



Reactome and SBGN

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16th August 2014
SBGN-10 Meeting



Ministry of Research and
Innovation



National Human
Genome Research
Institute

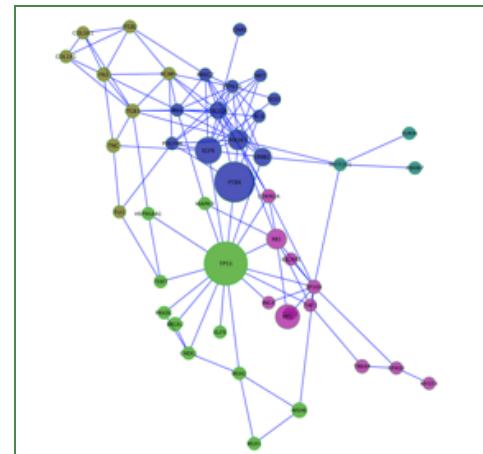
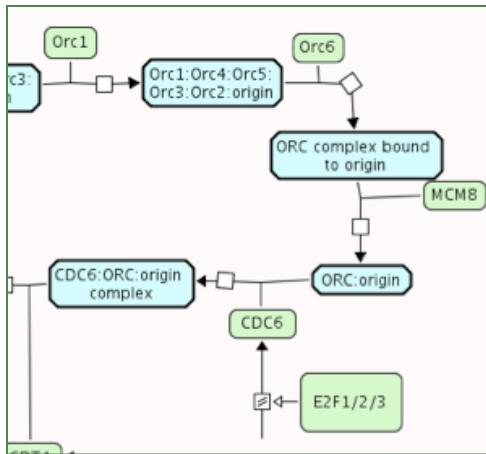
www.reactome.org



What is Reactome?

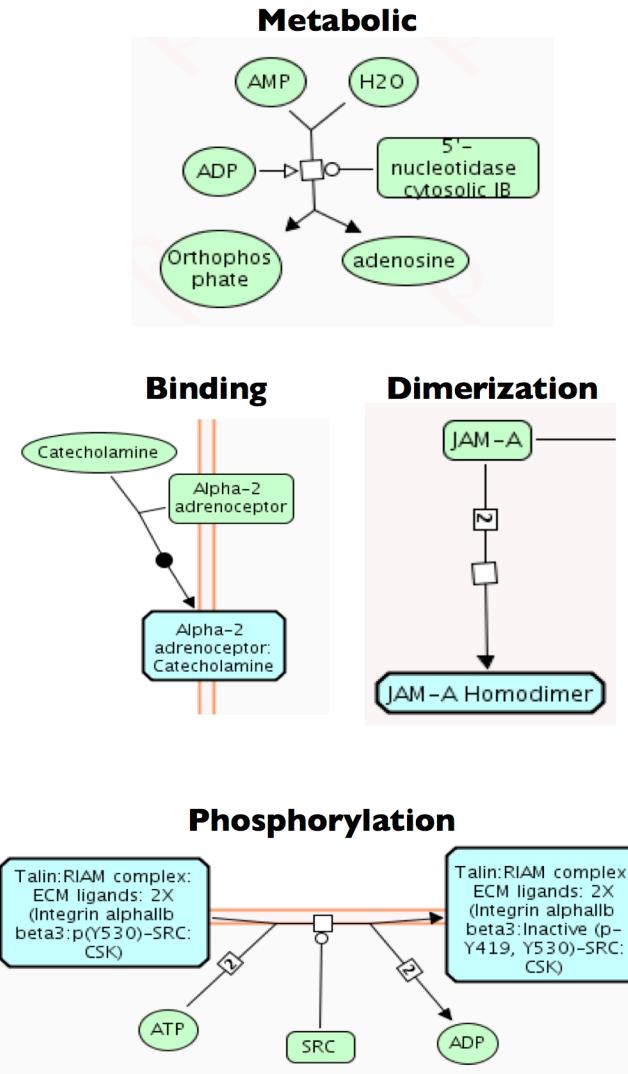
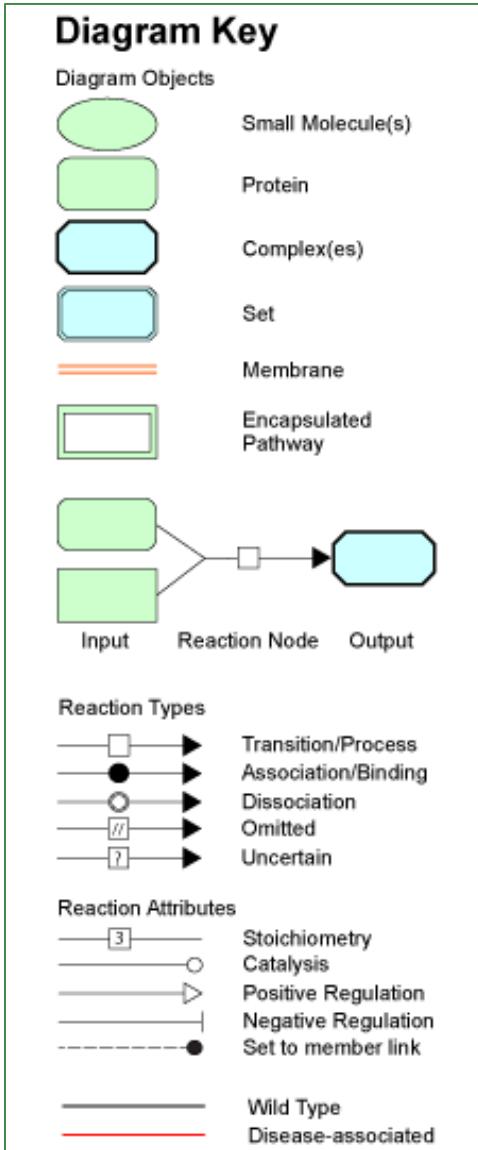


- Open source and open access pathway database
 - Reactome is a Reaction Network Database
 - 1500+ pathway modules encompassing many areas of human biology.
 - Expert authored, manually curated and peer-reviewed.
 - Every pathway is traceable to primary literature.
- Provides tools and datasets for browsing and visualizing pathway data.



www.reactome.org

Reactome – A Minimal PD glyphs



Reactome Complexes

- Any entity type can be united into a complex.
- Use a simple glyph for complexes in pathway diagrams
 - no details shown: decorations, etc.

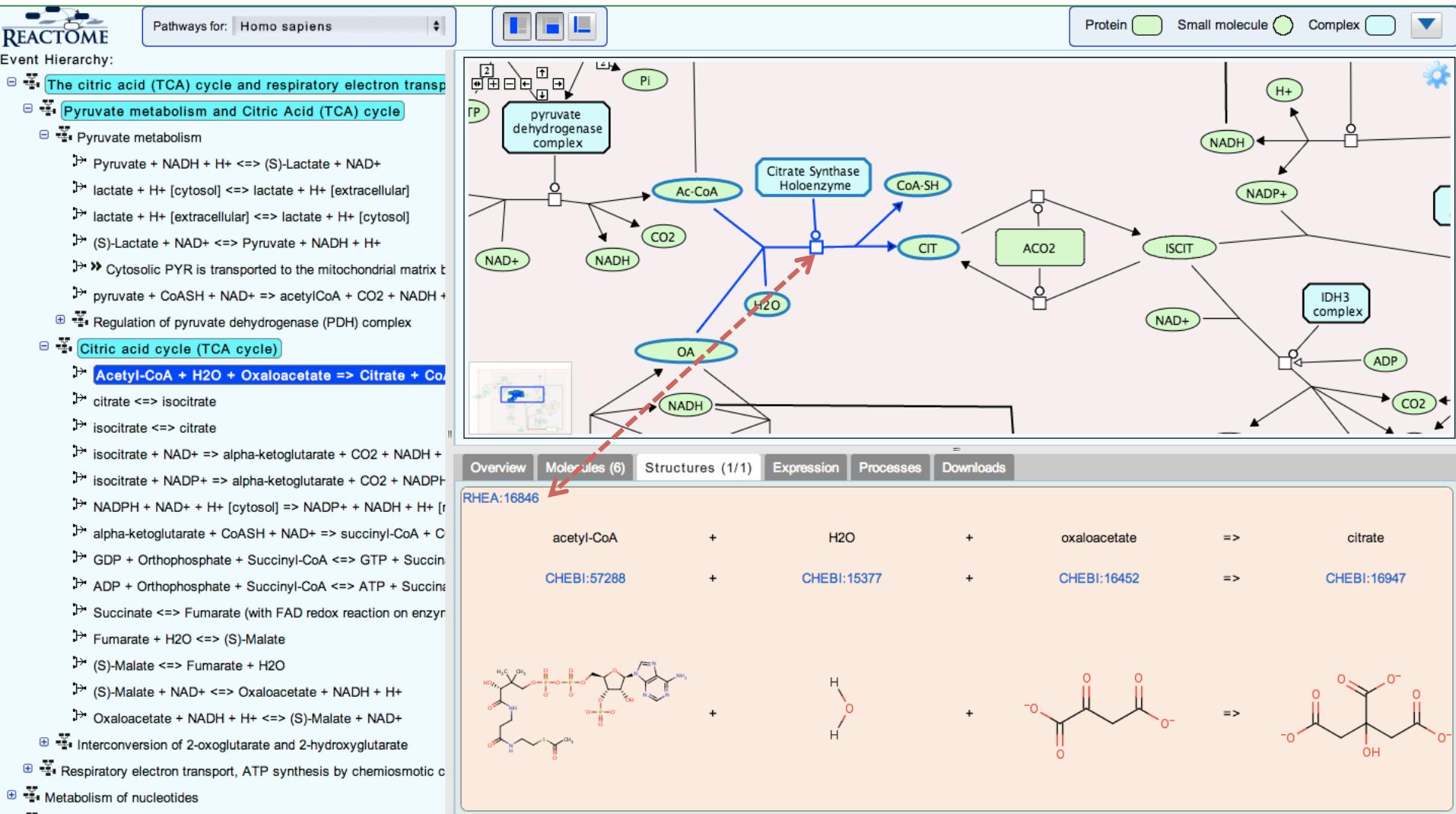
Reactome Sets

Three different types of set:

- CandidateSet: Entities that are hypothesised to do the job.
- DefinedSet: Any one of the set members can do the job.
- OpenSet: A set of example entities, where the number of possible entities is very large, e.g. alcohols.

SBGN Pathway Browser

- Google-map style pathway diagrams



Protein structures from PDBe

REACTOME

Pathways for: Homo sapiens

Event Hierarchy:

- The citric acid (TCA) cycle and respiratory electron transport**
 - Pyruvate metabolism and Citric Acid (TCA) cycle
 - Pyruvate metabolism
 - Pyruvate + NADH + H+ \leftrightarrow (S)-Lactate + NAD+
 - lactate + H+ [cytosol] \leftrightarrow lactate + H+ [extracellular]
 - lactate + H+ [extracellular] \leftrightarrow lactate + H+ [cytosol]
 - (S)-Lactate + NAD+ \leftrightarrow Pyruvate + NADH + H+
 - Cytosolic PYR is transported to the mitochondrial matrix
 - pyruvate + CoASH + NAD+ \Rightarrow acetylCoA + CO2 + NADH +
 - Regulation of pyruvate dehydrogenase (PDH) complex
 - Citric acid cycle (TCA cycle)
 - Acetyl-CoA + H2O + Oxaloacetate \Rightarrow Citrate + CoA
 - citrate \leftrightarrow isocitrate
 - isocitrate \leftrightarrow citrate
 - isocitrate + NAD+ \Rightarrow alpha-ketoglutarate + CO2 + NADH +
 - isocitrate + NADP+ \Rightarrow alpha-ketoglutarate + CO2 + NADPH +
 - NADPH + NAD+ + H+ [cytosol] \Rightarrow NADP+ + NADH + H+ [
 - alpha-ketoglutarate + CoASH + NAD+ \Rightarrow succinyl-CoA + C
 - GDP + Orthophosphate + Succinyl-CoA \leftrightarrow GTP + Succinyl-CoA
 - ADP + Orthophosphate + Succinyl-CoA \leftrightarrow ATP + Succinyl-CoA
 - Succinate \leftrightarrow Fumarate (with FAD redox reaction on enzyme)
 - Fumarate + H2O \leftrightarrow (S)-Malate
 - (S)-Malate \leftrightarrow Fumarate + H2O
 - (S)-Malate + NAD+ \leftrightarrow Oxaloacetate + NADH + H+
 - Oxaloacetate + NADH + H+ \leftrightarrow (S)-Malate + NAD+
 - Interconversion of 2-oxoglutarate and 2-hydroxyglutarate
 - Respiratory electron transport, ATP synthesis by chemiosmotic coupling
 - Metabolism of nucleotides

Protein Small molecule Complex

Overview Molecules Structures (5/5) Expression Processes Downloads

UniProt: P10515 DLAT Chain: A Resolution: 8.80 Coverage: 0.37 PDB Range: [1, 239] UniProt Range: [409, 647]

3b8k PDBe

All other structures for P10515

UniProt: P08559 PDHA1 Chain: C Resolution: 1.90 Coverage: 0.93 PDB Range: [5, 365]

2ozl PDBe

All other structures for P08559

Monofactorial genetic disease

Pathways for: Homo sapiens

Event Hierarchy:

- Disease
 - HIV Infection
 - Influenza Infection
 - Latent infection of Homo sapiens with Mycobacterium tuberculosis
 - Uptake and actions of bacterial toxins
 - Signaling by EGFR in Cancer
 - Amyloids
 - Signaling by FGFR in disease
 - Abnormal metabolism in phenylketonuria
 - Mucopolysaccharidoses**
 - MPS I - Hurler syndrome**
 - Defective IDUA does not hydrolyse Lido
 - Glycosaminoglycan metabolism
 - MPS II - Hunter syndrome
 - MPS IIIA - Sanfilippo syndrome A
 - MPS IIIB - Sanfilippo syndrome B
 - MPS IIIC - Sanfilippo syndrome C
 - MPS IID - Sanfilippo syndrome D
 - MPS IV - Morquio syndrome A
 - MPS IV - Morquio syndrome B
 - MPS VI - Maroteaux-Lamy syndrome
 - MPS VII - Sly syndrome
 - MPS IX - Natowicz syndrome
 - Diseases associated with visual transduction
 - PI3K/AKT Signaling in Cancer
 - Signaling by NOTCH1 in Cancer
 - Abnormal conversion of 2-oxoglutarate to 2-hydroxyglutarate
 - Glycogen storage diseases
 - Defects in vitamin and cofactor metabolism
 - Signaling by TGF-beta Receptor Complex in Cancer
 - Signaling by WNT in cancer
 - Processing-defective Hh variants abrogate ligand secretion

Reactome Pathway Browser

Protein Small molecule Complex

Event Hierarchy:

Pathway: MPS I - Hurler syndrome

Species: Homo sapiens

Stable Identifier: REACT_147857.2

Summation:

Mucopolysaccharidosis type I (MPS I, Hurler syndrome, Hurler's disease, gargoyleism, Scheie, Hirler-Scheie syndrome; MIM:607014, 607015 and 607016) is an autosomal recessive genetic disorder where there is a deficiency of alpha-L iduronidase (IDUA, MIM:252800), a glycosidase that removes non-reducing terminal alpha-L-iduronide residues during the lysosomal degradation of the glycosaminoglycans heparan sulphate and dermatan sulphate (McKusick 1959). In 1992, Scott and colleagues were able to clone and purify the gene that encodes this enzyme, IDUA, demonstrating that it spans approximately 19 kb and contains 14 exons (Scott et al. 1992).

Hurler syndrome is named after a German paediatrician Gertrud Hurler (1919, no reference available). The result is build up of heparan sulfate and dermatan sulfate in the body and increased urinary excretion of these GAGs. Symptoms and signs include hepatosplenomegaly, dwarfism, unique facial features, corneal clouding, retinopathy, progressive mental retardation appears during childhood and early death can occur due to organ damage (Campos & Monaga 2012). MPS I is divided into three subtypes, ranging from severe to mild phenotypes; Mucopolysaccharidosis type IH (MPSIH, Hurler syndrome, MIM:607014), mucopolysaccharidosis type IH/S (MPSIH/S, HurlerScheie syndrome, MIM: 607015) and mucopolysaccharidosis type IS (MPSIS, Scheie syndrome, MIM: 607016) respectively (McKusick 1972).

Disease:

mucopolysaccharidosis I

Polygenic disease

Pathways for: Homo sapiens

REACTOME

Event Hierarchy:

- Disease
 - HIV Infection
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 - Uptake and actions of bacterial toxins
 - Signaling by EGFR in Cancer**
 - Signaling by EGFR
 - Signaling by constitutively active EGFR
 - Amyloids
 - Signaling by FGFR in disease
 - Abnormal metabolism in phenylketonuria
 - Mucopolysaccharidoses
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 - PI3K/AKT Signaling in Cancer
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 - Glycogen storage diseases
 - Defects in vitamin and cofactor metabolism
 - Signaling by TGF-beta Receptor Complex in Cancer
 - Signaling by WNT in cancer
 - Processing-defective Hh variants abrogate ligand secretion
- DNA Repair
- DNA Replication
- Extracellular matrix organization
- Gene Expression
- Hemostasis
- Immune System
- Membrane Trafficking
- Metabolism
- Metabolism of proteins
- Muscle contraction
- Neuronal System

Tour this pathway browser? Hide

Protein Small molecule Complex

Overview Molecules Structures Expression Analysis Processes Downloads

Signaling by EGFR in Cancer Species: Homo sapiens

Stable Identifier
REACT_115871.4

Summation

The pathway "Signaling by EGFR in Cancer" shows "Signaling by constitutively active EGFR" in parallel with "Signaling by EGFR". This allows users to compare signaling by constitutively active EGFR cancer mutants with the wild-type EGFR protein. Red lines emphasize cancer related events and physical entities, while wild-type entities and events are shaded. Please refer to "Signaling by constitutively active EGFR" and "Signaling by EGFR" for detailed pathway summations.

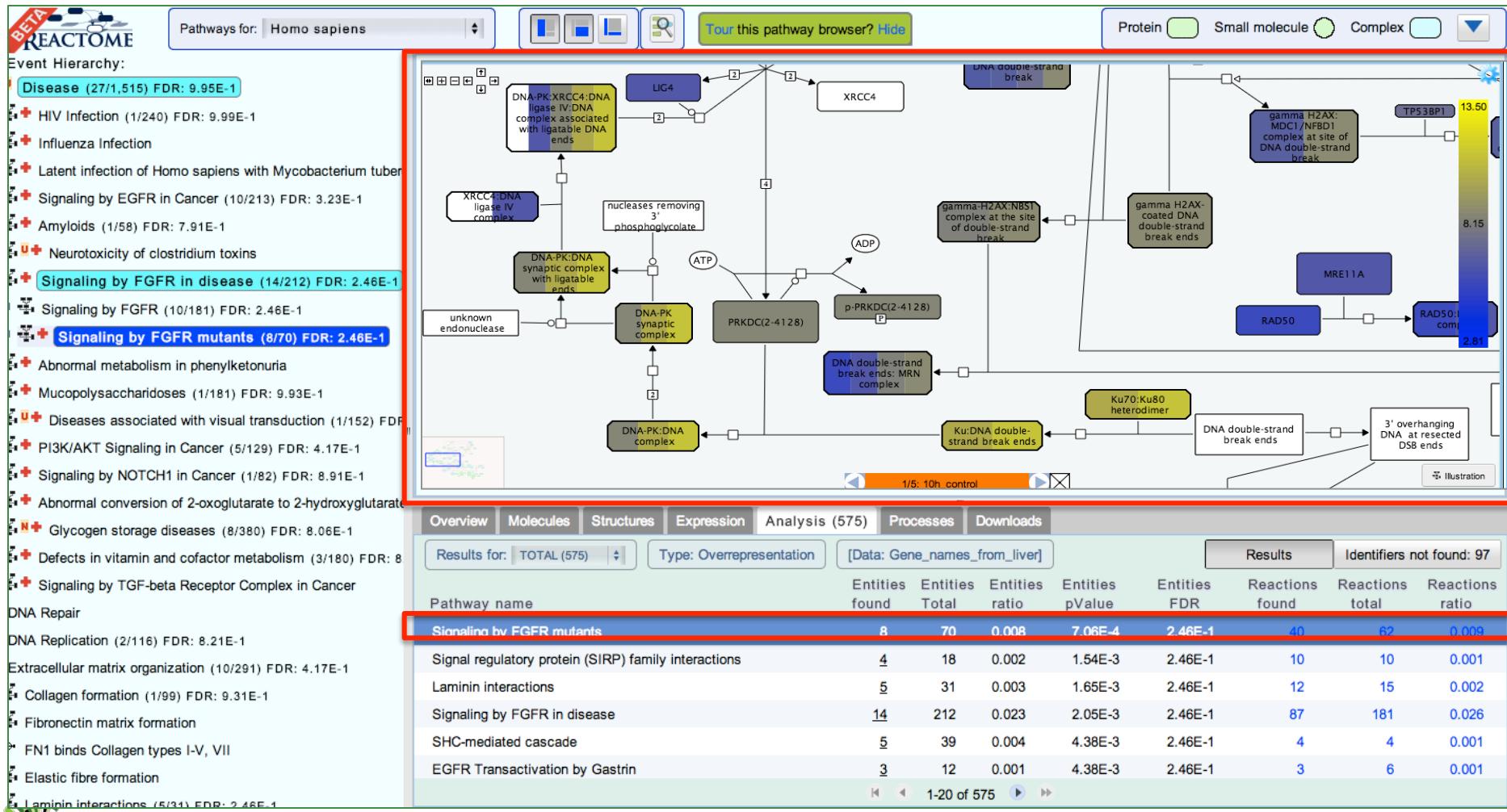
Disease

cancer

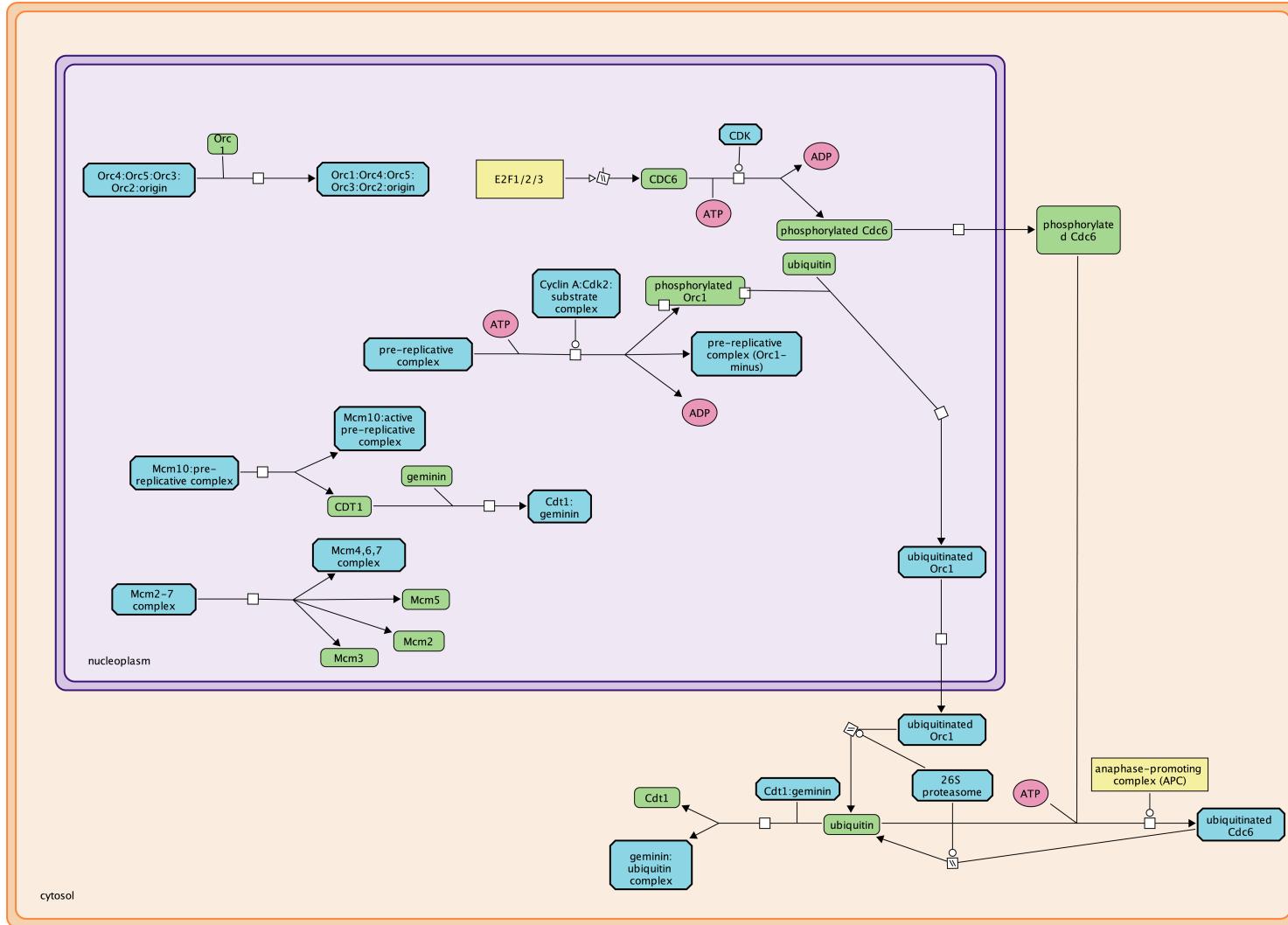
Pathway Diagrams support Reactome Tools

- Pathway Mapping and Enrichment Analysis
- Expression Overlay onto Pathways
- Compare Pathways between Species

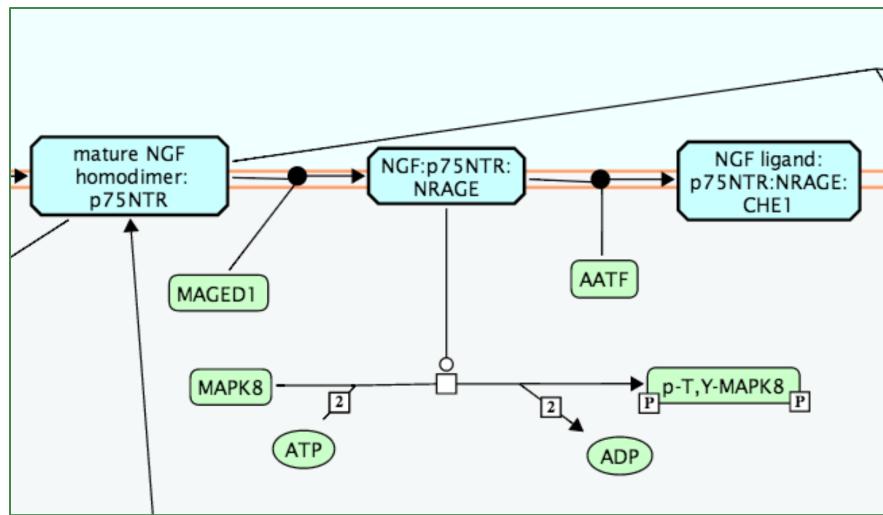
In 2 months reached 6,622 analysis
(15/09/14)



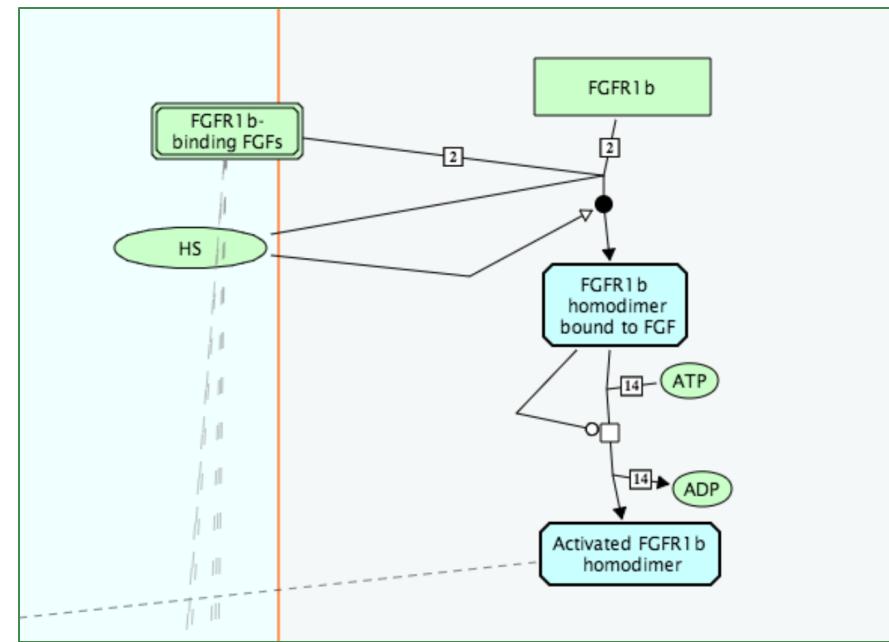
“Mutiny on the Bounty” - Entity Colour Scheme



Phosphorylation – simple entity vs complex

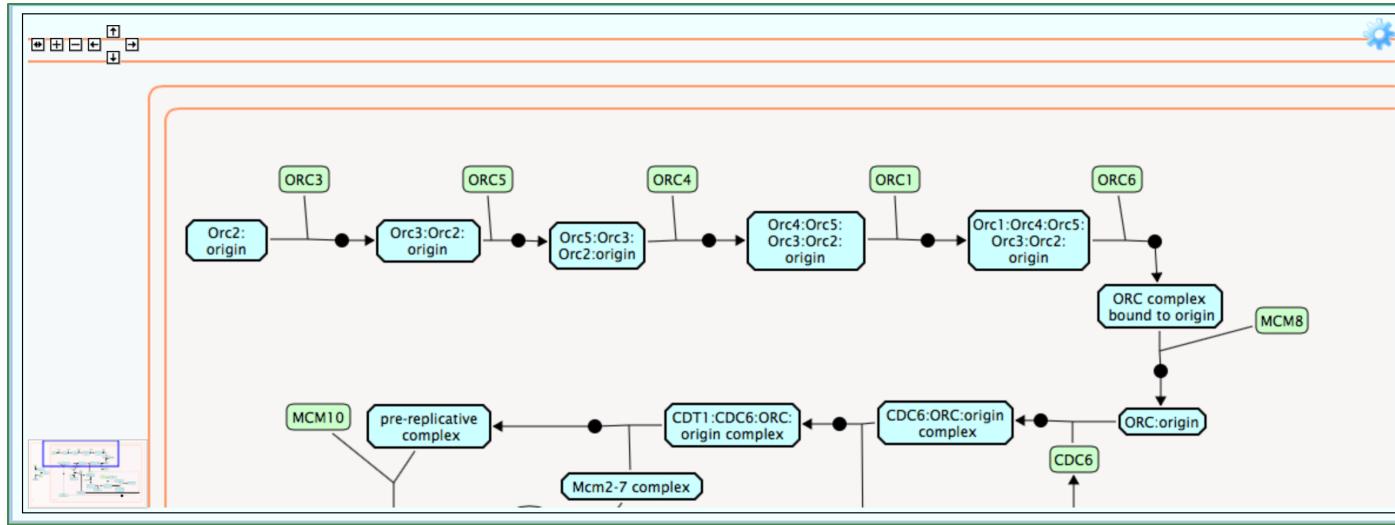


NRAGE activates JNK

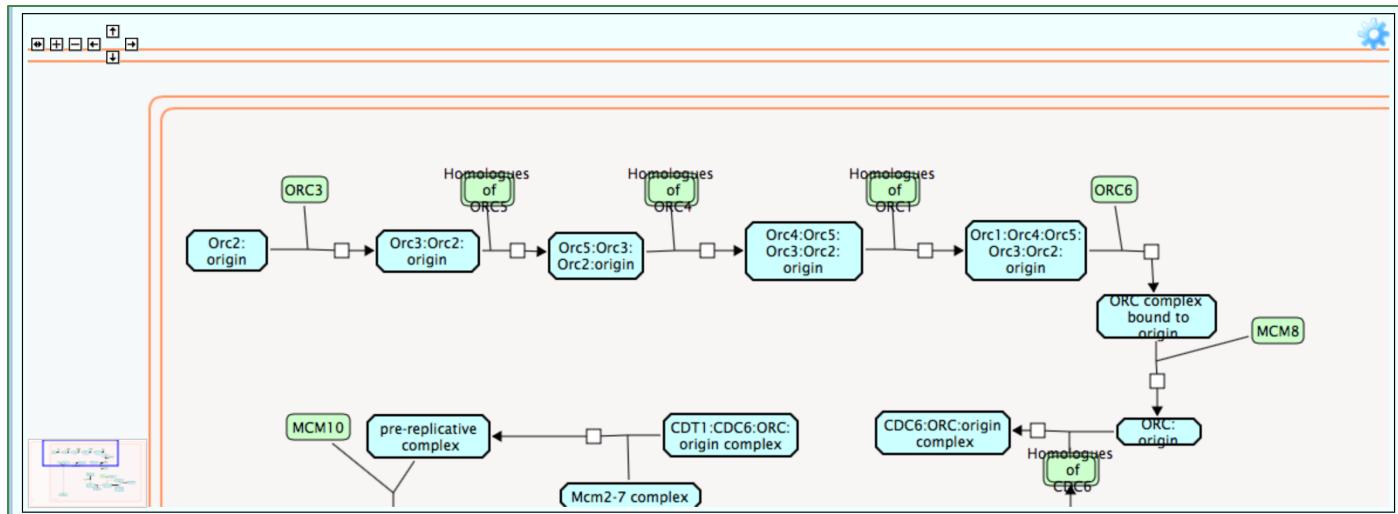


Autocatalytic phosphorylation of FGFR1b

Labels

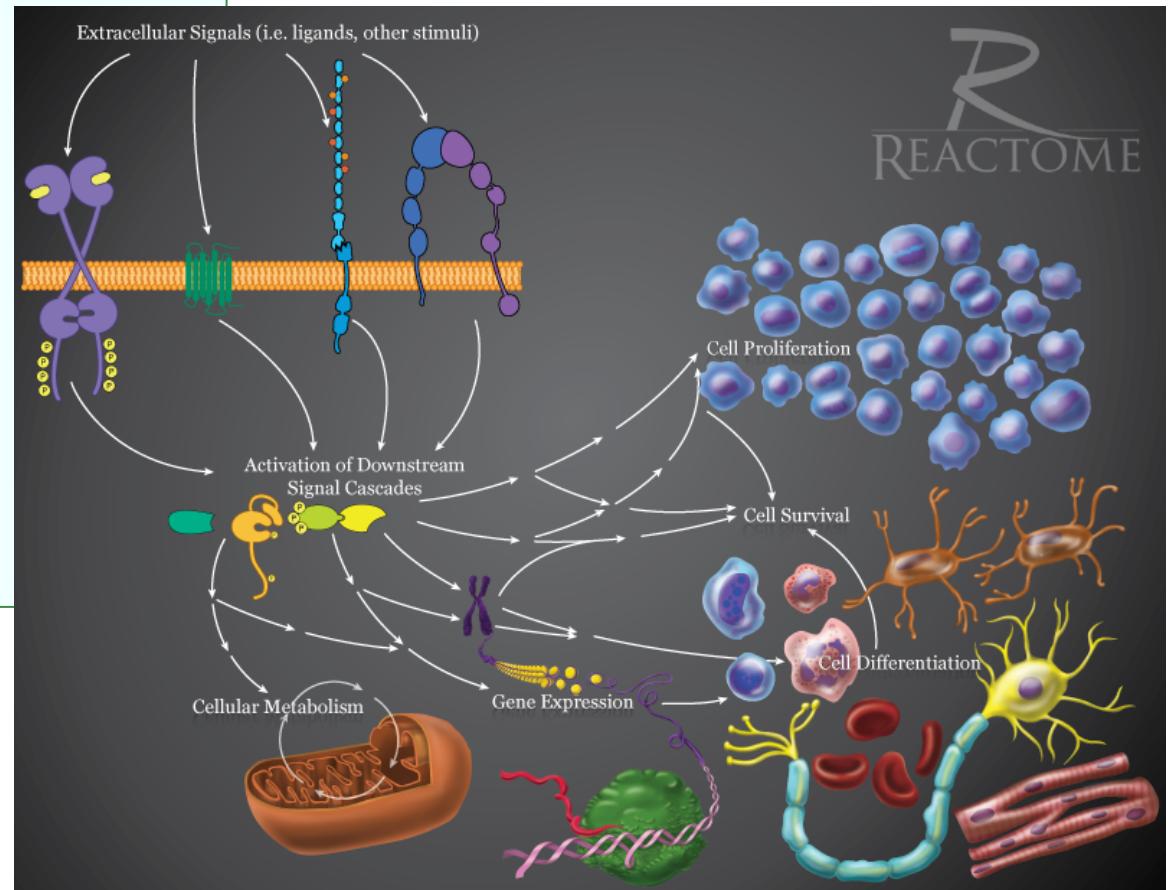
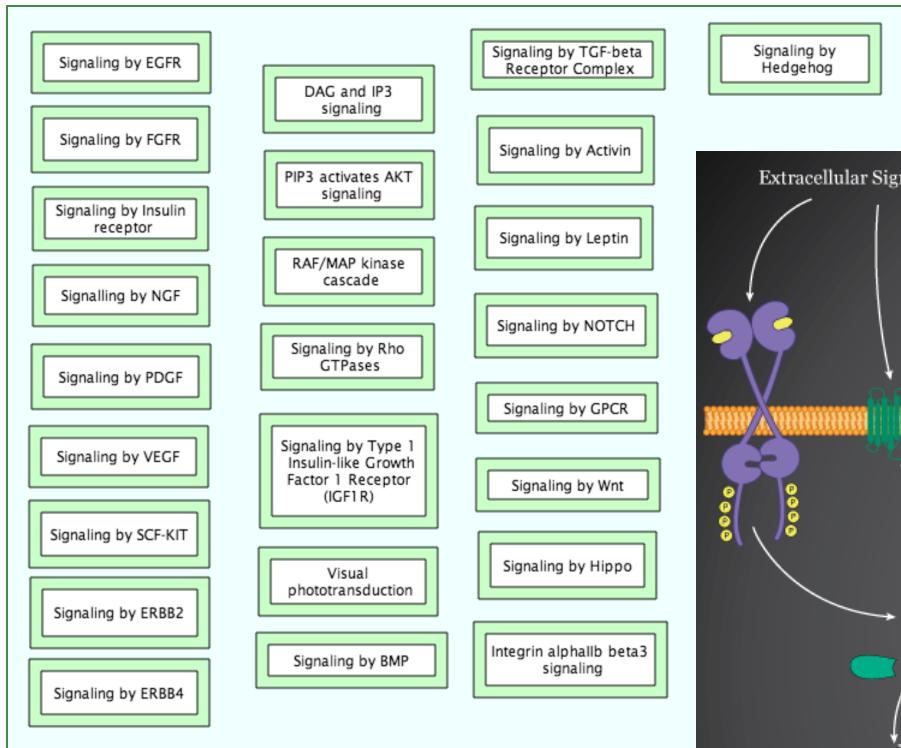


Human



Plant

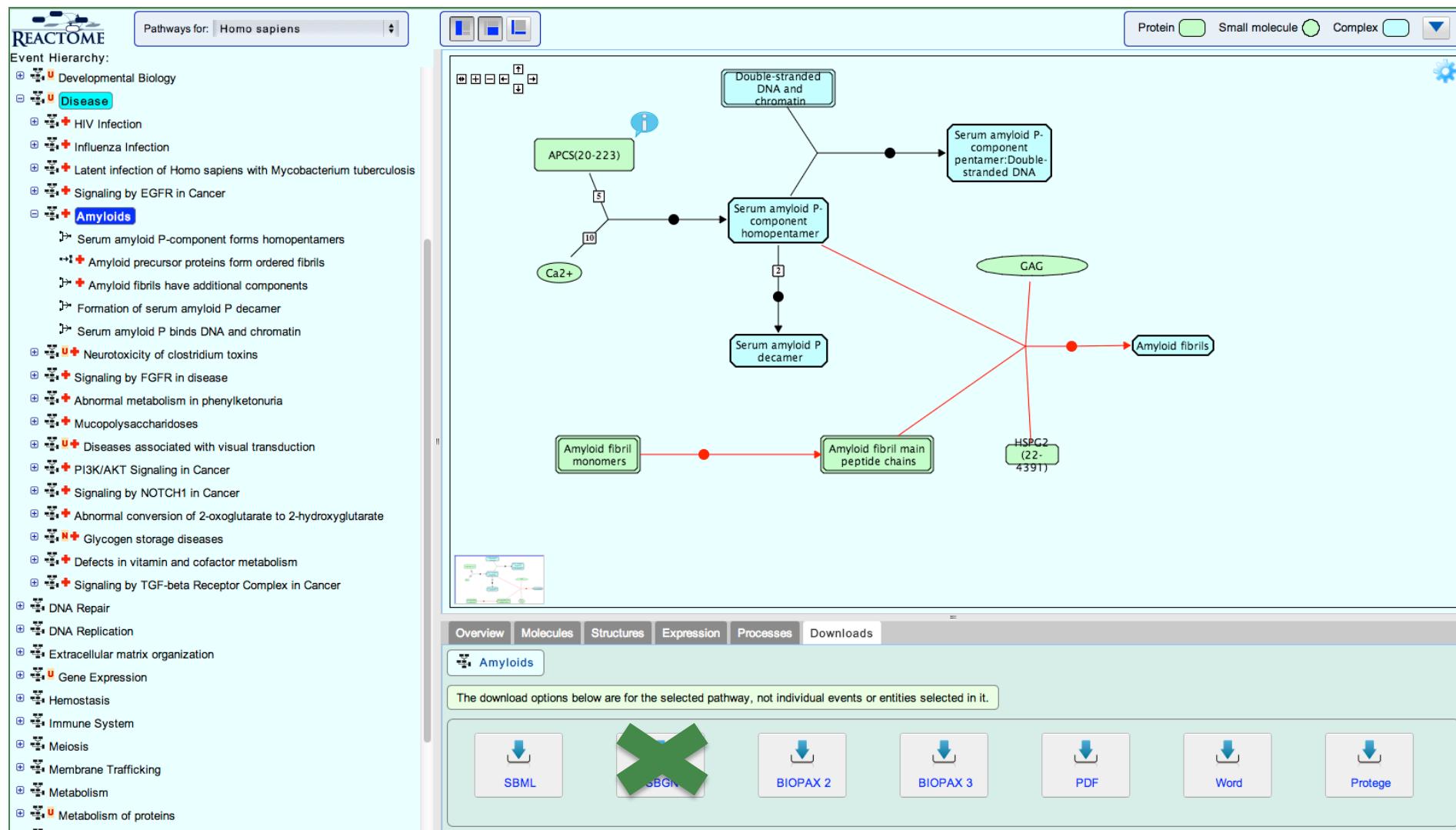
Integrating Illustrations



Reactome-SBGN Mapping

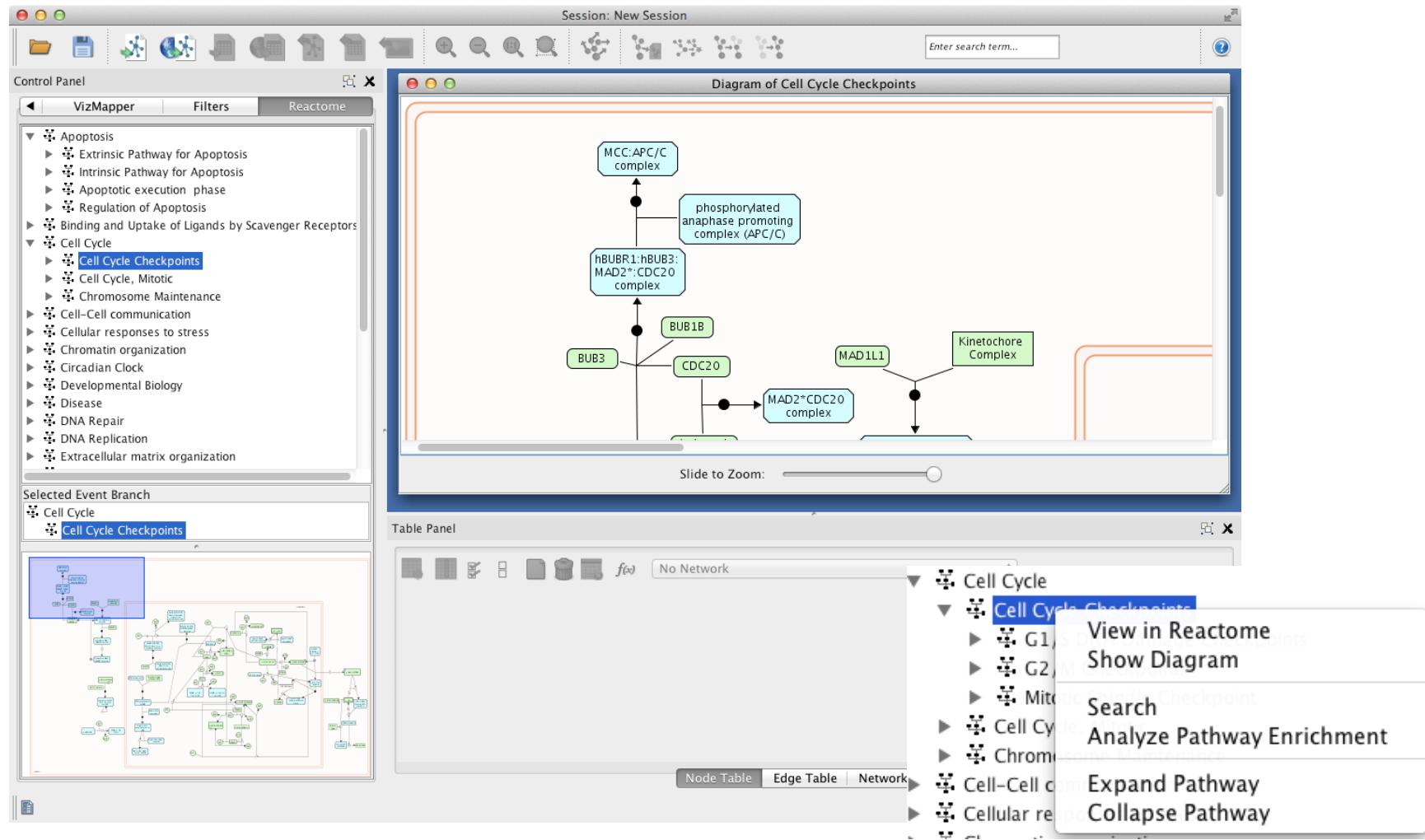
- LibSBGN and SBGN-ML
- We extract the following from Reactome's diagrams:
 - Compartments
 - Entities (proteins, complexes, compounds, complexes)
 - Reactions
 - Edges

Sorry: SBGN Export is missing



Reactome Pathways in Cytoscape

- Display Reactome pathways in Cytoscape



Display Reactome Pathways in the FI Network View

- Convert Reactome pathway into Reactome FI network

The screenshot illustrates the process of displaying Reactome pathways within the Reactome FI Network View. On the left, the 'Control Panel' shows a tree view of 'Cell Cycle Checkpoints' under the 'Reactome' tab. A selected event branch, 'Cell Cycle Checkpoints', is expanded to show a detailed pathway diagram. This diagram depicts a sequence of biological events: ATP-dependent phosphorylation of Cdc25C at Ser216, formation of a phospho-Cdc25C:14-3-3 protein complex, recruitment and activation of Chk1, and subsequent phosphorylation and activation of ATM. The diagram also shows the association of phospho-Cdc25C(Ser 216) with 14-3-3 proteins, retention of phospho-Cdc25C:14-3-3 complexes within the cytoplasm, phosphorylation of Wee1 kinase by Chk1, and Wee1-mediated phosphorylation of Cyclin B1:phospho-Cdc2 complexes. On the right, the 'FI Network for Diagram of Cell Cycle Checkpoints' window displays a complex network graph where nodes represent proteins and interactions are represented by edges. Below this main window is a 'Table Panel' showing details about the network, such as its ID (69620) and name ('FI Network for Diagram of Cell Cycle Checkpoints').

Acknowledgements



- Michael Caudy
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