data structure
- All new pathways are internally reviewed within Reactome
- New pathways sent for Review by another expert
- New data release every 3 months
- Regular Pathway updates.
- ORCID<sup>ind</sup> doi<sup>®</sup> 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

The screenshot shows the REACTOME 3.0 web application. In the top right corner, there is a dropdown menu labeled "Pathways for:" which is currently set to "Homo sapiens". Below this dropdown, a list of species is displayed in a blue-tinted box. The species listed are: Homo sapiens, Arabidopsis thaliana, Bos taurus, Caenorhabditis elegans, Canis familiaris, Danio rerio, Dictyostelium discoideum, Drosophila melanogaster, Gallus gallus, Mus musculus, Mycobacterium tuberculosis, Oryza sativa, Plasmodium falciparum, Rattus norvegicus, Saccharomyces cerevisiae, Schizosaccharomyces pombe, Sus scrofa, Taeniopygia guttata, and Xenopus tropicalis. A cursor arrow points to the word "Saccharomyces cerevisiae". The background of the page features a light blue header bar with the REACTOME logo and version information, and a faint diagram of biological pathways on the right side.

REACTOME 3.0  
Pathways for: **Homo sapiens**

- Homo sapiens
- Arabidopsis thaliana
- Bos taurus
- Caenorhabditis elegans
- Canis familiaris
- Danio rerio
- Dictyostelium discoideum
- Drosophila melanogaster
- Gallus gallus
- Mus musculus
- Mycobacterium tuberculosis
- Oryza sativa
- Plasmodium falciparum
- Rattus norvegicus
- Saccharomyces cerevisiae**
- Schizosaccharomyces pombe
- Sus scrofa
- Taeniopygia guttata
- Xenopus tropicalis

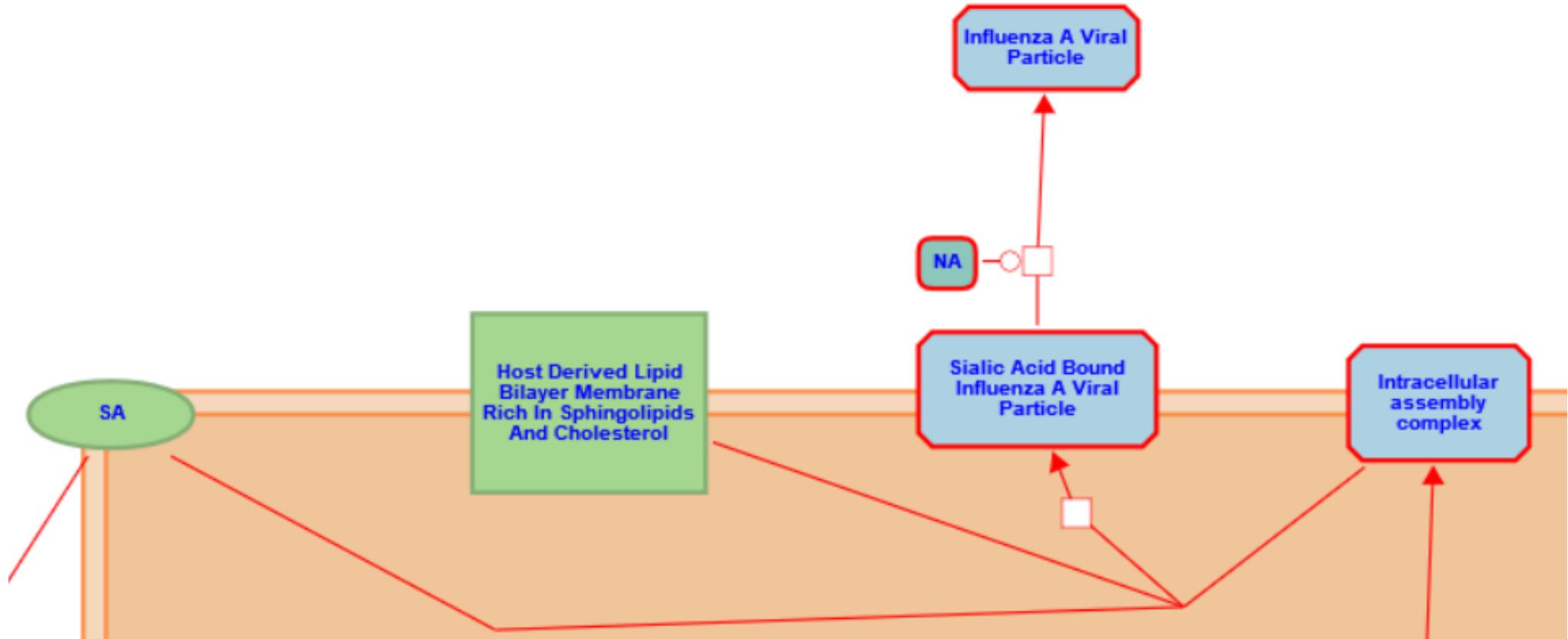
# Disease annotation in Reactome

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

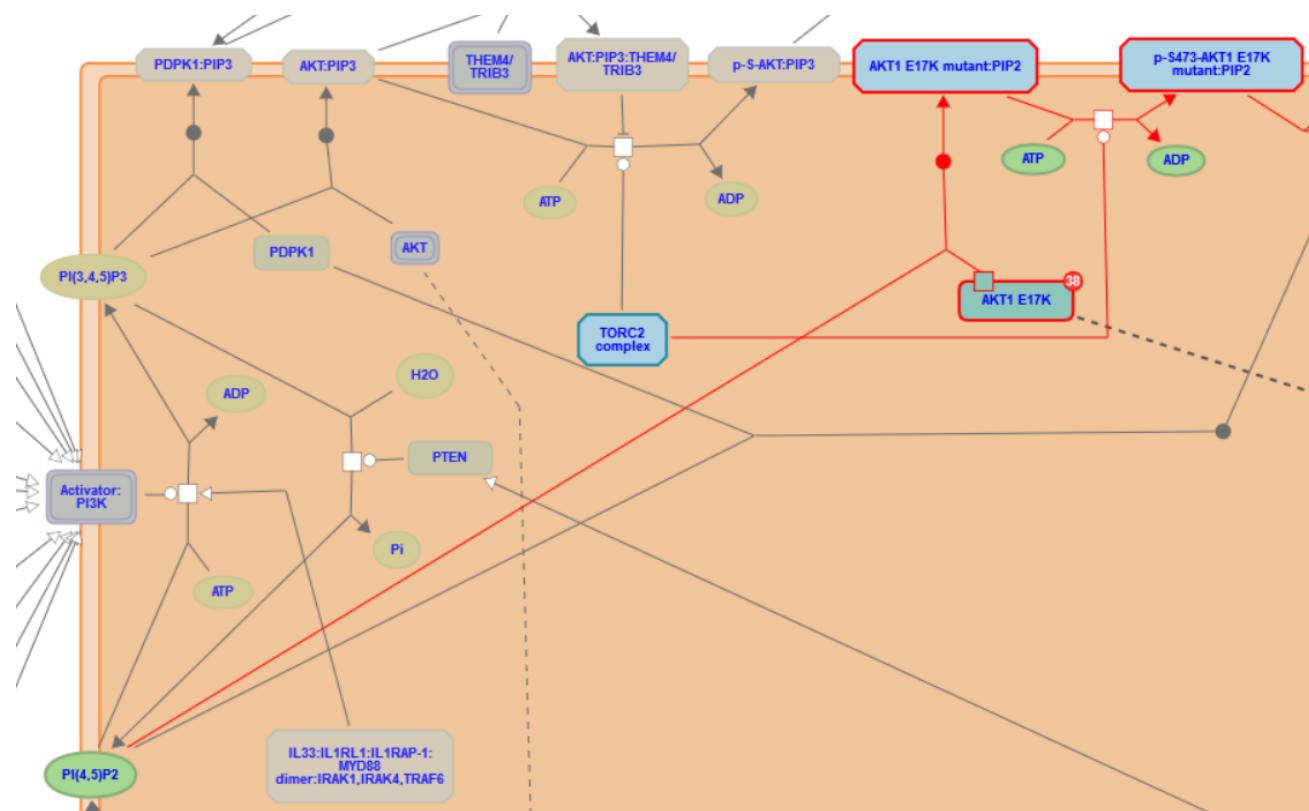
# Disease display in Reactome - Infection

Influenza virus life cycle: budding



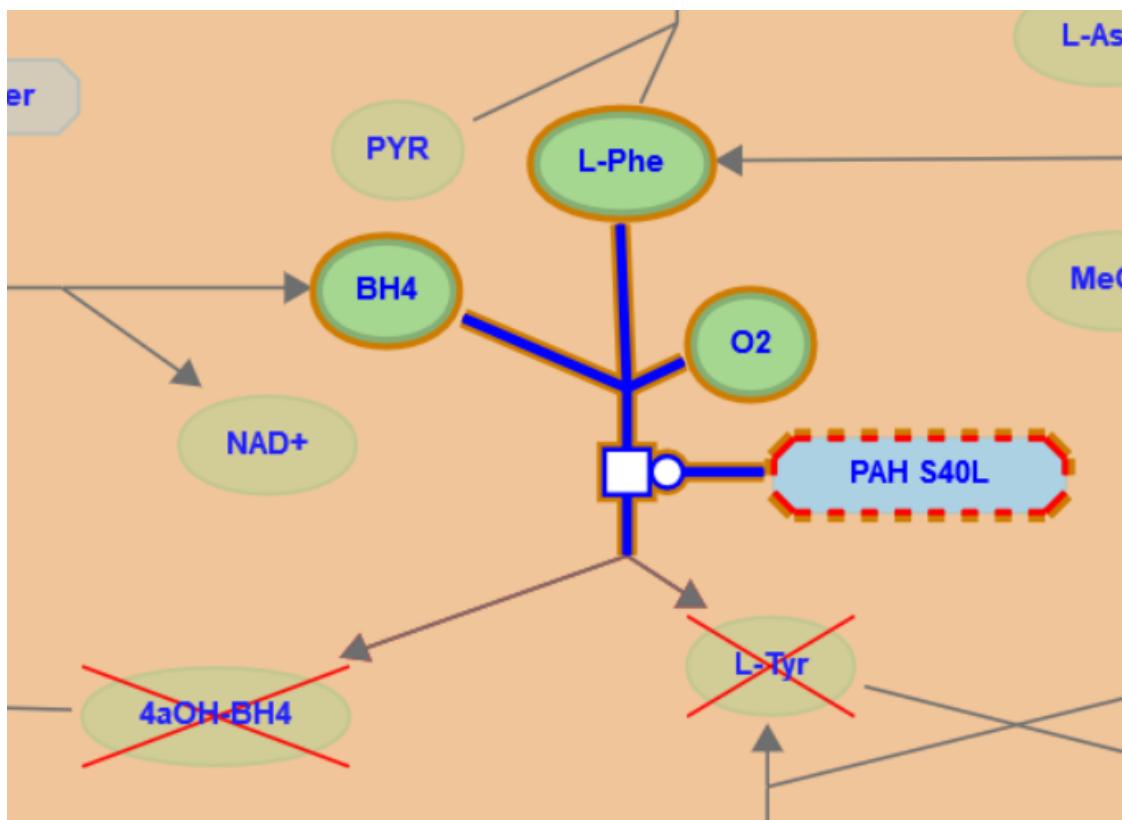
# Disease display in Reactome – Altered protein function in Cancer

## 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]<br>- Cell Cycle Checkpoints<br>- Cell Cycle, Mitotic<br>- Chromosome Maintenance<br>- 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, Nasl, S, Annibali, D, Joshi-Tope, G, Jupe, S, Watanabe, N, Hunter, T | 2011-12-06<br>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, Linden, C, Shah, K, Wang, Y, Colanzi, A, Malhotra, V, Longworth, MS, Mochida, S, Burgess, A, Gorjáñácz, 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]<br>- Cell junction organization (DOI)<br>- Signal regulatory protein family interactions (DOI)<br>- Neprin family interactions (DOI)  | Garapati, P, de Bono, B, Matthews, L, Jassal, B  | 2011-09-20<br>UPDATED |         | Barclay, AN, Huber, TB, Grahammer, Florian, Ebnet, K, Wu, C, Sonnenberg, A, Honig, B, Sanes, JR, D'Eustachio, P  | Garapati, P, Matthews, L, Jupe, S, Jassal, B, Wu, C  |
| Cellular responses to external stimuli [Homo sapiens]<br>- Response to metal ions (DOI)<br>- Macroautophagy (DOI)<br>- 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, Nasl, S, Annibali, D   | 2017-03-27<br>NEW     |         | Atrian, S, D'Eustachio, P, Klonsky, DJ, Tooze, SA, Ford, D, Wang, Q, Kavdia, M, Pani, B, Samarajiwa, S, Rothfels, K, Echeverri, 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, Maitepe, 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]<br>- 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, Faines, PQ   | May, B, Jupe, S, Jassal, B, Orlic-Milacic, M, Duenas, C, Shamovsky, V  |
| Circadian Clock [Homo sapiens] (DOI)<br>- BMAL1::CLOCK::NPAS2 activates circadian gene expression<br>- RORA activates gene expression<br>- 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]<br>- Axon guidance (DOI)<br>- Myogenesis (DOI)<br>- Regulation of beta-cell development (DOI)<br>- Signaling by NODAL (DOI)<br>- Transcriptional regulation of white adipocyte differentiation<br>- Transcriptional regulation of pluripotent stem cells (DOI)<br>- Activation of HOX genes [Homo | Garapati, P, Ferrer, J, Tello-Ruiz, MK, May, B, Jupe, S, Orlic-Milacic, M, Jassal, B, Heldin, CH, Moustakas, A, Huminiecki, L, Rezzohazy, R, Nasi, S, Annibali, D, Charalambous, M, Akkerman, JW   | 2011-09-20<br>UPDATED |         | Maness, PF, Krauss, RS, Walmod, PS, Jensen, J, Peng, C, D'Eustachio, P, Sethi, JK, Wang, J, Blasi, F, Rezzohazy, 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, Chan, 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, SE       |

And many more...

|  |  |                       |   |  |
|--|--|-----------------------|---|--|
| Digestion and absorption [Homo sapiens]<br>- Digestion<br>- Intestinal absorption  | Jassal, B, D'Eustachio, P, Shamovsky, V  | 2017-03-27<br>NEW     | D'Eustachio, P, Jassal, B, Nichols, BL, Wright, EM, Nam, HY, Amiri, M   | D'Eustachio, P, Jassal, B  |
|  |  |                       | Moltra, K, Spillmann, D, D'Eustachio, P, Anira, S, Drews, J, Kauer, S, Everett, S   |  |
| Disease [Homo sapiens]<br>- Diseases of signal transduction<br>- Disorders of membrane transport<br>- Diseases of metabolism<br>- Diseases of nucleic acids<br>- Infectious disease<br>- Diseases of immune system<br>- Neoplasms, benign (DOI)<br>- Diseases of mismatch repair (DOI)   | Kornblith, M, D'Eustachio, P, Shamovsky, V, Shamovsky, V   | 2012-12-04            | Paula, M, Zhao, X, Willis, L, Cacatava, P, Karppinen, F, Harries, J, Hwang, J, Lai, L, Freedman, LP, Hernandez, N, Toman, V, Li, LC, Strynowska-Czerwinski, A, Sato, K, Di Croce, L, Pfleiderer, GP, Mukherji, M  | D'Eustachio, P, Jupe, S, Garapati, P, D'Eustachio, P   |
| Gene expression (Transcription factor)<br>- RNA Polymerase I Transcription<br>- RNA Polymerase II Transcription<br>- RNA Polymerase III Transcription<br>- Transcription from promoter<br>- Gene expression by RNA<br>- Epigenetic regulation of gene expression   | D'Eustachio, P, Shamovsky, V, Shamovsky, V   | 2012-12-04            | Shamovsky, V, Shamovsky, V  | Shamovsky, V, Shamovsky, V   |
| DNA Repair [Homo sapiens]<br>- Base Excision Repair (DOI)<br>- Double-Strand Break Repair (DOI)<br>- DNA Damage Repair (DOI)<br>- DNA Double-Strand Break Repair (DOI)<br>- Mismatch Repair (DOI)<br>- Non-cancer Anticancer Pathway (DOI)   |  | 2011-09-20<br>UPDATED | Wunderlich, T, Rush, MG, Enikolopov, G, Graves, J, Sessa, S, D'Eustachio, P, Rouault, TA, Tong, WH, Jassal, B, Silverman, DN, Urings, EJ, Kerstan, S, Gillespie, ME, Gopinathrao, G, Hannun, YA, Luberto, C, Ferguson, SJ, Ito, S, D'Eustachio, M, Birnbaum, J, Kornblith, M, Zaccara, S, Wakselman, MA, Stephan, R, Liang, G, Potouli, V, Kebde, M, Madaraju, MS, Akkerman, JV, Sevigny, J, Banerjee, MS, Kawamura, M, Neale, JH, Peterson, B, He, L, Letza, AM, Sethi, JK, Delaunay, F, Liu, Y, Chiu, C, Kuo, J, Kay, SA, Hirota, T, Levy, BD, Journe, JL, Calamita, G, Belotti, E, Catagnoli, L, Burmester, T, Metal, BH, Ito, R, Rosenblatt, DS, Drosatz, J, Restituito, S, Porteu, F, Greene, LA, Thorpe, L, Yuzugullu, H, Zhao, JJ, Leslie, K, Kriplani, N, Divecha, N, May, B, Nakaki, T | D'Eustachio, P, Schmidt, EE, Williams, MG, Joshi-Tope, G, Jassal, B, Gillespie, ME, May, B, Gopinathrao, G, Jupe, S, Orlic-Milacic, M, Vastrik, I, Mahajan, SS |
| Hemostasis [Homo sapiens]<br>- Platelet hemostasis<br>- Thrombin generation to exposed surfaces<br>- Thrombin activation, signaling & aggregation  | D'Eustachio, P, Shamovsky, V, Shamovsky, V   | 2011-09-20<br>UPDATED | O'Donnell, P, Schreiber, EE, Williams, MG, Jassal, B, Gillespie, ME, Gopinathrao, G, Henrich, J, Akkerman, JV, Sevigny, J, Banerjee, MS, Kawamura, M, Neale, JH, Peterson, B, He, L, Letza, AM, Sethi, JK, Delaunay, F, Liu, Y, Chiu, C, Kuo, J, Kay, SA, Hirota, T, Levy, BD, Journe, JL, Calamita, G, Belotti, E, Catagnoli, L, Burmester, T, Metal, BH, Ito, R, Rosenblatt, DS, Drosatz, J, Restituito, S, Porteu, F, Greene, LA, Thorpe, L, Yuzugullu, H, Zhao, JJ, Leslie, K, Kriplani, N, Divecha, N, May, B, Nakaki, T   | D'Eustachio, P, Schmidt, EE, Williams, MG, Joshi-Tope, G, Jassal, B, Gillespie, ME, May, B, Gopinathrao, G, Jupe, S, Orlic-Milacic, M, Vastrik, I, Mahajan, SS |
| Drosophila signaling pathways [Drosophila melanogaster]<br>- Conserved core pathway (DOI)<br>- Hedgehog pathway (DOI)<br>- Hippo/Warrior pathway (DOI)<br>- Insulin signaling pathway (DOI)<br>- Insulin receptor mediated signal (DOI)<br>- JAK/STAT pathway (DOI)<br>- JNK pathway (DOI)<br>- Toll pathway (DOI)<br>- Wingless pathway (DOI)   |  |                       |   |  |
| Extracellular matrix organization (sacculi)<br>- Collagen formation<br>- Extracellular matrix formation (DOI)<br>- Elastic fibre formation (DOI)<br>- Laminin interactions (DOI)<br>- Non-migratory membrane ECM   | D'Eustachio, P, D'Eustachio, P, Schmid, C  | 2011-12-06            | Harris, RA, D'Eustachio, P, D'Eustachio, P  | D'Eustachio, P, D'Eustachio, P   |
| Immune System [Homo sapiens]<br>- Adaptive immune system   |  |                       |   |  |
| Metabolism of proteins [Homo sapiens]<br>- Transport<br>- Protein folding (DOI)<br>- Post-translational protein modification (DOI)<br>- Mitochondrial protein import<br>- Peptides hormone metabolism<br>- Regulation of insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)<br>- Unfolded Protein Response (UPR)<br>- Protein repair (DOI)<br>- Surface metabolism<br>- Amyloid fiber formation (DOI) | Matthews, L, Merrick, WC, Bernards, A, Gallo, V, Jassal, B, Barlow, B, Gross, SR, Ortiz, PA, Ostrik, S, Pimman, YR, Ulloque, R, Hentze, MW, Kinzy, TG, D'Eustachio, P, May, B, Jupe, S, Jassal, B, Gopinathrao, G, Dall'Olio, GM, Romfeir, A, Gillespie, ME, Orlic-Milacic, M, Johansson, HE, Williams, MG, Garapati, P, Jupe, S, Yang, WC, Kavala, T, Akira, S, Rajakulendran, N, van Amerongen, R, Kusuki, A, Kufer, TA, Rittinger, K, Wong, E, Lin, WC, Deng, L, Pomerantz, JL, Yu, X, Zhu, B, Myung, K, Cimprich, KA, Lahiri, RJ, van den Boom, DJ, Lepreiro, D, Bae, J, Crisponi, L, Thibaut, P | 2009-04-01<br>UPDATED |   |  |

# Reactome Tools

- Interactive Pathway Browser
- Analysis
  - Over-representation
  - Pathway topology
  - Expression overlay
- Molecular Interaction overlay
- Species Comparison

# Front Page

<http://www.reactome.org>

The screenshot shows the Reactome website's homepage. At the top, there is a navigation bar with links for About, Content, Docs, Tools, Community, and Download. Below the navigation is a search bar with the placeholder "Find Reactions, Proteins and Pathways" and a "Go!" button. The main content area features four large blue icons representing different tools: "Pathway Browser" (with a 3D bar chart icon), "Analyze Data" (with a bar chart icon), "ReactomeFIViz" (with a network graph icon), and "Documentation" (with a document icon). Each tool has a brief description below it. A black banner at the bottom of the main content area says "USE REACTOME GRAPH DATABASE IN YOUR PROJECT" and includes a "LEARN MORE" button. The footer contains sections for "Why Reactome" (with text about the database being free, open-source, and peer-reviewed, and logos for EMBL-EBI, NYU Langone Health, and OICR), "Tweets" (with a tweet from the reactome account), and a large "reactome" logo.

reactome

About Content Docs Tools Community Download

Find Reactions, Proteins and Pathways

e.g. O95631, NTN1, signaling by EGFR, glucose

Go!

Pathway Browser

Analyze Data

ReactomeFIViz

Documentation

Visualize and interact with Reactome biological pathways

Merges pathway identifier mapping, over-representation, and expression analysis

Designed to find pathways and network patterns related to cancer and other types of diseases

Information to browse the database and use its principal tools for data analysis.

USE REACTOME GRAPH DATABASE IN YOUR PROJECT

LEARN MORE

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](http://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.

Tweets

reactome @reactome

Exciting times for us! Our brand new [reactome.org](#) website features a #clean and #userfriendly interface that adjusts to browsers on your desktop and all your devices #webdesign #uxdesign #ResponsiveDesign #newlogo

reactome

# The Pathway Browser

The screenshot shows the Reactome Pathway Browser interface. At the top, there are navigation links: Home, Species, Analyse Data, Video Tour, and Layout. On the left, the Hierarchy Panel displays a tree structure of biological pathways. The central area features the Pathway Panel, which contains a complex network diagram of pathways like Immune System, Signal Transduction, and Metabolism. Below the diagram is the Detail Panel, which provides a description of selected items. The bottom navigation bar includes buttons for Description, Molecules, Structures, Expression, Analysis, and Downloads. On the right side, there are additional controls: Key, Export, Settings Sidebar, and Zoom/Move. A large orange box labeled "Thumbnail" points to a small preview image at the bottom left of the main panel.

Home

Species

Analyse Data

Video 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
- Hemostasis
- Immune
- Metab
- Metabol
- Metabol
- Mitophagy
- Muscle contraction
- Neuronal System
- Organelle biogenesis and maintenance
- Programmed Cell Death
- Reproduction
- Signal Transduction
- Transport of small molecules
- Vesicle-mediated transport

Pathways for: Homo sapiens

Analysis: Tour: Layout:

Key

Export

Settings Sidebar

Zoom/Move

Open Diagram

Search Diagram

Fit to Page

Illustrations

Thumbnail

Description

Molecules

Structures

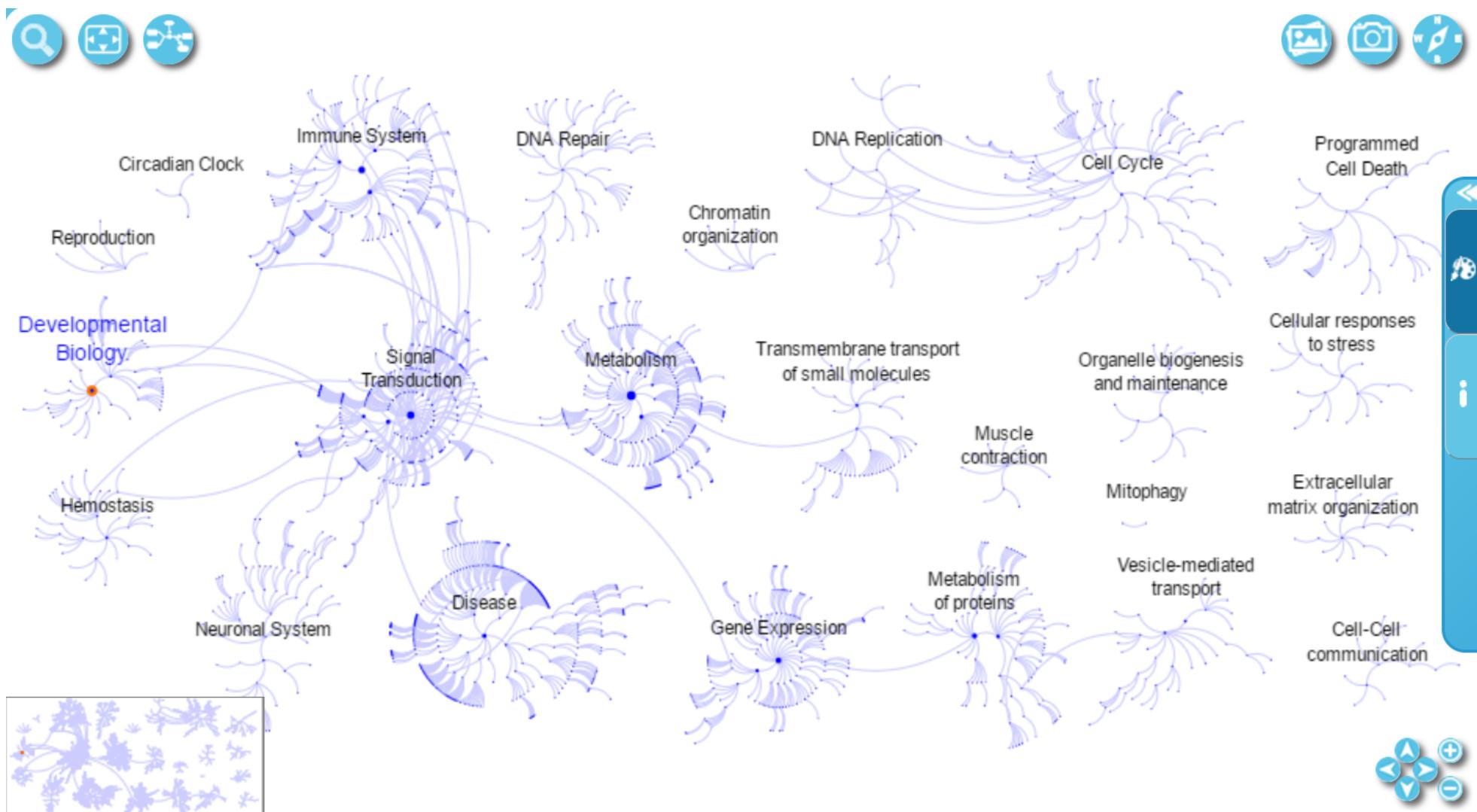
Expression

Analysis

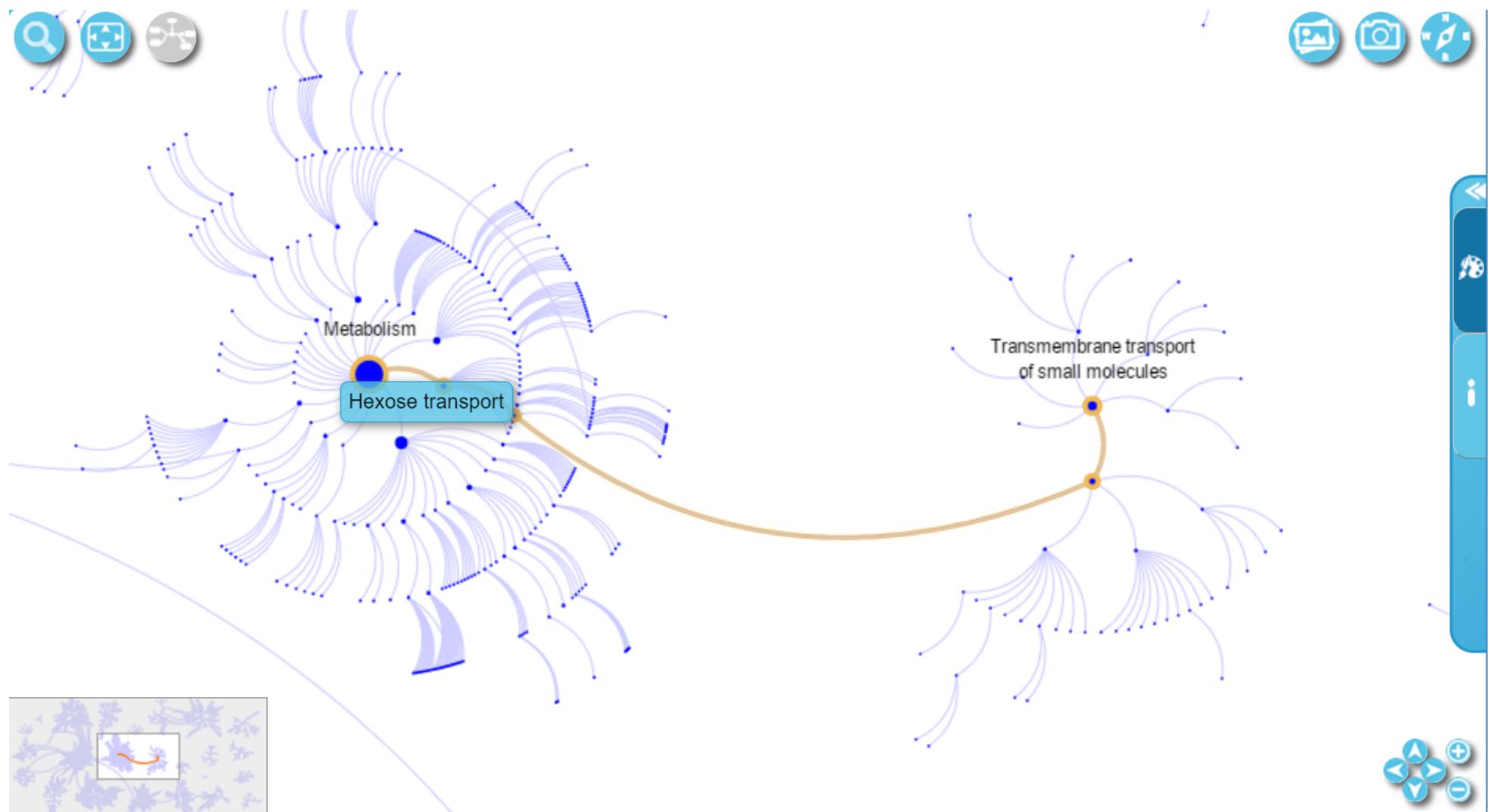
Downloads

Detail Panel

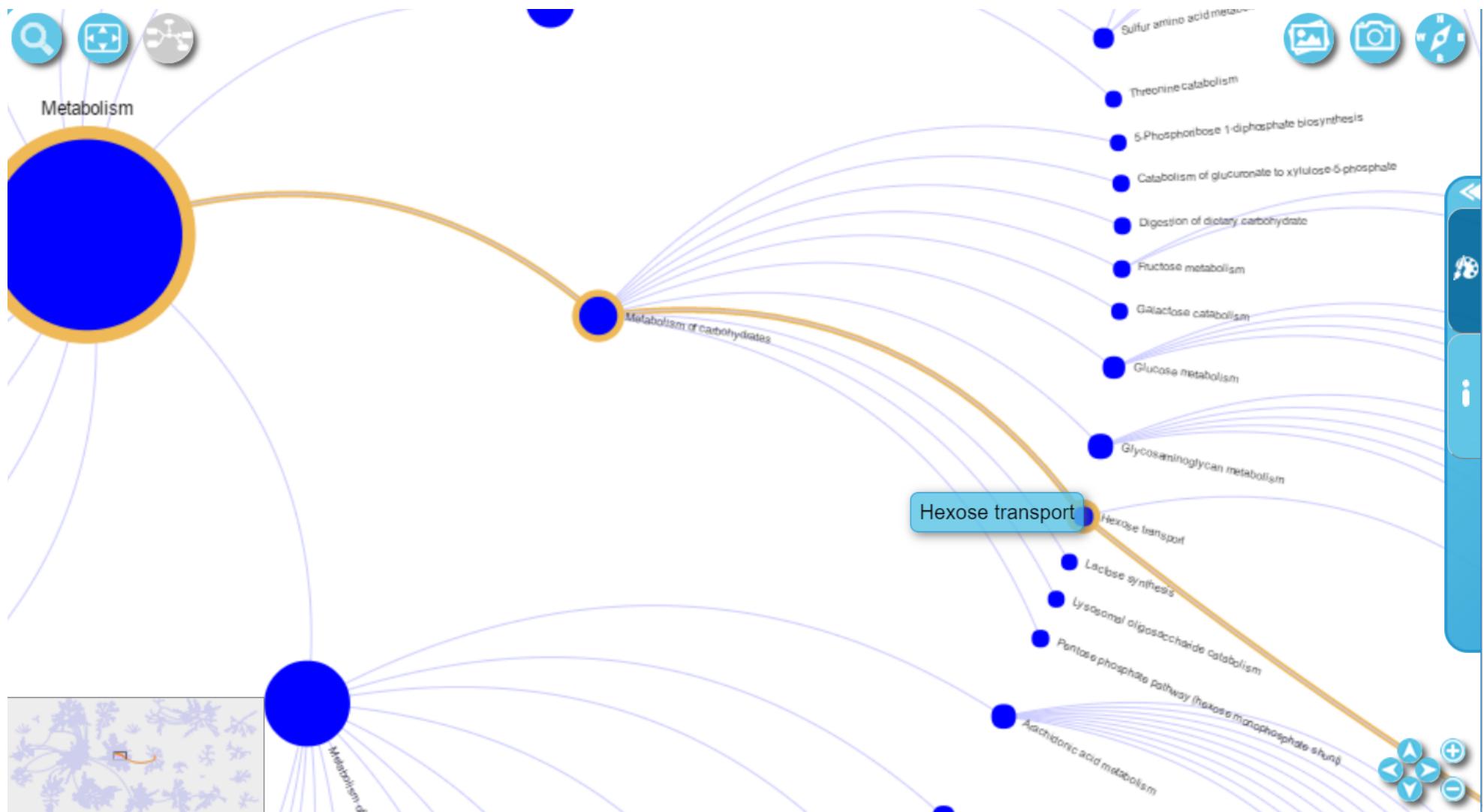
# Pathway Overview



# Edges = shared pathways



# Zoom in for pathway names



# Hierarchy Panel

REACTOME 3.0    54 Pathways for: **Homo sapiens**

**Event Hierarchy:**

- ⊕  Cell Cycle
- ⊕  Cell-Cell communication
- ⊕  Cell junction organization
- ⊕  Signal regulatory protein (SIRP) family interactions
- ⊕  DSCAM interactions
- ⊕  Nephrin interactions
- ⊕  Cellular responses to stress
- ⊕  Chromatin organization
- ⊕  Circadian Clock
- ⊕  Developmental Biology
- ⊕  Disease
- ⊕  DNA Repair
- ⊕  DNA Replication
- ⊕  Extracellular matrix organization
- ⊕  Gene Expression
- ⊕  Hemostasis
- ⊕  Immune System
- ⊕  Mitophagy
- ⊕  Metabolism
- ⊕  Metabolism of proteins
- ⊕  Muscle contraction
- ⊕  Neuronal System
- ⊕  Organelle biogenesis and maintenance
- ⊕  Programmed Cell Death
- ⊕  Reproduction
- ⊕  Signal Transduction
- ⊕  Transmembrane transport of small molecules
- ⊕  Vesicle-mediated transport



Pathway



Reaction



Black-box



Inferred from



New



Updated



Disease

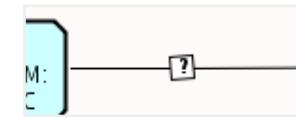
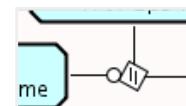
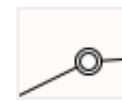
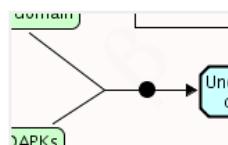
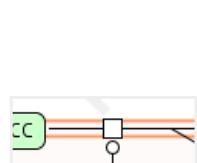
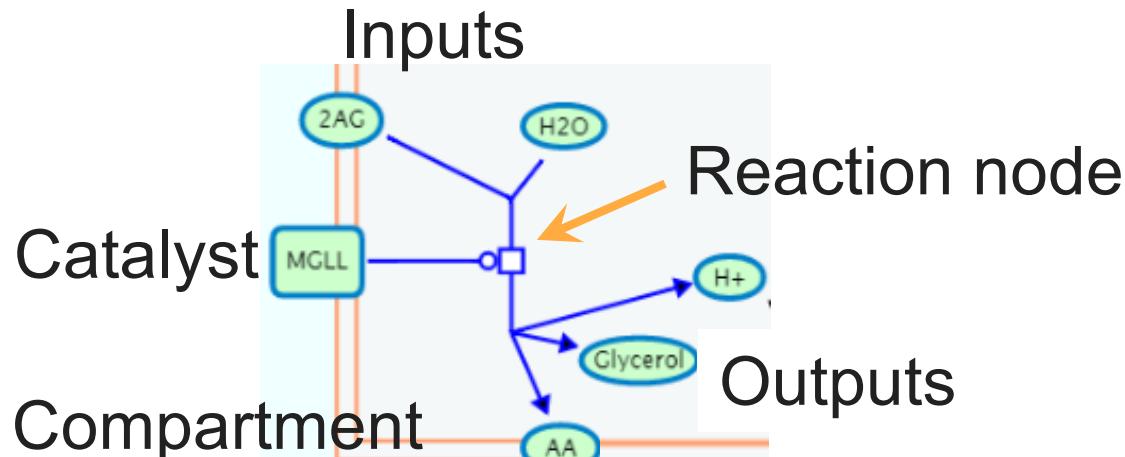
# The Pathway Browser - Pathway Diagrams

Ovals are small molecules (or sets of)

Green boxes are proteins,

Blue are complexes,

Blue with double-boundary are sets



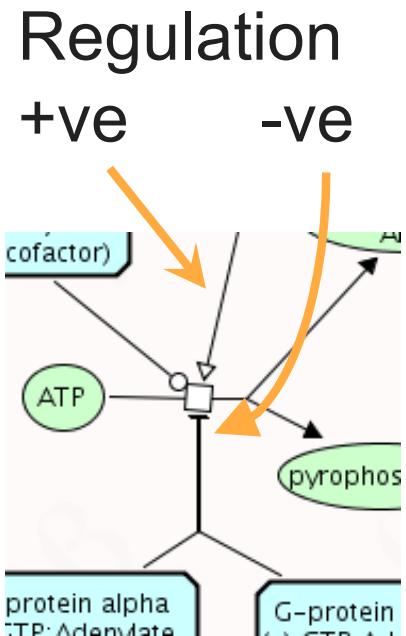
Transition

Binding

Dissociation

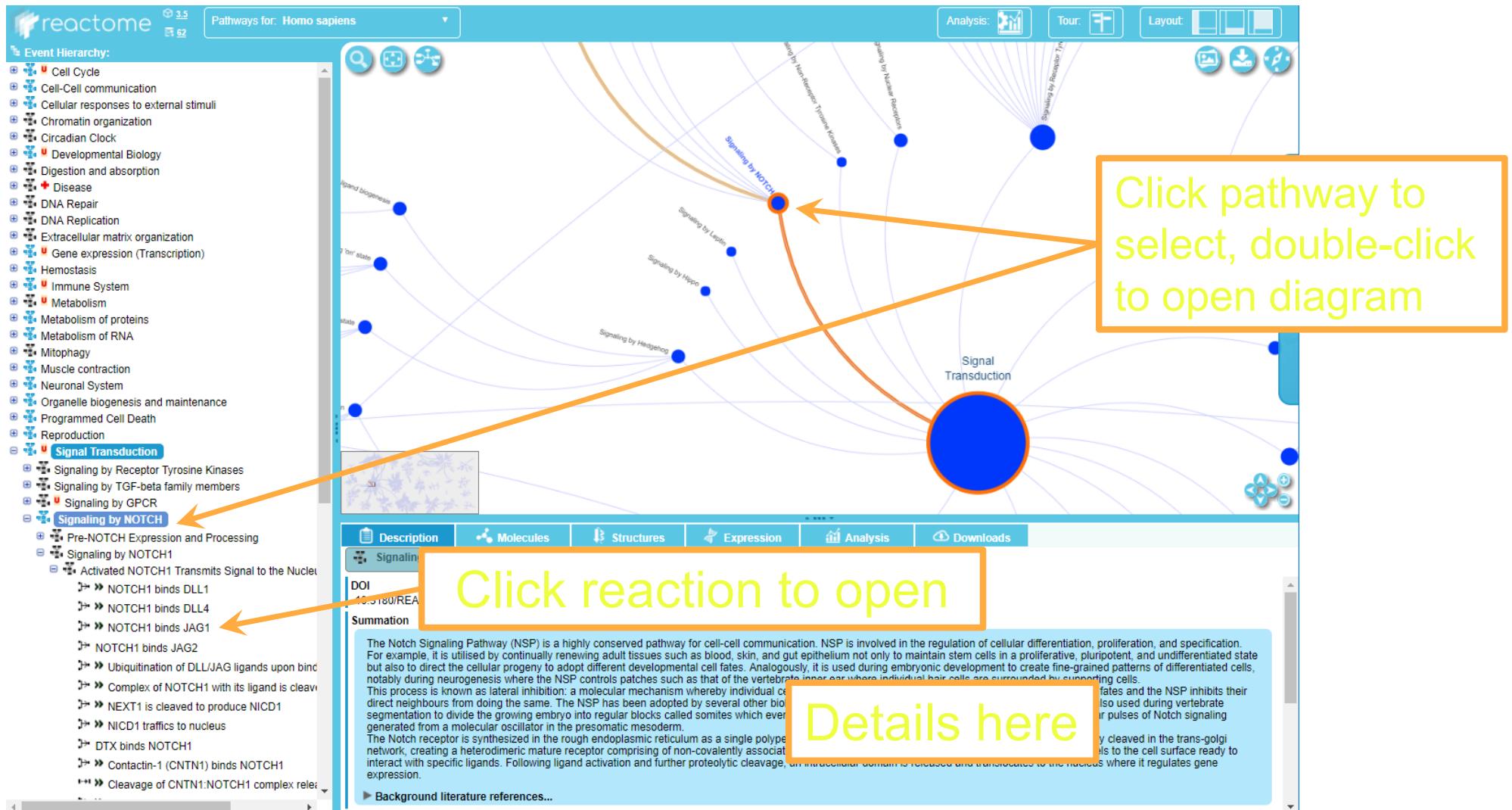
Omitted

Uncertain

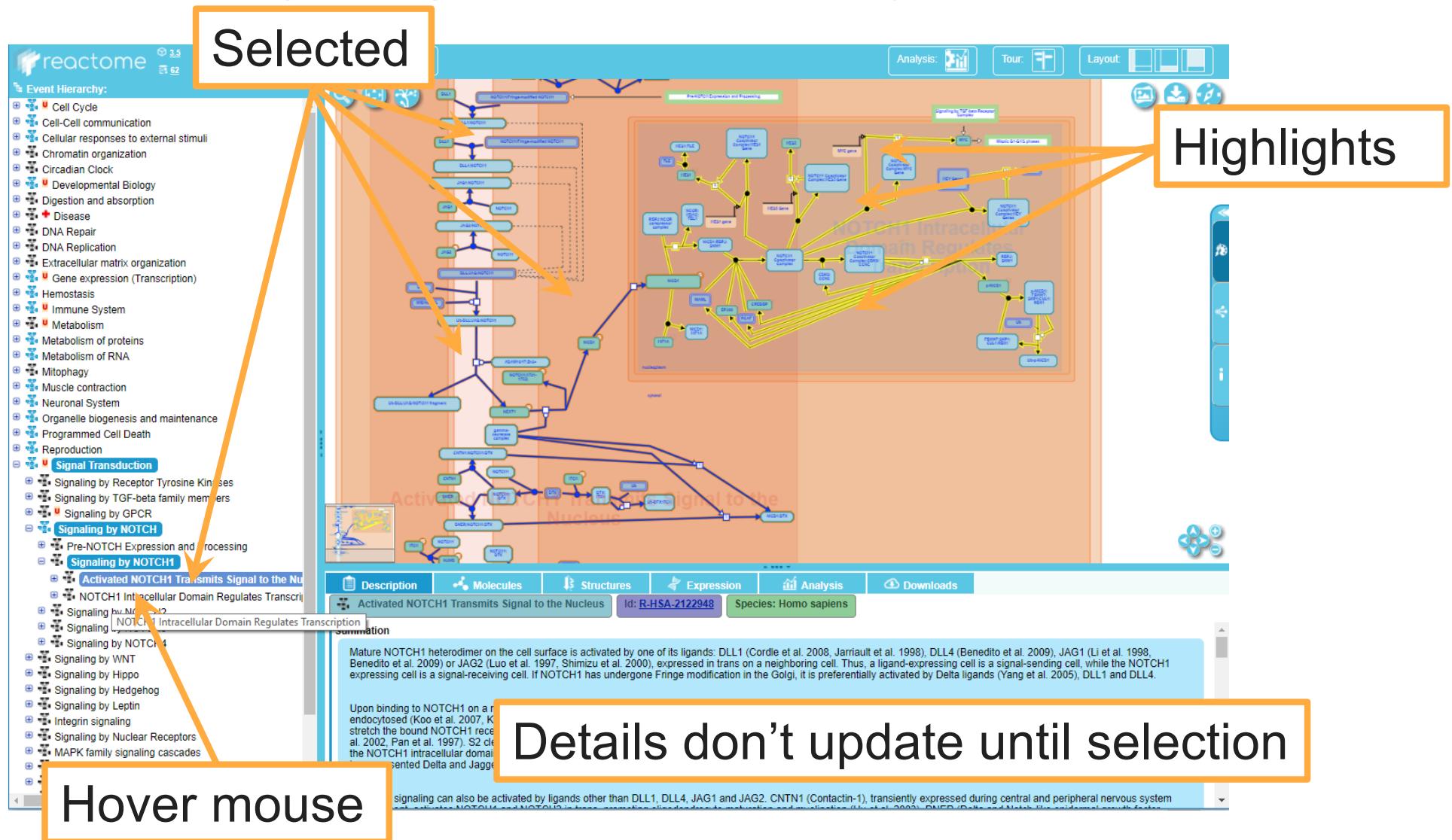


# Navigating in the Pathway Browser

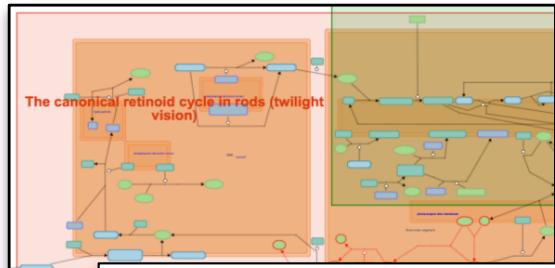
# Home button



# Navigating in the Pathway Browser

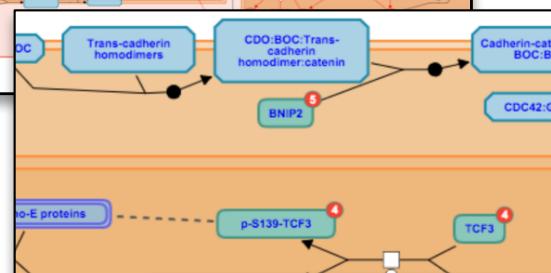


# Pathway Diagram Viewer



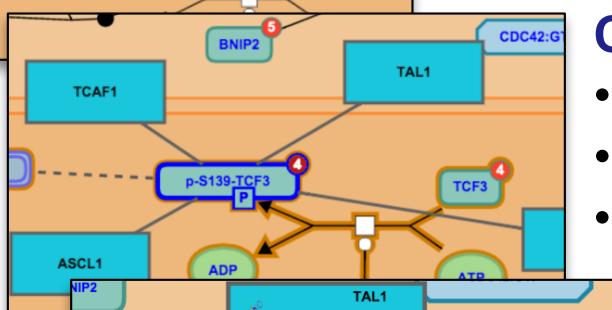
## Zoomed-out view

- Subpathway boxes
- No glyph labels, No trivial molecules



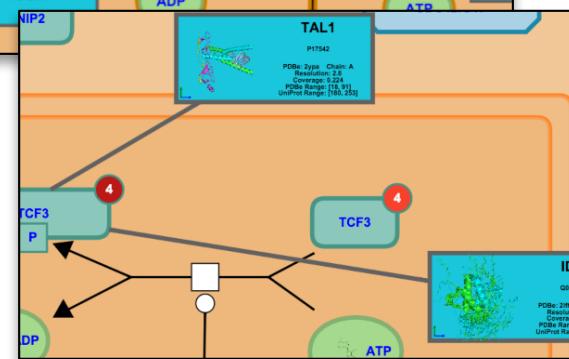
## Close view

- Glyph labels
- Trivial molecules and interactor summary appear



## Closer view

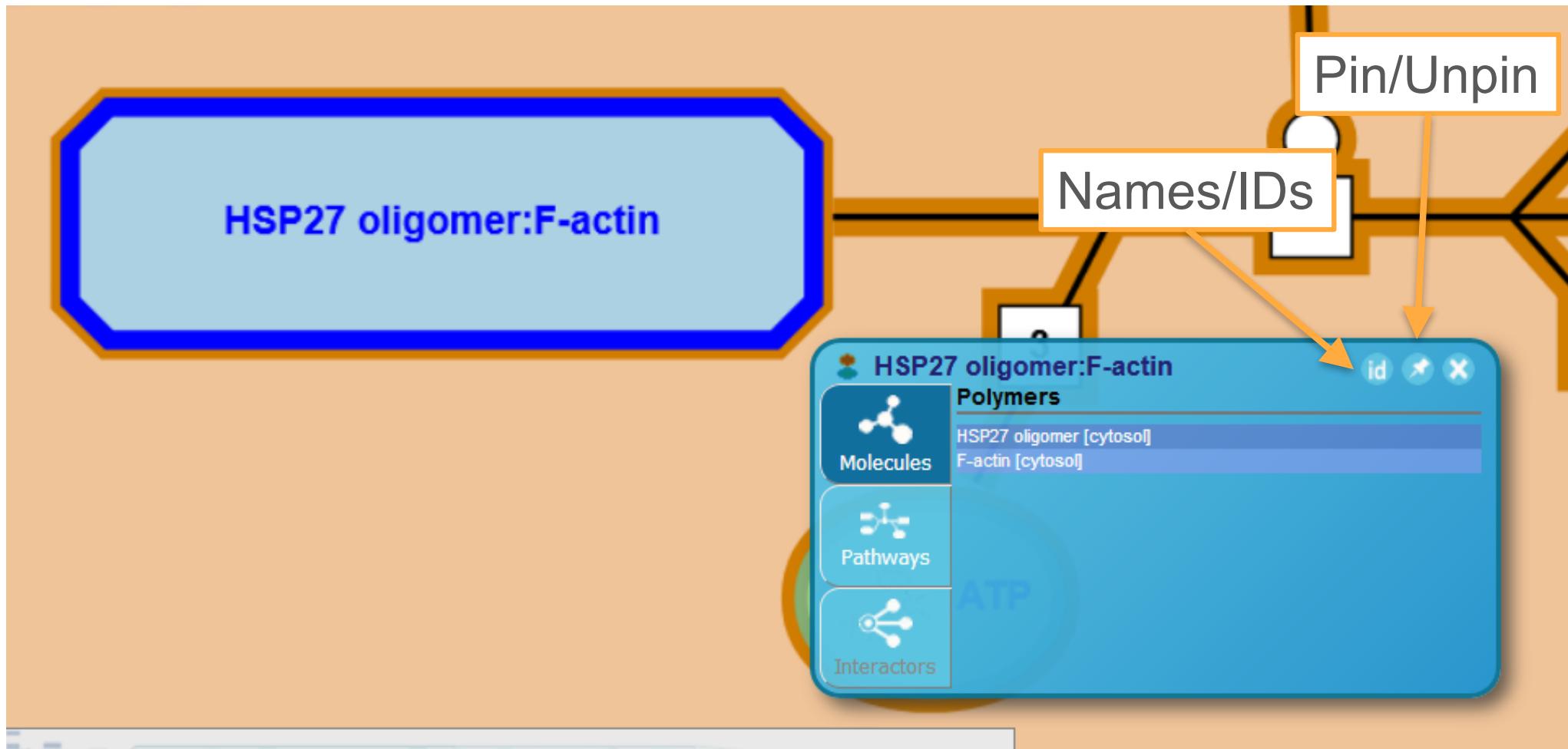
- Stoichiometry shown
- Node attachments appear
- Interactors show gene or chemical name



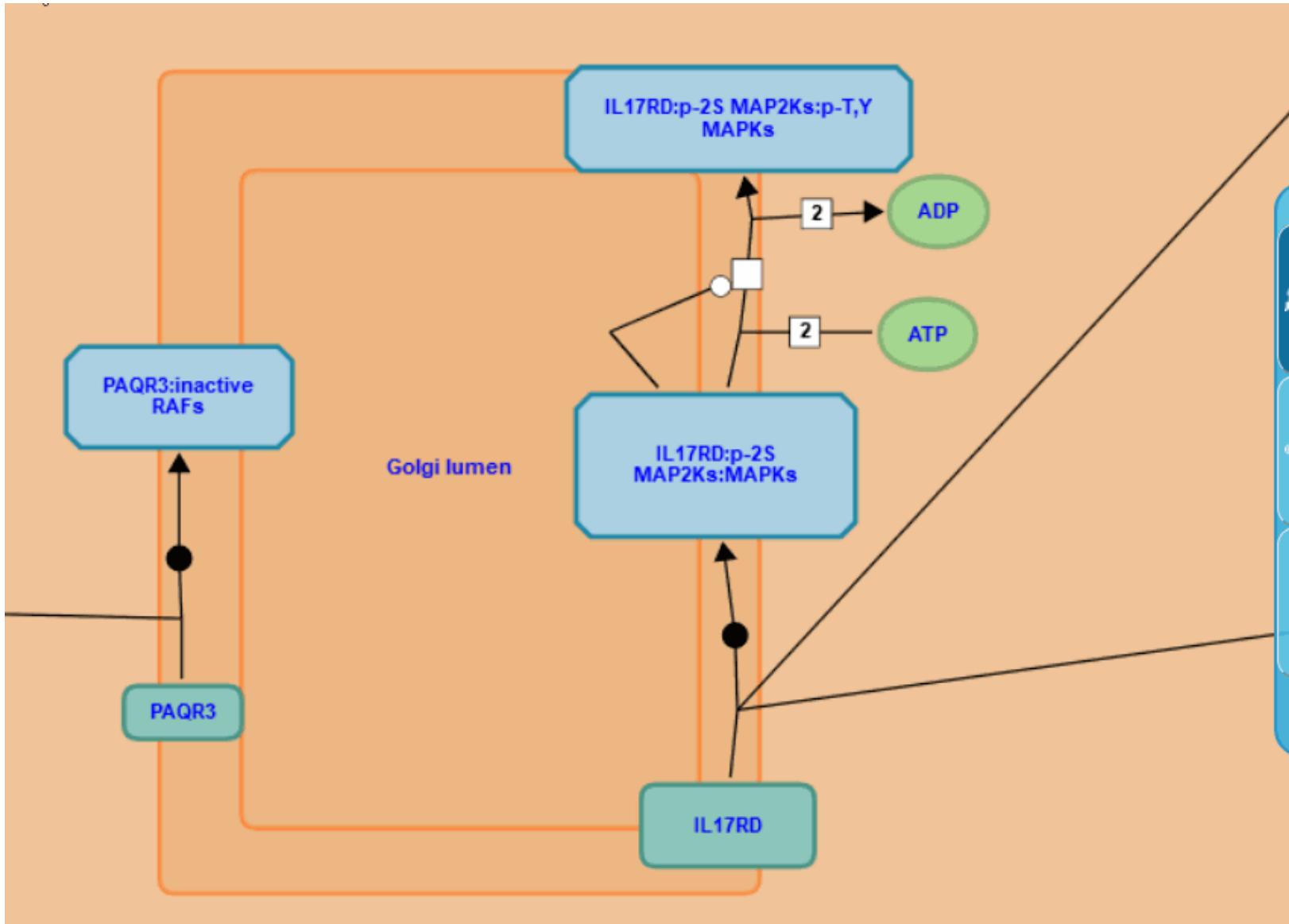
## Zoomed-in view

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

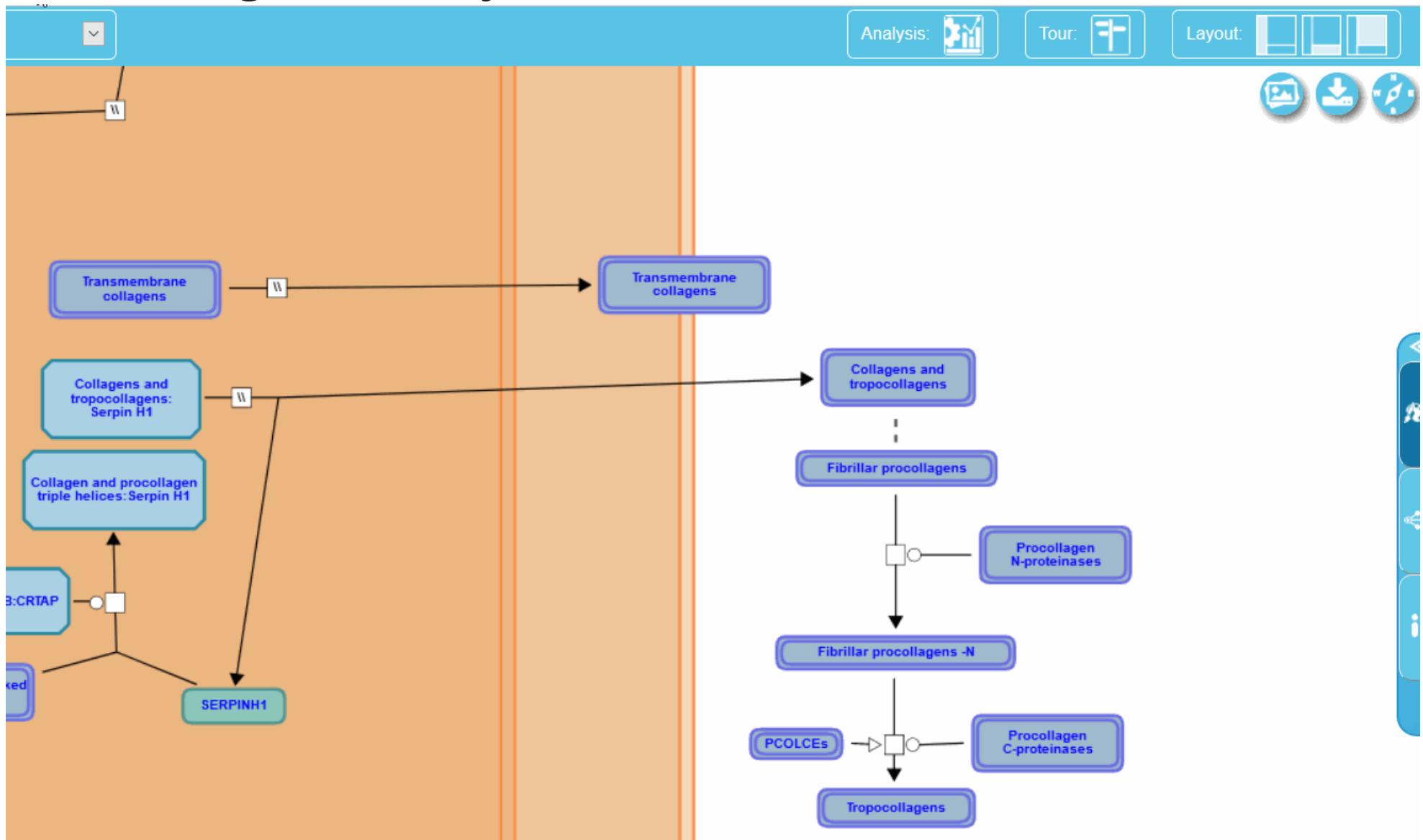
# Contextual Information Panel



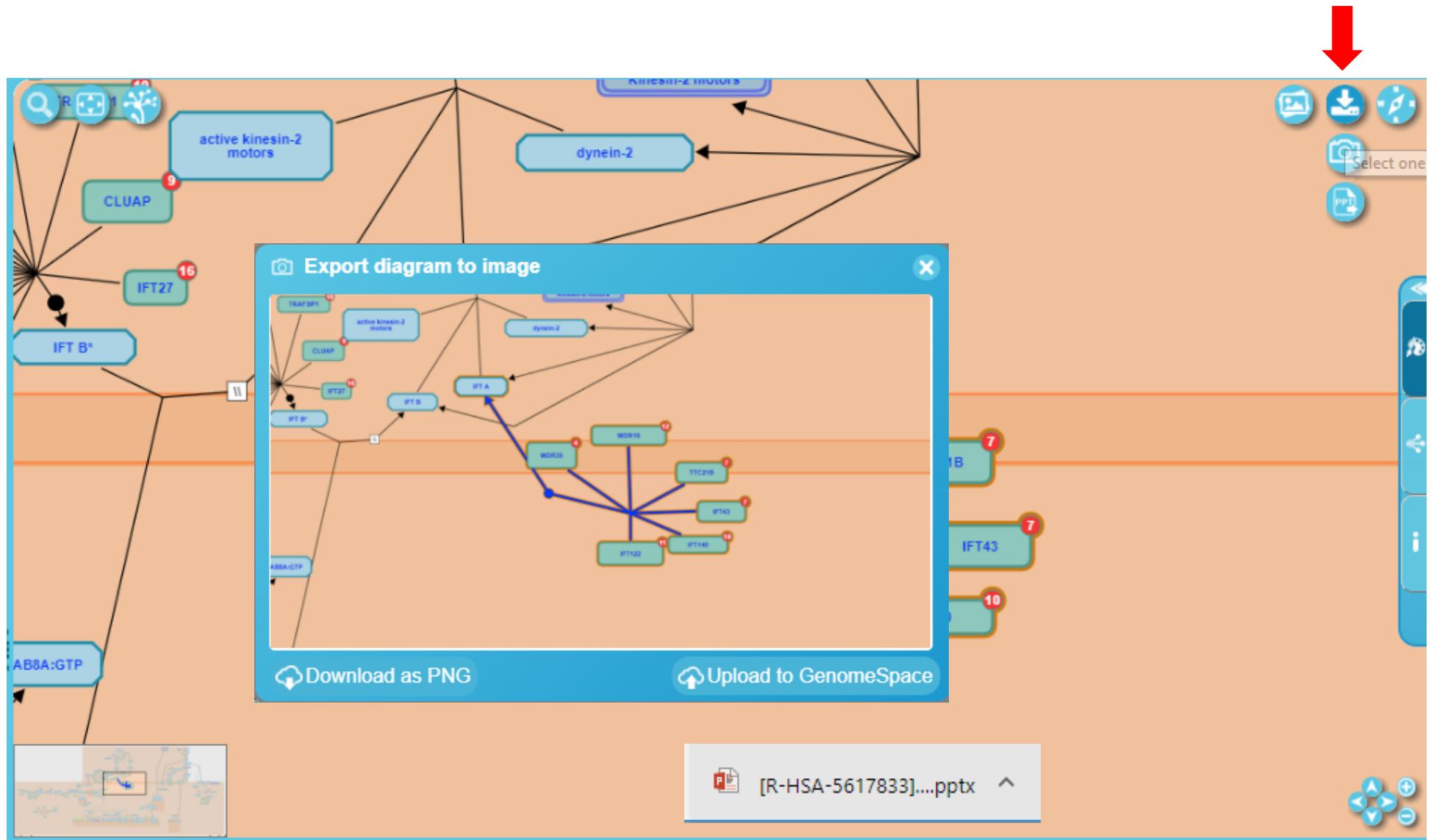
# Colour Profiles



# Diagram Key



# Export Diagram



# Show Illustration

REACTOME 3.2 Pathways for: Homo sapiens Analysis: Tour: Layout:

Event Hierarchy:

- Effects of PIP2 hydrolysis
- Response to elevated platelet cytosolic Ca<sup>2+</sup>
- Formation of Fibrin Clot (Clotting Cascade)
- Dissolution of Fibrin Clot
- Cell surface interactions at the vascular wall
- Factors involved in megakaryocyte development
- Immune System
- Mitophagy
- Metabolism
- Metabolism of proteins
- Muscle contraction
- Neuronal System
- Organelle biogenesis and maintenance**
- Mitochondrial biogenesis
- Mitochondrial translation
- Assembly of the primary cilium**
- Anchoring of the basal body to the plasma membrane
- Cargo trafficking to the periciliary membrane
- Intraflagellar transport
- ATAT acetylates microtubules
- HDAC6 deacetylates microtubules
- Programmed Cell Death
- Apoptosis
- Regulated Necrosis
- Reproduction
- Signal Transduction

**CILIOGENESIS**

**ASSEMBLY OF THE PRIMARY CILIJUM INTRAFAGELLAR TRANSPORT AND CARGO TRAFFICKING**

ANTEROGRADE TRAFFIC      RETROGRADE TRAFFIC

Description Molecules Structures Expression Analysis Downloads

Analysis results are shown here when an analysis has been run. To start an analysis, click on the Analyse Data button in the top bar.

# The Details Panel - Overview

The screenshot shows the 'Details' panel for a biological interaction. At the top, there are several tabs: Description, Molecules, Structures, Expression, Analysis, and Downloads. The 'Description' tab is active, showing the summation of the interaction: 'Collagen type I binds integrin alpha1beta1, alpha2beta1, alpha10beta1'. Below this, the ID is listed as 'R-HSA-114563' and the species as 'Homo sapiens'. The main content area is divided into sections: Summation, Input, Output, Cellular compartment, Inferred from another species, Authored, Reviewed, and Revised. Each section contains a list of items with a '+' icon to expand them. Orange callout boxes with arrows point to specific parts: 'Background' points to the 'Summation' section; 'Select' points to the 'Input' section; 'Reveal Details' points to the '+' icon in the 'Output' section; 'Orthologues' points to the 'Inferred from another species' section; and 'Key literature' points to the 'Reviewed' section.

Description

Molecules

Structures

Expression

Analysis

Downloads

Collagen type I binds integrin alpha1beta1, alpha2beta1, alpha10beta1

Id: R-HSA-114563

Species: Homo sapiens

**Summation**

Integrin alpha1beta1 binds to collagen type IV and VI with higher affinity than to types I-III, whereas alpha2beta1 has a higher affinity for collagen types I-III than for type IV. Integrin alpha10beta1 binds collagen types I, IV, and VI with similar affinities (Tulla et al. 2001). Integrin alpha11beta1 binds preferentially to the fibril-forming collagen types I and II, binding to type III is weaker and collagens IV and VI are poor ligands (Zhang et al. 2003).

Binding to collagen type I occurs at sites corresponding to the six-residue sequence G(F/L)GER (Knight et al. 1998, 2000, Xu et al. 2000).

Integrin alpha2beta1 is the major platelet collagen receptor (Kunicki et al. 1988). It requires Mg<sup>2+</sup> to interact with collagen and may require initiation mediated by the activation of Integrin alphaiibBeta3 (van de Walle 2007).

► Background literature references...

**Input**

- Collagen type I fibril [extracellular region]
- Mg<sup>2+</sup> [extracellular region]
- Integrin alpha1beta1, alpha2beta1, alpha10beta1 [plasma membrane]

**Output**

- Integrins alpha1beta1, alpha2beta1:Collagen type I fibril:Mg<sup>2+</sup> [plasma membrane]

**Cellular compartment**

- extracellular region
- plasma membrane

**Inferred from another species**

- Collagen type I binds integrin alpha1beta1, alpha2beta1, alpha10beta1 [Homo sapiens, Rattus norvegicus]

**Authored**

- Geiger, B, Horwitz, R, 2008-05-07 08:30:32

**Reviewed**

- Yamada, K, Humphries, MJ, Hynes, R, 2008-05-07 08:53:37
- Ricard-Blum, Sylvie, 2013-08-13

**Revised**

- Jupe, S, 2013-08-13

Background

Select

Reveal Details

Orthologues

Key literature

[Description](#)[Molecules](#)[Structures 5/6](#)[Expression](#)[Analysis](#)[Downloads](#)

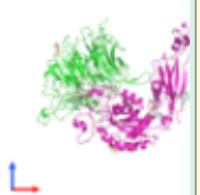
UniProt: P17301 ITGA2 Chain: C Resolution: 1.9 Coverage: 0.174 PDB Range: [1, 200]  
UniProt Range: [167, 366]

1v7p

PDBe



► All other structures for P17301



► All other struct

ChEBI Name

3-phospho-D-glyceroyl dihydrogen phosphate

ChEBI ID

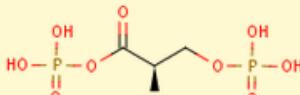
CHEBI:16001

Definition

The (R)-enantiomer of 3-phosphoglyceroyl dihydrogen phosphate.

Stars

★★★



Secondary ChEBI IDs

CHEBI:1658, CHEBI:11881, CHEBI:20189

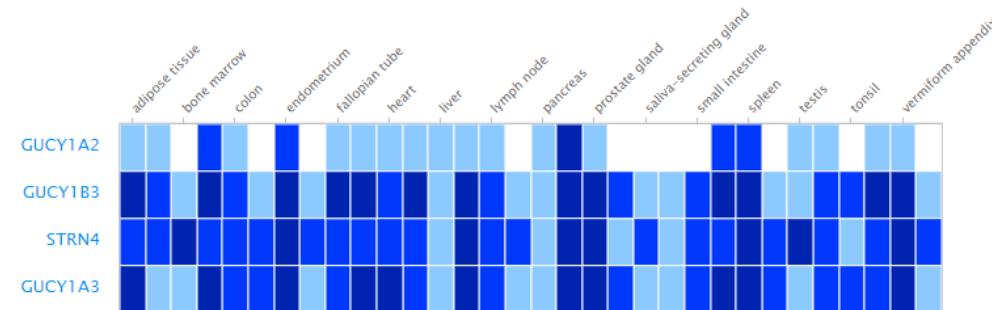
[RNA-seq of coding RNA from tissue samples of 122 human individuals representing 32 different tissues](#)

Showing 4 genes:



Expression level in FPKM

0 43

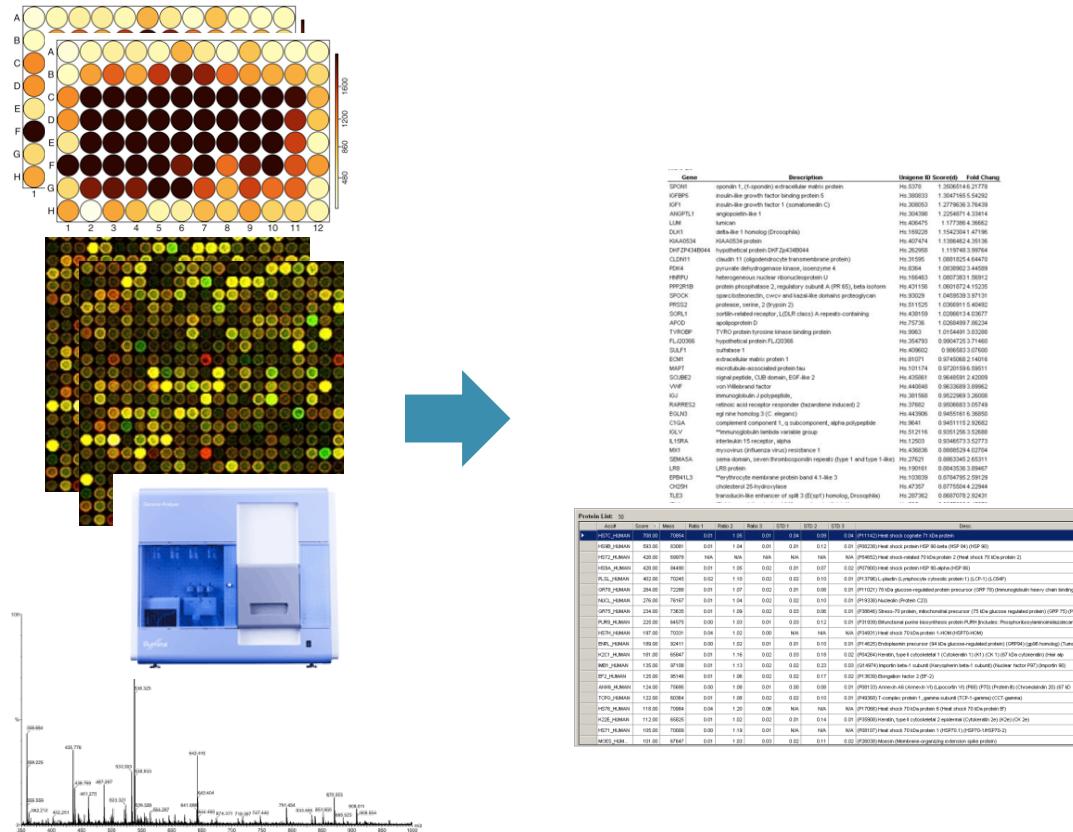


[See more expression data at Expression Atlas.](#)

This expression view is provided by [Expression Atlas](#).

Please send any queries or feedback to [arrayexpress-atlas@ebi.ac.uk](mailto:arrayexpress-atlas@ebi.ac.uk).

# Understanding gene lists...Reactome Tools



# Analysis

The Reactome website features a central search bar at the top:

Find Reactions, Proteins and Pathways  
e.g. O95631, NTN1, signaling by EGFR, glucose

Below the search bar are four main navigation links:

- Pathway Browser (Icon: blue square with white nodes)
- Analyze Data (Icon: blue square with white bar chart)
- ReactomeFIViz (Icon: blue square with white share symbol)
- Documentation (Icon: blue square with white document)

The "Analyze Data" link is circled in orange.

The main content area displays a complex network graph of biological pathways. A specific node in the center of the graph is highlighted with a blue box, which is also circled in orange. This node is part of the "Signal Transduction" pathway.

The top navigation bar includes several icons:

- About
- Content
- Docs
- Tools
- Community
- Download

The "Analysis" icon in the top right corner is circled in orange.

A sidebar on the left provides information about the "Why Reactome" section:

USE REACTOME GRAPH DATABASE IN YOUR PROJECT

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](http://reactome.ncpsb.org).

Sponsors: EMBL-EBI, NYU Langone Health, Ontario Cancer Institute, and the European Molecular Biology Laboratory.

The development of Reactome is supported by grants from the US National Institutes of Health (R41 HG003751 and U54GM11483-01), Ontario Cancer Institute, and the European Molecular Biology Laboratory.

The sidebar also lists various biological processes and diseases:

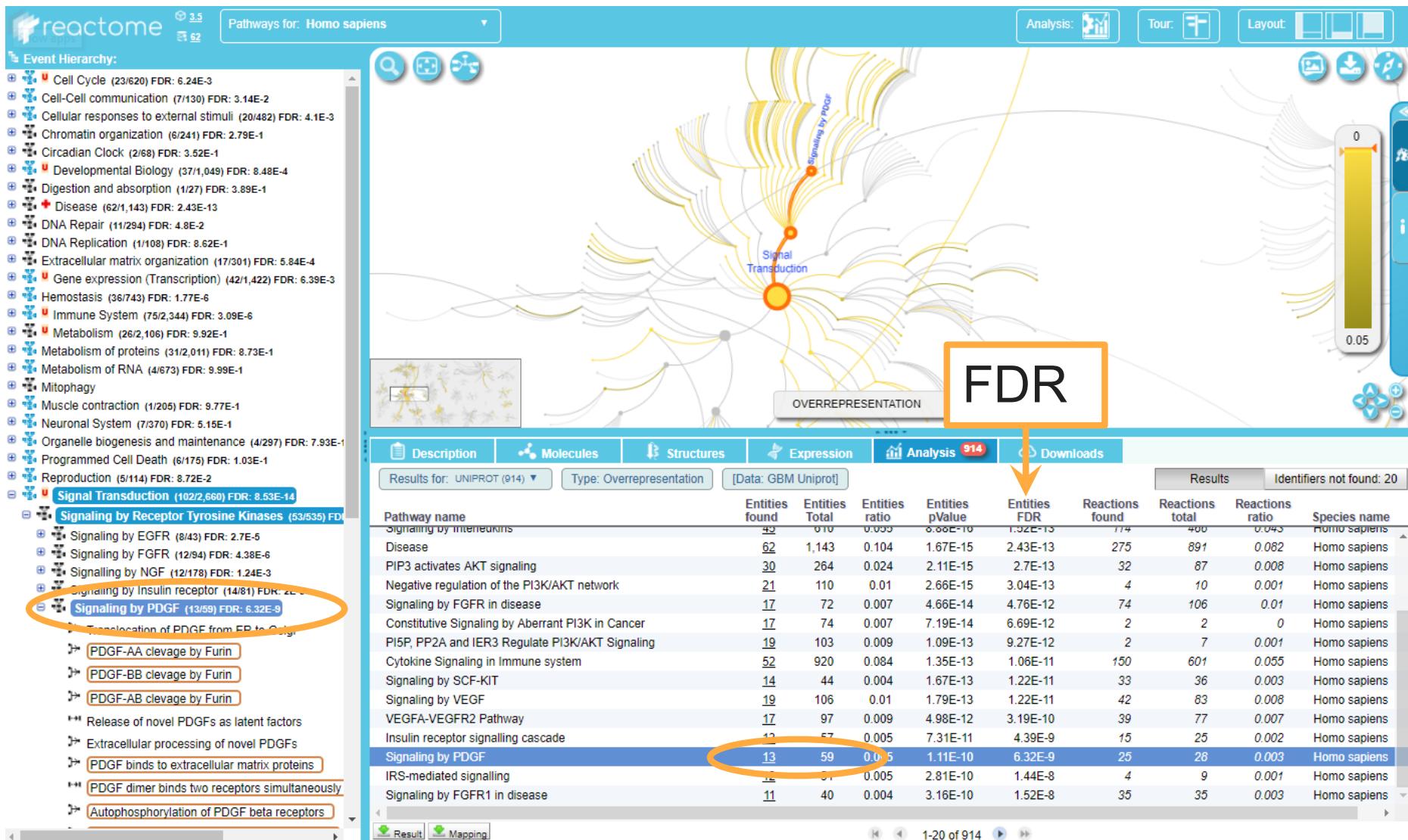
- Cell Cycle
- Cell-Cell communication
- Cellular responses to external stimuli
- Chromatin organization
- Circadian Clock
- Developmental Biology
- Digestion and absorption
- Disease
- DNA Repair
- DNA Replication
- Extracellular matrix organization
- Gene expression (Transcription)
- Hemostasis
- Immune 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

The bottom of the page features a legend for the pathway browser:

- Description
- Molecules
- Structures
- Expression
- Analysis
- Downloads

The "Analysis" icon in the legend is circled in orange.

# Analysis Result – Over-representation



# Analysis - Pathway topology matching

Event Hierarchy:

- Signalining by Insulin receptor (14/81) FDR: 2E-8
- Signalining by PDGF (13/69) FDR: 6.32E-9
  - Translocation of PDGF from ER to Golgi
  - PDGF-AA cleavage by Furin
  - PDGF-BB cleavage by Furin
  - PDGF-AB cleavage by Furin
- Release of novel PDGFs as latent factors
- Extracellular processing of novel PDGFs
- PDGF binds to extracellular matrix proteins
- PDGF dimer binds two receptors simultaneously
- Autophosphorylation of PDGF beta receptors
- Autophosphorylation of PDGF alpha receptors
- Autophosphorylation of PDGF alpha/beta receptors

Downstream signal transduction (10/30) FDR: 1.52

- PI3-kinase binds to the active receptor
- PI3K catalyses the phosphorylation of PIP2 to PIP3
- PLC-gamma binds to the active receptor
- Phosphorylation of PLCgamma by PDGFR
- Activated PLC gamma dissociates from the Fc receptor
- SH2 domain of Src binds to the active receptor
- Activation of Src
- SHP2 binds to the active receptor
- GAP binds to PDGF-beta receptors only
- Grb2/Sos1 complex binds to the active receptor
- Sos-mediated nucleotide exchange of Ras (F)
- STAT binds to the active receptor
- Crk binds to the active PDGF receptor
- p130Cas and C3G bind PDGFR bound Crk
- Nck binds to the active PDGF receptor
- Grb7 binds to the active PDGF receptor

Pathway name

Negative regulation of the PI3K/AKT network

Signaling by FGFR in disease

Constitutive Signaling by Aberrant PI3P, PP2A and IER3 Regulation

Cytokine Signaling in Immune System

Signaling by SCF-KIT

Signaling by VEGF

VEGFA-VEGFR2 Pathway

Insulin receptor signalling cascade

Signaling by PDGF

IRS-mediated signalling

Signaling by FGFR1 in disease

Result Mapping

Analysis: Tour: Layout:

Event Hierarchy:

Downstream signal transduction

OVERREPRESENTATION

Description Molecules Structures Expression Analysis 914 Downloads

Results Identifiers not found: 20

Pathway name

Negative regulation of the PI3K/AKT network

Signaling by FGFR in disease

Constitutive Signaling by Aberrant PI3P, PP2A and IER3 Regulation

Cytokine Signaling in Immune System

Signaling by SCF-KIT

Signaling by VEGF

VEGFA-VEGFR2 Pathway

Insulin receptor signalling cascade

Signaling by PDGF

IRS-mediated signalling

Signaling by FGFR1 in disease

Result Mapping

Entities found Entities Total Entities ratio Entities pValue Entities FDR Reactions found Reactions total Reactions ratio Species name

Identifiers not found

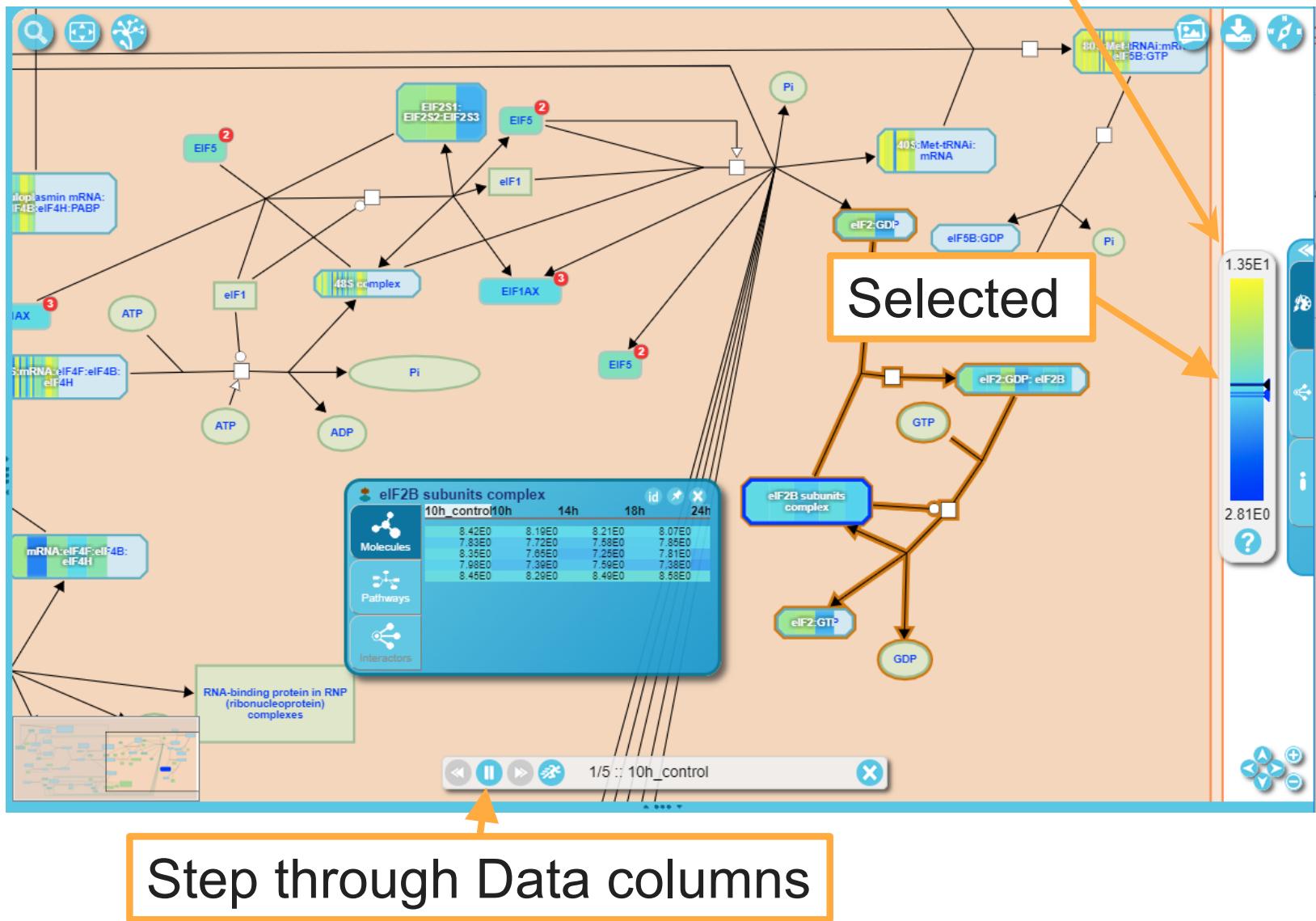
| Entity        | Pathway Identifier                                      | Pathway name                          |
|---------------|---|---------------------------------------|
| O95031        | R-HSA-5663202   | Diseases of signal transduction       |
| Q8IIV1        | R-HSA-9006934   | Signaling by Receptor Tyrosine Kinase |
| Q13214        | R-HSA-2219528   | PI3K/AKT Signaling                    |
| P35716        | R-HSA-162582  | Signal Transduction                   |
| O43692        | R-HSA-9006925   | Intracellular signaling               |
| P08922        | R-HSA-449147  | Signaling by Integrins                |
| Q16799        | R-HSA-1643686   | Disease                               |
| Q18766        | R-HSA-1257604   | PIP3 activates                        |
| R-HSA-199418  | Negative regulation                                     |                                       |
| R-HSA-1226099 | Signaling by Receptor Tyrosine Kinase                   |                                       |
| R-HSA-2219530 | Constitutive Signaling                                  |                                       |
| R-HSA-6811558 | PI3P, PP2A and IER3                                     |                                       |
| R-HSA-1280215 | Cytokine Signaling                                      |                                       |
| R-HSA-143357  | Signaling by SCF  |                                       |
| R-HSA-194138  | Signaling by VEGF                                       |                                       |
| R-HSA-4420097 | VEGFA-VEGFR2  |                                       |
| R-HSA-74751   | Insulin receptor  |                                       |
| R-HSA-186797  | Signaling by PI3K                                       |                                       |
| R-HSA-112399  | IRS-mediated  |                                       |
| R-HSA-5655302 | Signaling by FGFR1                                      |                                       |
| R-HSA-186763  | Downstream signal transduction                          |                                       |
| R-HSA-6785807 | Interleukin-4 and 13 signaling                          |                                       |
| R-HSA-74752   | Signaling by Insulin receptor                           |                                       |
| R-HSA-2428928 | IRS-related events triggered by IGF1R                   |                                       |
| R-HSA-2428924 | IGF1R signaling cascade                                 |                                       |
| R-HSA-2404192 | Signaling by Type 1 Insulin-like Growth Factor Receptor |                                       |

Identifiers not found: 20

1-20 of 20

# Expression overlay

Scaled to Data



# Species Comparison I

 Analysis tools X

  
Analyse your data

  
Species Comparison

## Species Comparison

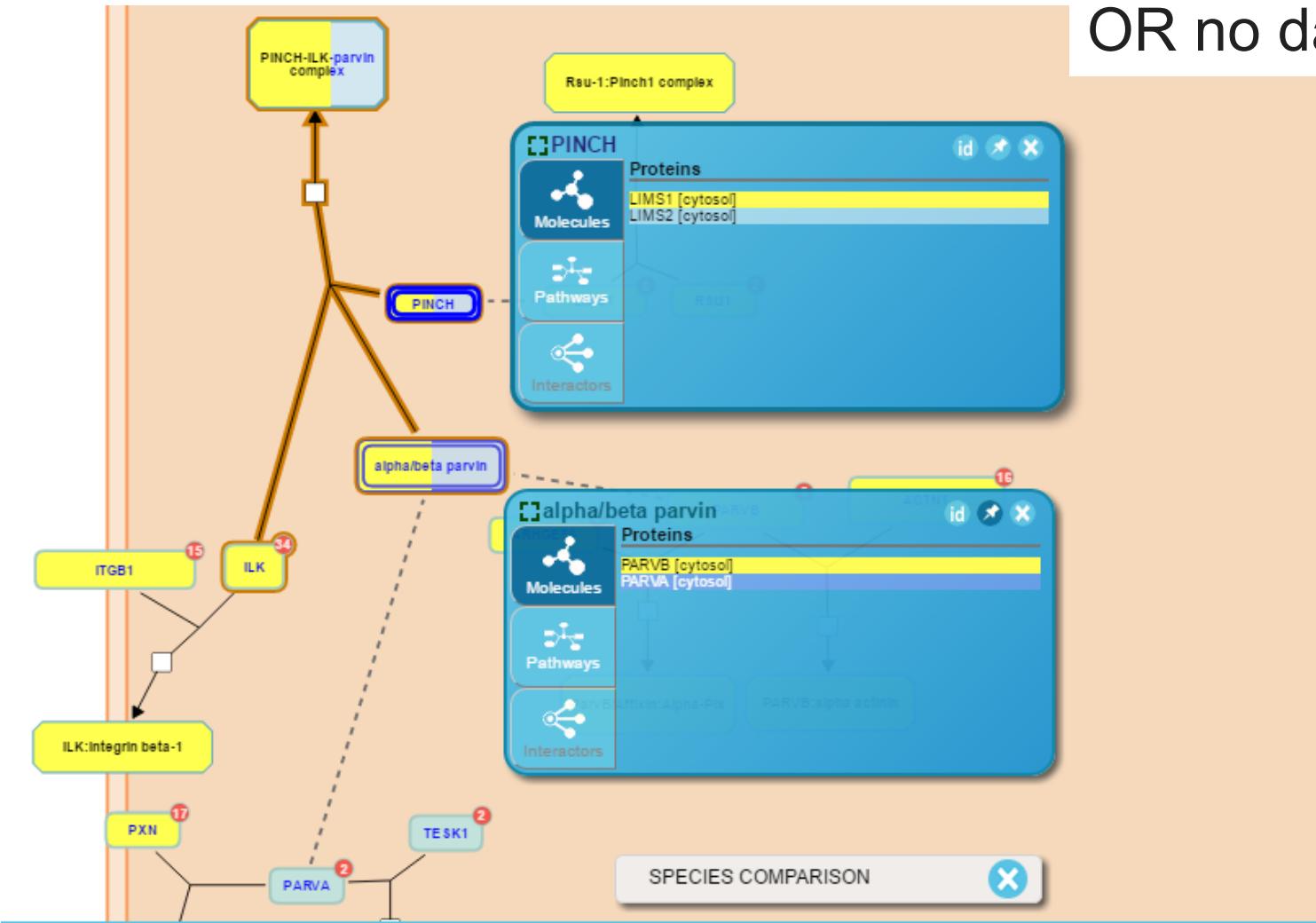
This tool allows you to compare human pathways with those in any of the other species inferred from Reactome by orthology.

Use the species selector to choose the other species and click on the "GO" button to perform the comparison.

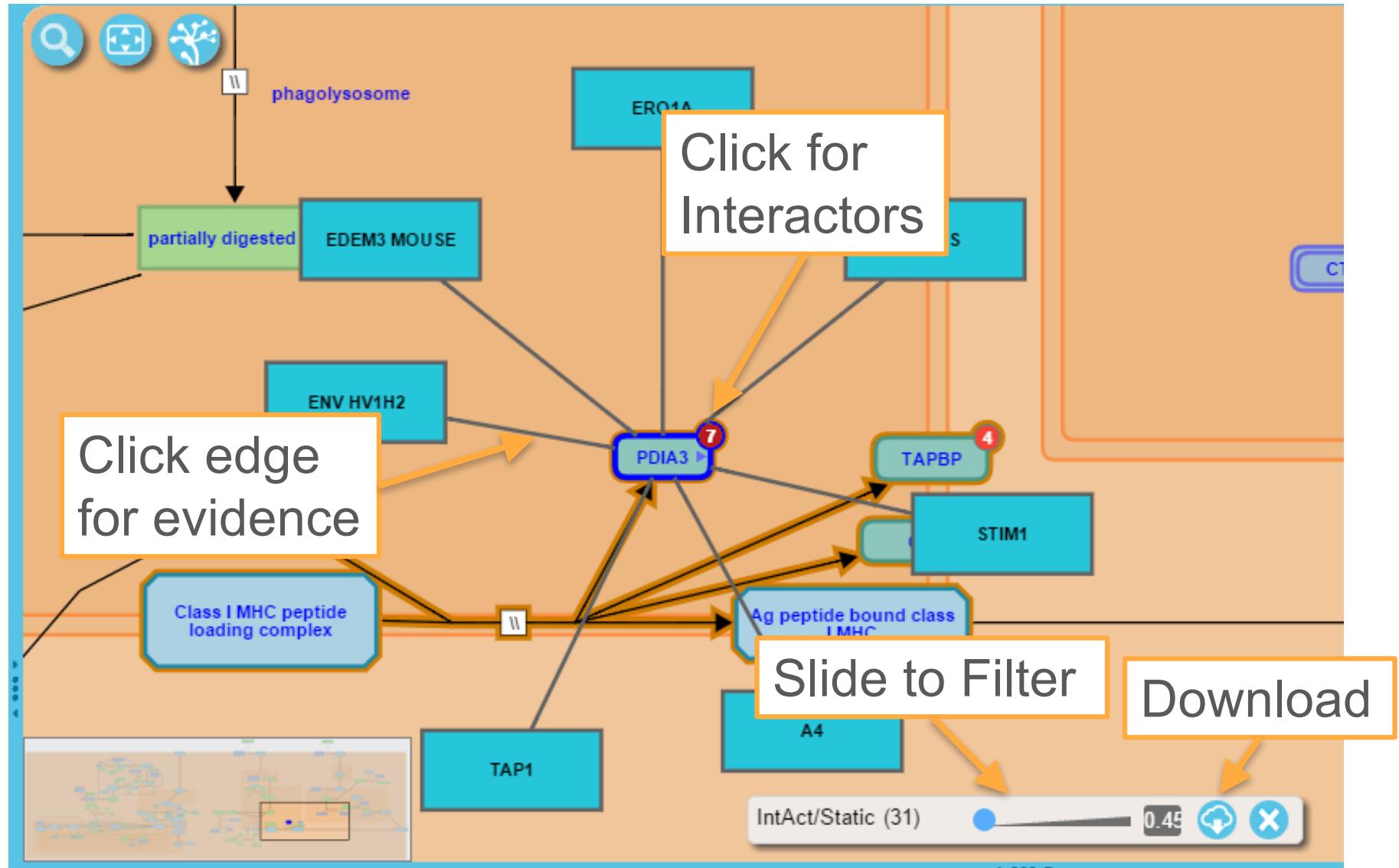
Compare **Homo sapiens** with **Mus musculus** ▼ Go!

# Species Comparison II

Yellow = orthologue  
No colour = not found  
OR no data



# Interactors



# Molecular Interaction Overlay - Data

EMBL-EBI

IntAct

Services | Research | Training | About us

EBI-8686389 OR EBI-8686371 OR EBI-7209397  
Examples: BRCA2, Q06809, dmc1, 10831611

Search | Advanced

Home | Advanced Search | About | Resources | Download | Feedback

IntAct > IntAct Search Results

+ Show more data from EMBL-EBI

7 binary interactions found for search term  
*EBI-8686389 OR EBI-8686371 OR EBI-7209397 OR EBI-8686317 OR EBI-8623527 OR EBI-72094*

Interactions (7) | Interactors | Interaction Details | Graph

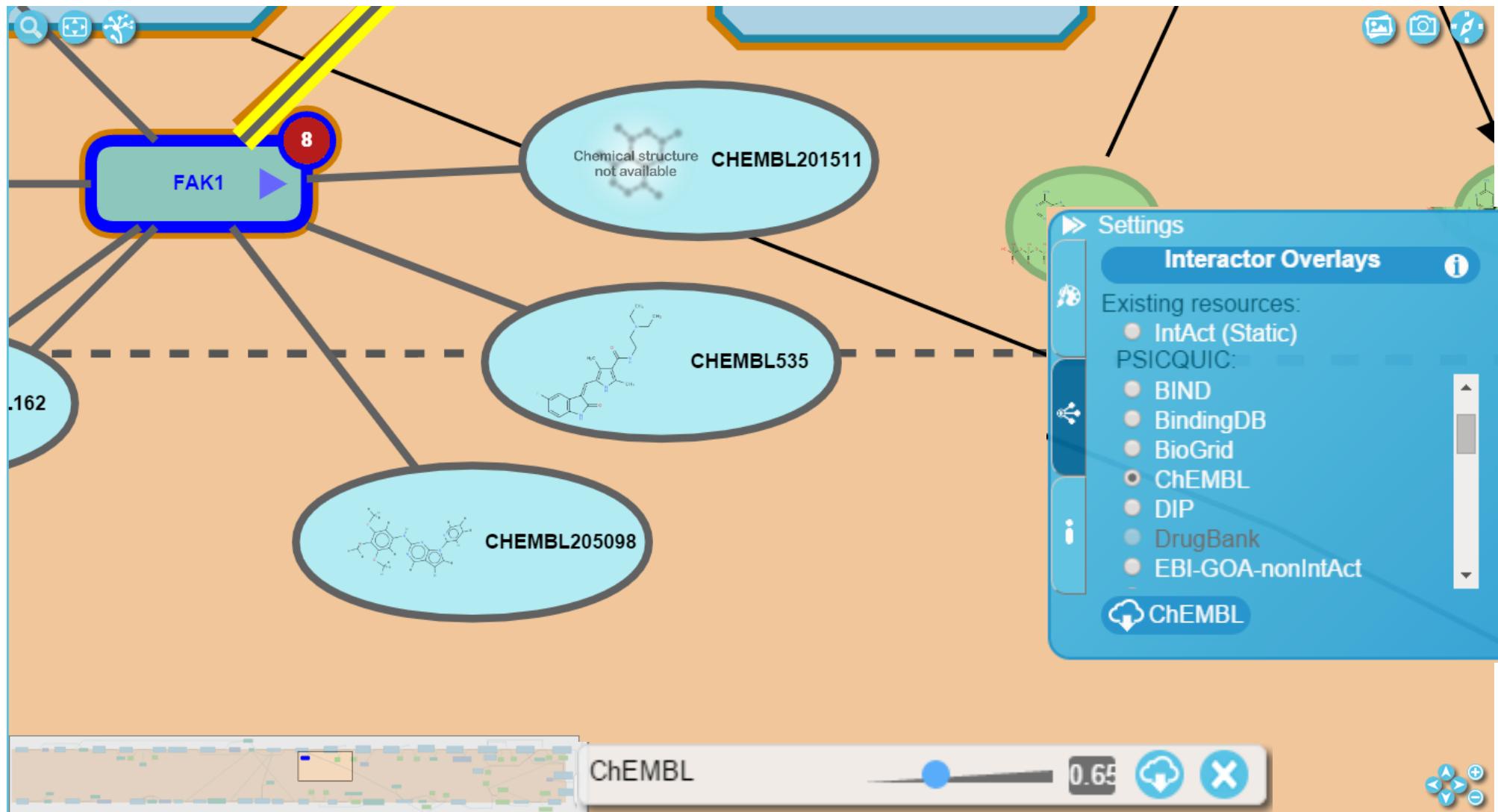
No results in other databases.

What is this view?

| Customize view |              | Select format to Download |              | Download             |                              |                             |                 |
|----------------|--------------|---------------------------|--------------|----------------------|------------------------------|-----------------------------|-----------------|
| Dts            | Molecule 'A' | Links 'A'                 | Molecule 'B' | Links 'B'            | Interaction Detection Method | Interaction AC              | Source Database |
| •              | PECAM1       | P16284<br>EBI-716404      | PTPN11       | Q06124<br>EBI-297779 | pull down                    | EBI-8623527<br>MINT-8033235 | MINT            |
| •              |              |                           |              |                      | pull down                    | EBI-8686299<br>MINT-8031324 | MINT            |
| •              |              |                           |              |                      | pull down                    | EBI-8686371<br>MINT-8033280 | MINT            |
| •              |              |                           |              |                      | surface plasmon resonance    | EBI-8686317<br>MINT-8031339 | MINT            |
| •              |              |                           |              |                      | surface plasmon resonance    | EBI-8686389<br>MINT-8033295 | MINT            |
| •              |              |                           |              |                      | lambda phage display         | EBI-7209397<br>MINT-8031354 | MINT            |
| •              |              |                           |              |                      | lambda phage display         | EBI-7209415<br>MINT-8033310 | MINT            |

IntAct View version: 4.2.3.2

# Molecular Interaction Overlay – Set source



# Developer's Zone



[About](#) [Content](#) [Docs](#) [Tools](#) [Community](#) [Download](#)

e.g. O95631, NTN1, signaling by EGFR, glucose

Go!

## Developer's Zone

Explore our tools and web services and learn how to include them in your applications



### 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



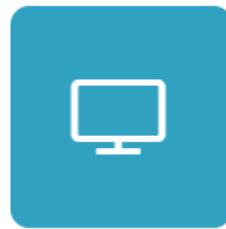
### Graph Database

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

# 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**  
BIOLOGICAL PROTEIN EXPRESSION LEVELS IN TISSUES AND CELLS

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

**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  
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**PRIDE**

compliant, public data repository for proteomics data, including protein and peptide identifications, post-translational modifications and supporting spectral evidence.

Analysis Service  
 Widgets  
 Graph Database

**iLINCs**

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.

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**COPaKB**  
Comics Organizer Protein Action Knowledgebase

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

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**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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**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

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**PINT**

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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**Integrated Proteomics Applications**

Integrated Proteomics Applications provides a comprehensive proteomic data analysis solution, the Integrated Proteomics Pipeline (IP2), which allows researchers to identify,

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**Tabloid Proteome**

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

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# Schema



e.g. O95631, NTN1, signaling by EGFR, glucose

## Graph Database :: Data Schema

| Attribute name      | Cardinality | value type           | Attribute Origin |
|---------------------|-------------|----------------------|------------------|
| authored            | +           | InstanceEdit         | Event            |
| compartment         | +           | Compartment          | Event            |
| created             | 1           | InstanceEdit         | DatabaseObject   |
| crossReference      | +           | Databaseldentifier   | Event            |
| dbId                | 1           | Long                 | DatabaseObject   |
| definition          | 1           | String               | Event            |
| disease             | +           | Disease              | Event            |
| displayName         | 1           | String               | DatabaseObject   |
| doi                 | 1           | String               | Pathway          |
| edited              | +           | InstanceEdit         | Event            |
| eventOf             | +           | Pathway              | Event            |
| evidenceType        | 1           | EvidenceType         | Event            |
| figure              | +           | Figure               | Event            |
| followingEvent      | +           | Event                | Event            |
| goBiologicalProcess | 1           | GO_BiologicalProcess | Event            |
| hasDiagram          | 1           | Boolean              | Pathway          |
| hasEvent            | +           | Event                | Pathway          |
| inferredFrom        | +           | Event                | Event            |

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# More Information

- From the Reactome Homepage

- Reactome User Guide

The screenshot shows the Reactome homepage with a search bar containing "e.g. O95631, NTN1, signaling by EGFR, glucose". Below the search bar is a breadcrumb navigation: Home > Docs > User Guide > User Guide. The main content area has three buttons: Analysis, Tour, and Layout. A tooltip over the Tour button says "Starts the tour...". At the top right, there is a navigation bar with About, Content, Docs (which is currently selected), and Tools. A dropdown menu for Docs is open, showing options: User Guide (which is highlighted), Developer's Zone, and Icon Info.

- [help@reactome.org](mailto:help@reactome.org)
  - Tour

The screenshot shows the Reactome Pathway Portal. At the top, it says "Pathway Browser Tour" and "Reactome Pathway Browser 3.2 - Short introduction". Below that is a video player with the text "v 3.2". To the left of the video player is a "Starts the tour..." button. At the bottom, there are logos for BD2K, CTTV, NIH, EMBL-EBI, OICR, and NYU Langone Medical Center.

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

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