PATHWAY STUDIO

Guide to Building Pathways in Mammal using Pathway Studio® Web

Pathway Studio Web   Document Version 1.2

The ResNet Mammal database contains a vast amount of information derived from Elsevier's large collection of biomedical literature as well as additional third party content. Pathway Studio provides you the tools to easily access this large dataset to build *de novo* pathways based on your specific research interests.

This guide will demonstrate basic workflows for building networks. The beginning of your inquiry can be a single protein or a collection of proteins, or other entity types such as: small molecules, diseases, cell processes, etc. The guide is divided into two sections:

> **Section 1. Demonstrations of the steps to follow and tools to use for building a network** and
> **Section 2. Examples of how to build networks that answer specific biological questions.**

In addition to this guide, please visit Elsevier's Pathway Studio support site for additional support and training resources: http://www.elsevier.com/online-tools/pathway-studio/customer-support#guides-and-manuals including information on how to arrange web-based or on-site training programs.


Section 1: Steps to follow to Build Networks in Pathway Studio

A. Add protein(s) to a new pathway view, select the protein(s) (or other entity types) and open the building pathway wizard to access the algorithms for building different types of networks.
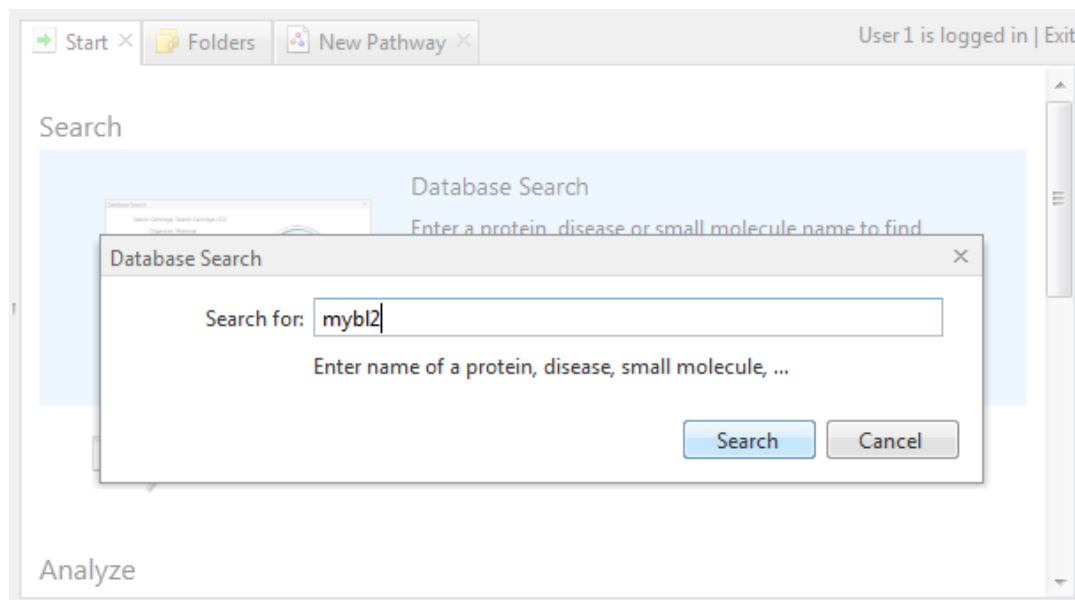
Open a new pathway view by selecting "New Pathway" from the Information Pane on the left. A New Pathway tab will open in the right.
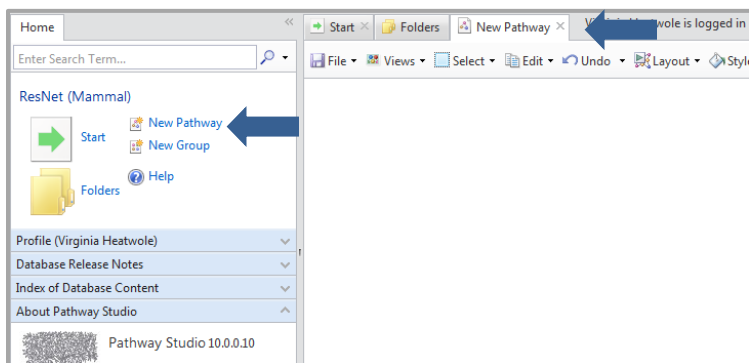

Go to the Start tab and select Search>Database Search>Launch.
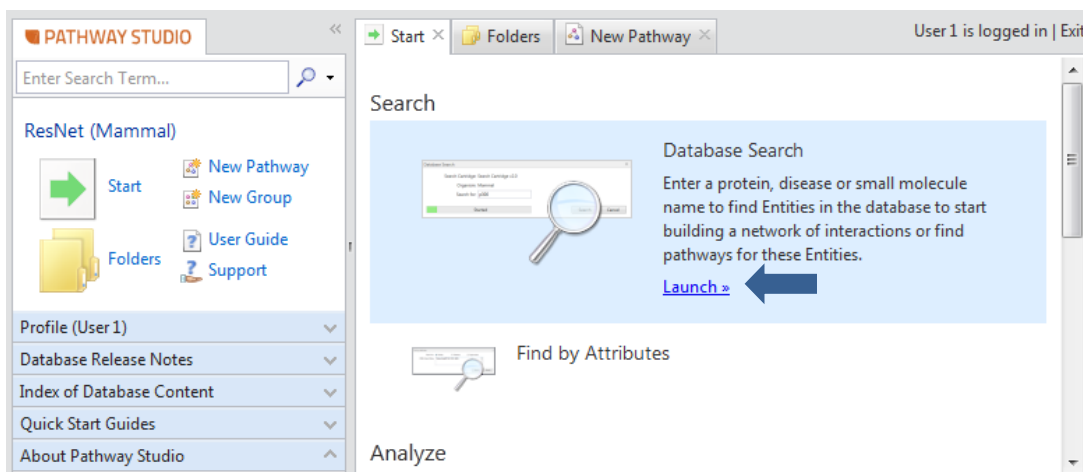
In the Database Search window, type in the entity (protein / gene / complex / functional class / small molecule / disease / cell process) name and select "Search."


The results of your search will appear in the List Pane at the bottom. Find the protein you are interested in, right-click to copy it and the right click to paste it in the New Pathway view in the upper-right. You can repeate this if you have more than one entity you are interested in using to build a pathway.
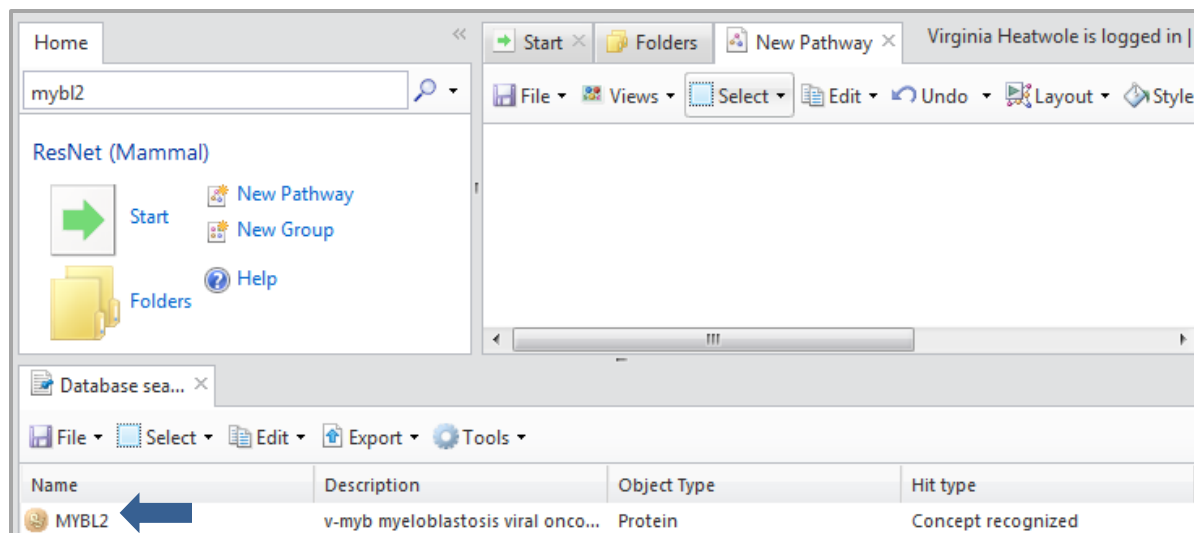
Find the entity you are interested in, right-click to copy it and then right click to paste it in the New Pathway view in the upper-right.
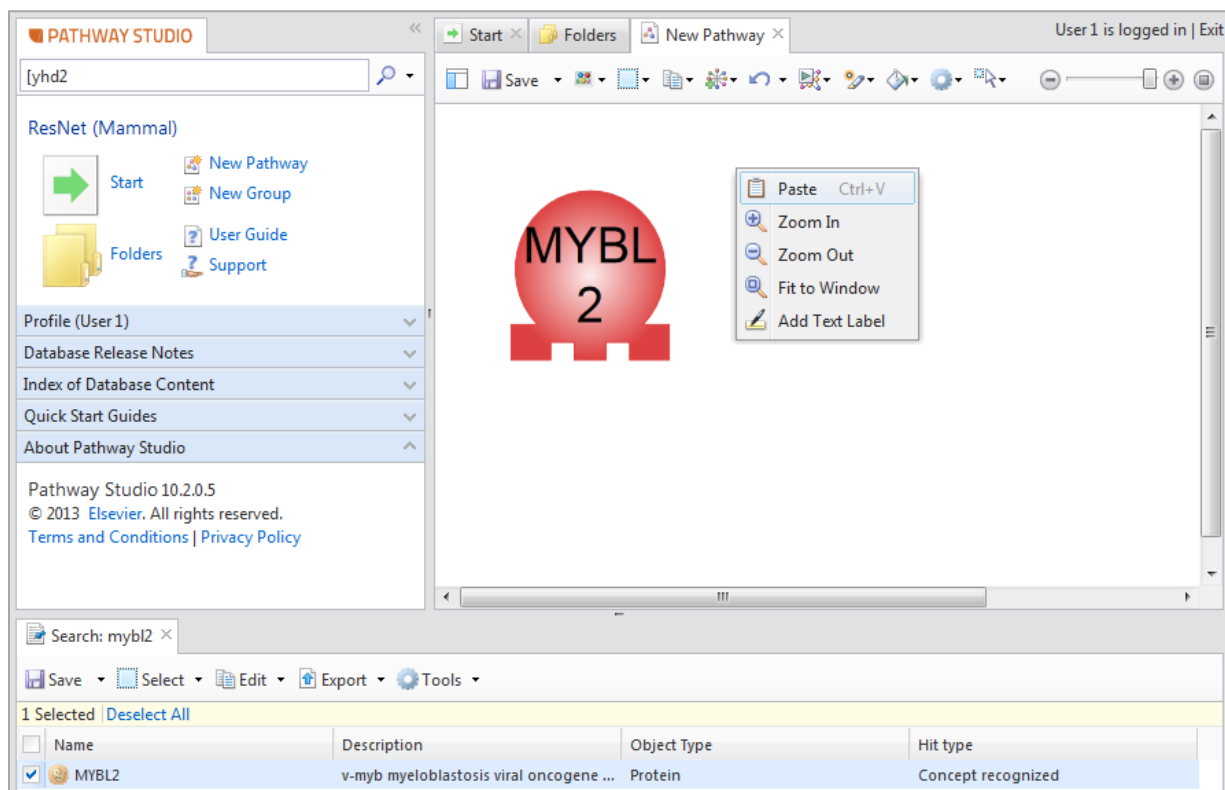
Repeat this process to add more entities if needed. Once you have added all your desired entities to the New Pathway view, select them. Selected entities have a halo around them. Next, go to the Add menu and select "Neighbors or Connections".
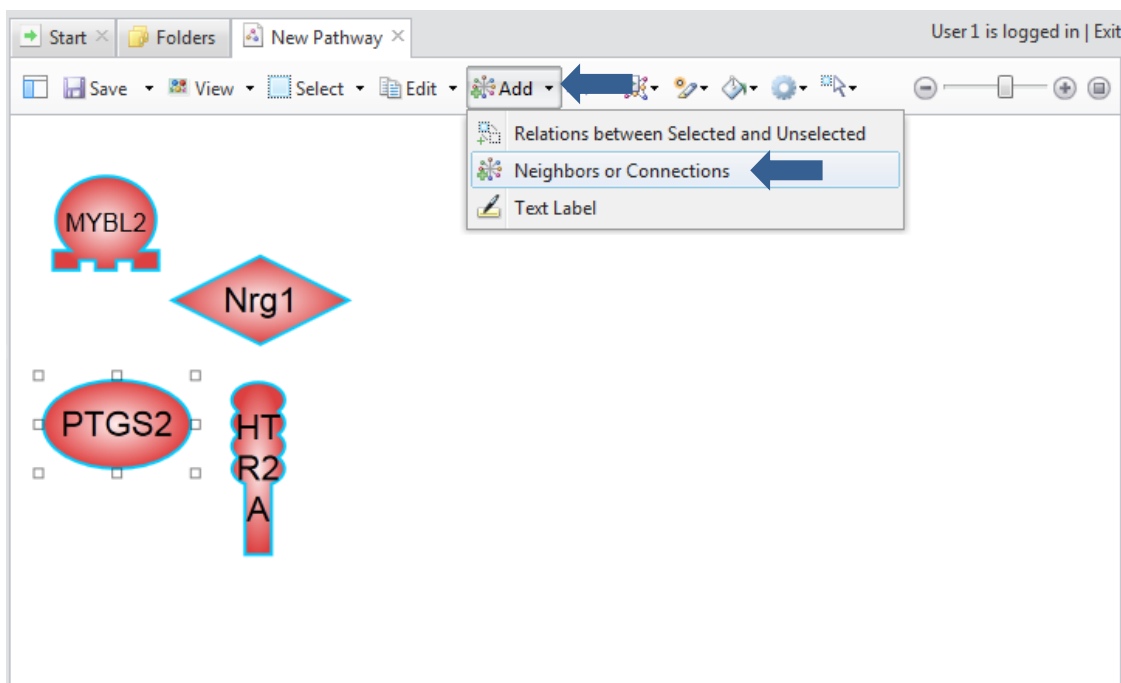
B. Select the algorithm most appropriate for the desired resultant network and select relation directionality.

After selecting "Build Pathway" a wizard appears. By simply walking through the steps of the wizard you can build a pathway that answers biological questions (see Section 2 for specific examples).

Wizard Step 1: Select the desired build pathway algorithm and the directionality of the relationships.
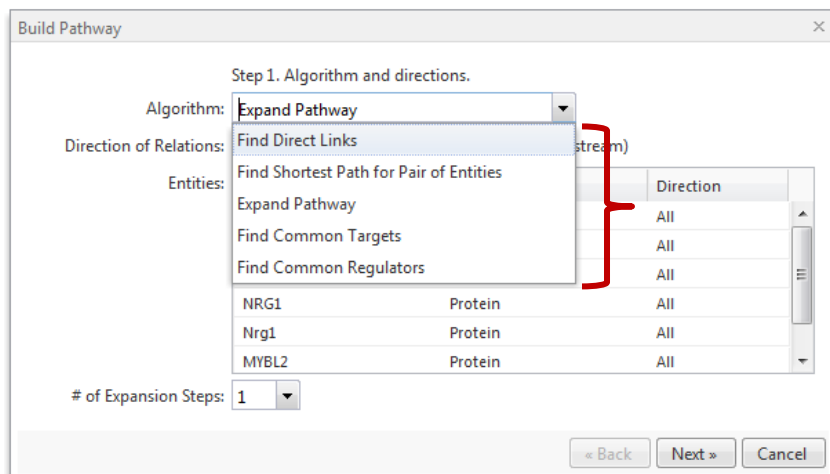
The select algorithm type dialog provides you with the choices to:

Find Direct Links: find relationships between two or more selected entities on the network diagram.
Find Shortest Path for a Pair of Entities: find relationships between two selected entities on the network diagram, adding entities as needed to form the relationship.
**Expand Pathway**: find entities directly connected to the entity / entities selected on the network diagram from the ResNet database.
Find Common Targets: find one or more downstream targets that are regulated by at least two or more of the selected entities in the network diagram.
Find Common Regulators: find one or more upstream regulators that regulate two or more of the selected entities in the network.
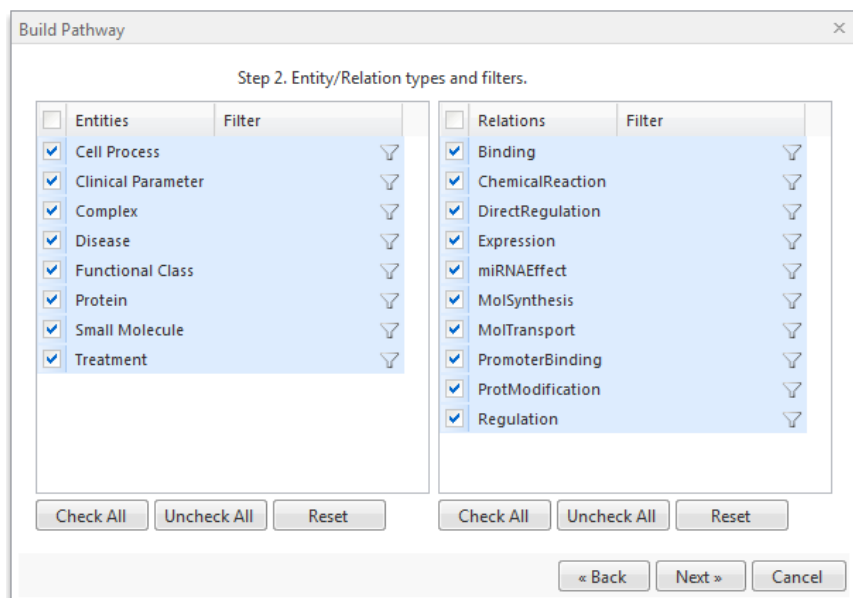
Wizard Step 1 (continued): select the direction of the relations to be added to your network (relative to your selected entities). Note: The relation "binding" does not have directionality.
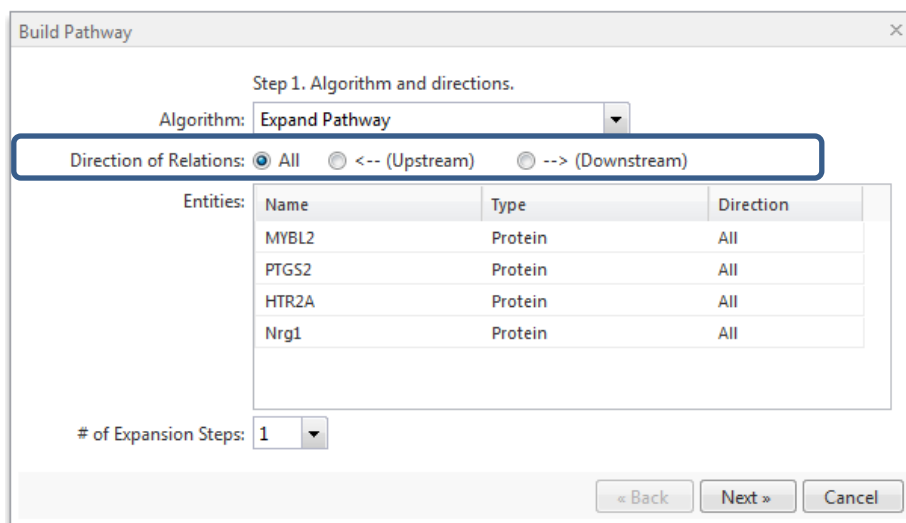
C. Select the entity type(s) and relationship type(s) for the desired network.

Wizard Step 2: Select the desired entities and relations to add to your network.

(Entity types and Relation Types available in this vew are dependent on the content of the active database.)

After selecting the desired entity and relation types, select "Next" to build the pathway.

Entity Types:

Cell Process* – biological processes, most coincide with Gene Ontology (container entity)

Clinical Parameter – measured parameters of the human body used in clinical practice

Complex* – several polypeptides that form a complex via physical interactions (container entity)

Disease – health conditions and disease terms from MeSH

Functional Class* – most functional classes coincide with Gene Ontology. (container entity)

Medical Procedure – a medical procedure used in clinical practice

Protein – defined by Entrez Gene (represents both genes and the gene products – proteins. miRNAs also belong to this category)

Small Molecule – naturally occurring metabolites in mammalian cells (ResNet Mammal); also drugs and non-naturally occurring in mammalian cell small molecules and metabolites (ChemEffect).

Treatment – non-chemical treatments and environmental conditions, such as cold shock.

* Cell Process, Complex and Functional Class are container entities which can have proteins mapped to them.

Relation Types:

Binding – direct physical interaction between two molecules.

ChemicalReaction – enzyme catalyzed reaction involving small molecules.

DirectRegulation – influences target activity by direct physical interaction (excluding promoter binding interactions).

Expression – regulator changes protein abundance by affecting levels of transcript or protein stability.

miRNAEffect – the inhibitory effect of a miRNA on its mRNA target.

Regulation – changes the activity of the target by an unknown mechanism (may be direct or indirect). *This is a less specific relation type than others provided.*

MolSynthesis – regulator changes the concentrations of the target (usually a small molecule target).

MolTransport – a regulator that changes the localization of the target (molecular translocation, export, import etc.)

PromoterBinding – a regulator that binds to the promoter of a gene.

ProtModification – a regulator that changes the modification of the target molecule, usually by a direct interaction such as phosphorylation, glycosylation, acetylation etc.

The Preview window shows the summary of the pathway. To view the pathway in the graph view, select "Finish."
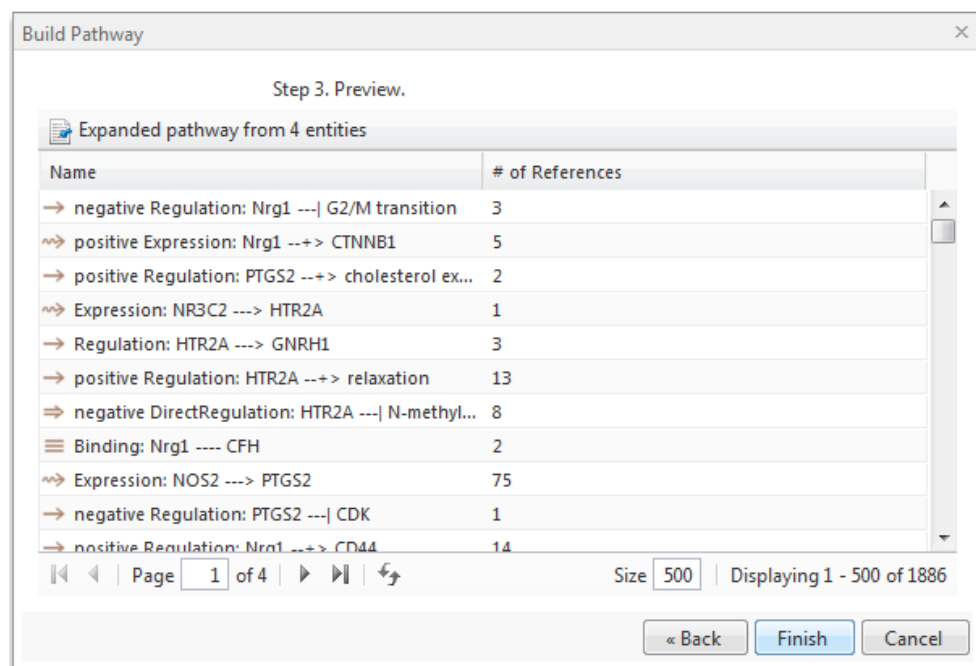
With these tools you can query the ResNet database to answer specific biological questions.

The following section gives some examples of pathway building work flows. Keep in mind that these examples do not show all possible questions that can be answered using Pathway Studio and Mammal. They serve only as introductory examples.

Section 2: Examples of biological questions and the pathway building wizard settings used to answer questions using the ResNet database.

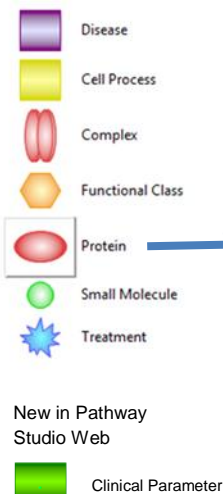## A. What are all the known associations with my protein in the ResNet database?

Add a protein to a new pathway view and select the protein.

Wizard settings: **algorithm**: Expand Pathway; **directionality**: All; **entity type**: check all; **relation type**: check all.
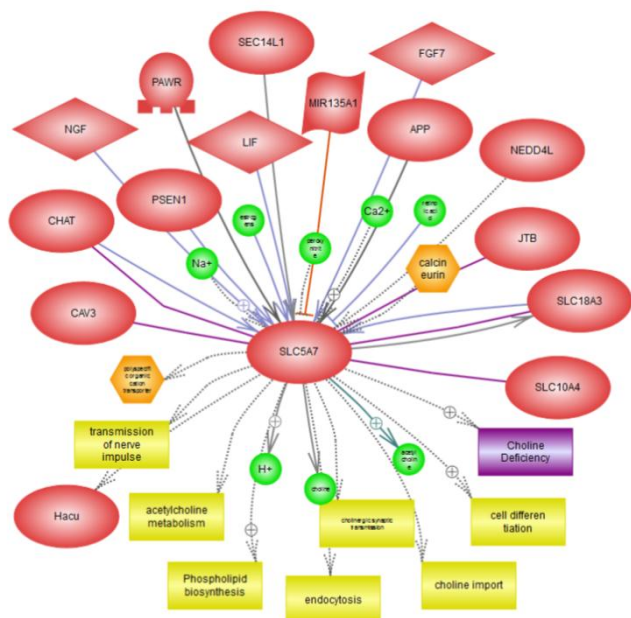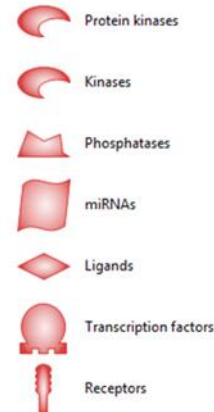

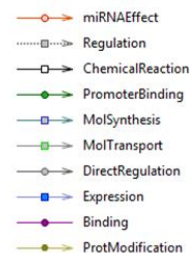The "by type" style sheet colors relation types for easy identification.
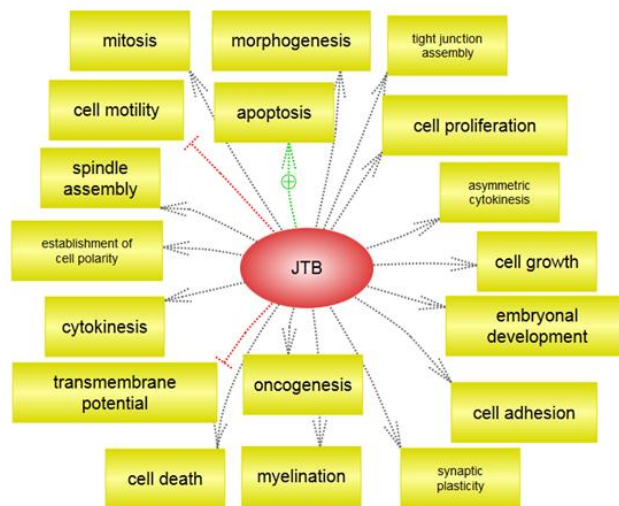
B. What cell processes are my protein involved in?

Add a protein to a new pathway view and select the protein.

Wizard settings: **algorithm**: Expand Pathway; **directionality**: downstream; **entity type**: cell process; **relation type**: regulation.
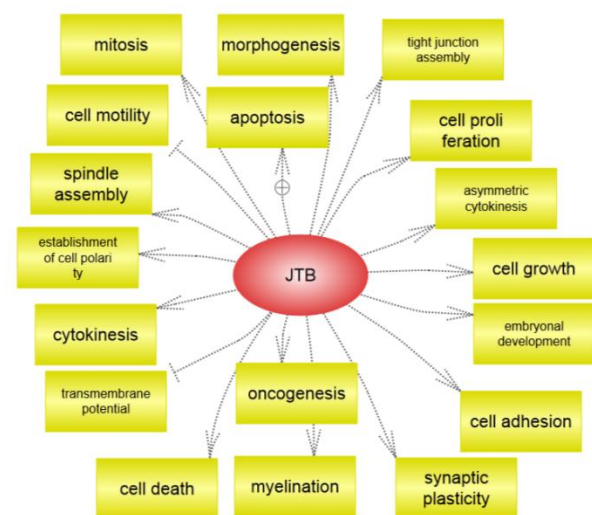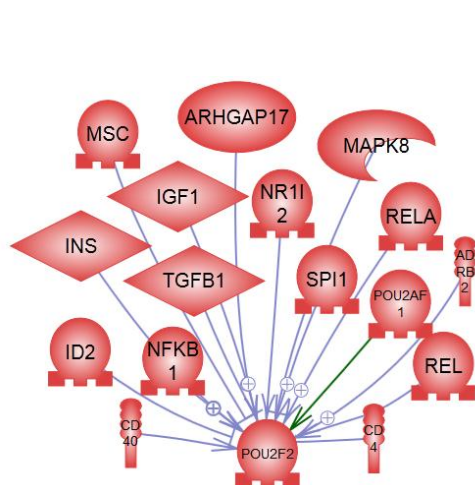

Style sheet: By Type   Style sheet: By Effect (positive/negative/unknown)
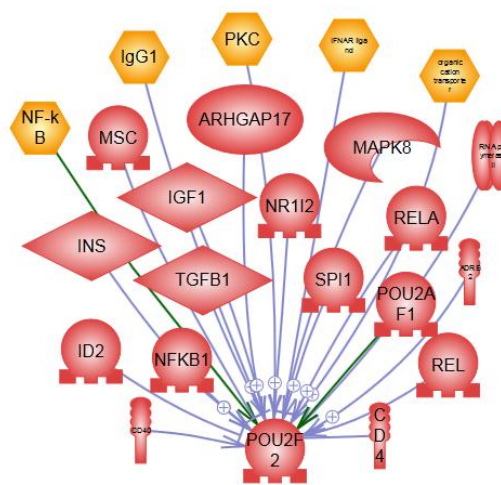
C. What proteins regulate the expression of my protein?

Add a protein to a new pathway view and select the protein.
Wizard settings: **algorithm**: Expand Pathway; **directionality**: upstream; **entity type**: protein or protein/functional class/complex;
relation type: expression & promoter binding.

Proteins only   Proteins, complexes and functional classes

For ONLY transcriptional regulation use only the relation type "promoterbinding".

It is common to group "proteins", "complexes" and "functional classes" together when examining protein mediated activities.

D. Do any proteins modify (ex. phosphorylate, dephosphorylate etc.) my protein?

Add a protein to a new pathway view and select the protein.
Wizard settings: **algorithm**: Expand Pathway; **directionality**: upstream; **entity type**: protein or protein/functional class/complex;
**relation type**: direct regulation
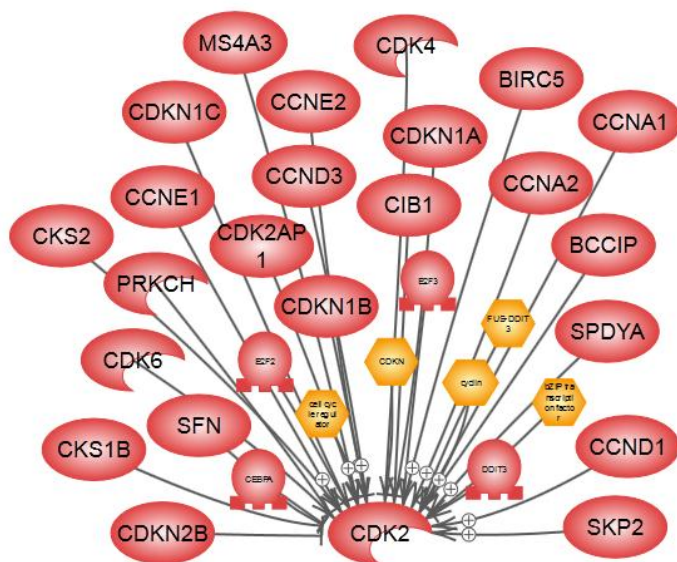
DirectRegulation describes events where regulation of a protein (such as modification) occurs through a direct physical interaction.

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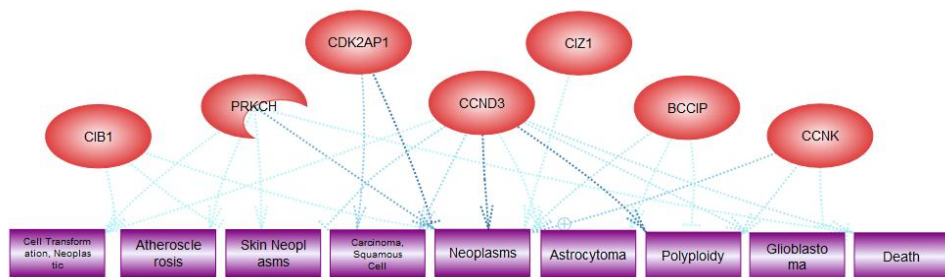## E. Are my proteins associated with any similar diseases?

Add proteins to a new pathway view and select all the proteins.
Wizard settings: **algorithm**: Find Common Targets; **directionality**: NA; **entity type**: disease; **relation type**: regulation

The "Common targets" algorithm means a target for two or more members of the selected group.
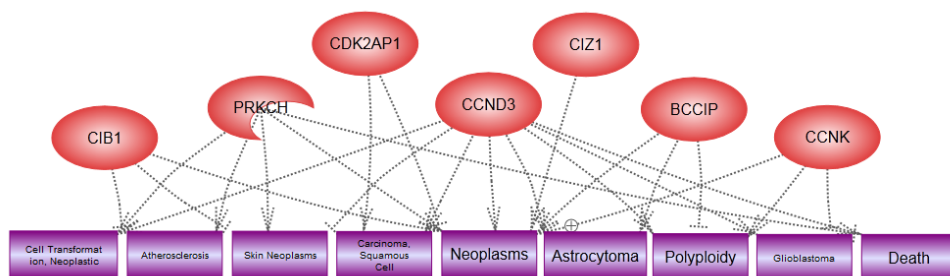

Style Sheet:
By Type

Style Sheet:
By Reference
Count

Darker lines represent more references for a relation. The higher the number of references for a relation, the more times it is described in the literature and the more confidence you can have in the relationship.

F. Do any of my proteins physically interact with each other?

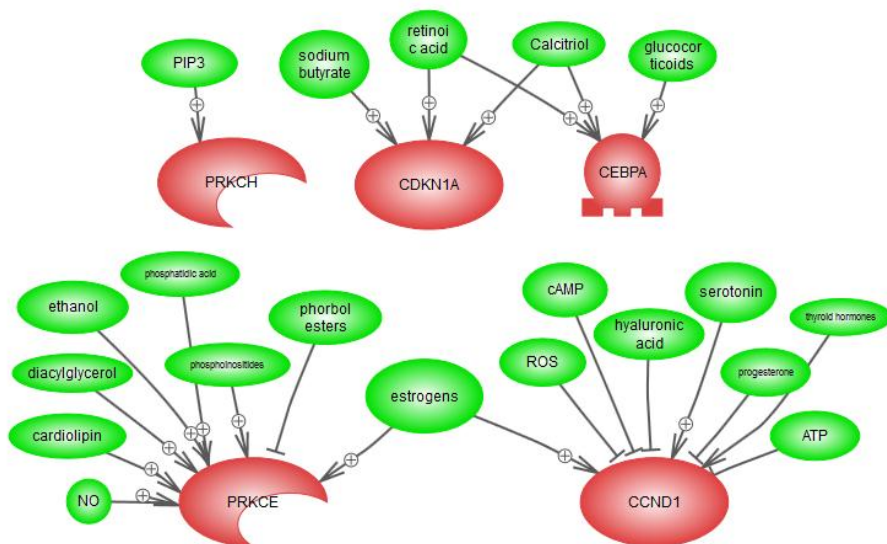Add proteins to a new pathway view and select all the proteins.
Wizard settings: **algorithm**: Find Common Targets; **directionality**: NA; **entity type**: NA; **relation type**: binding, direct regulation, protmodification
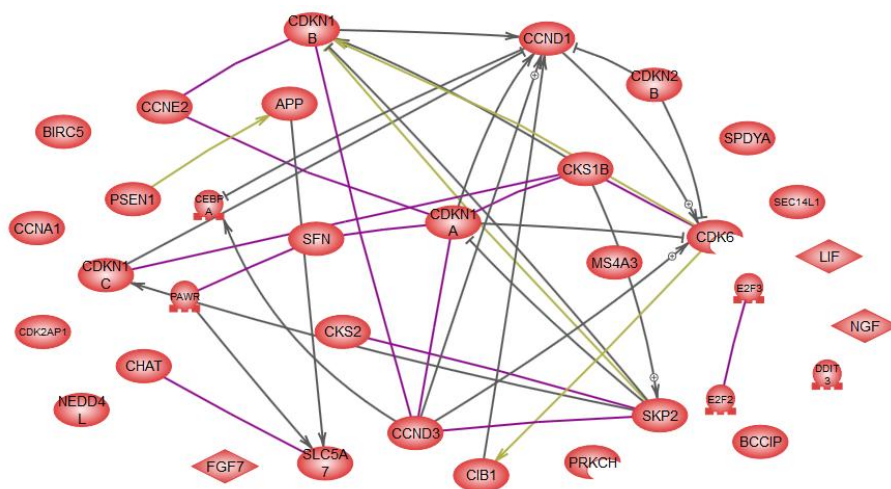
G. Are my proteins regulated by any small molecules?

Add proteins to a new pathway view and select all the proteins.
Wizard settings: **algorithm**: Expand Pathway; **directionality**: upstream; **entity type**: small molecules; **relation type**: regulation/moltransport/expression/direct regulation
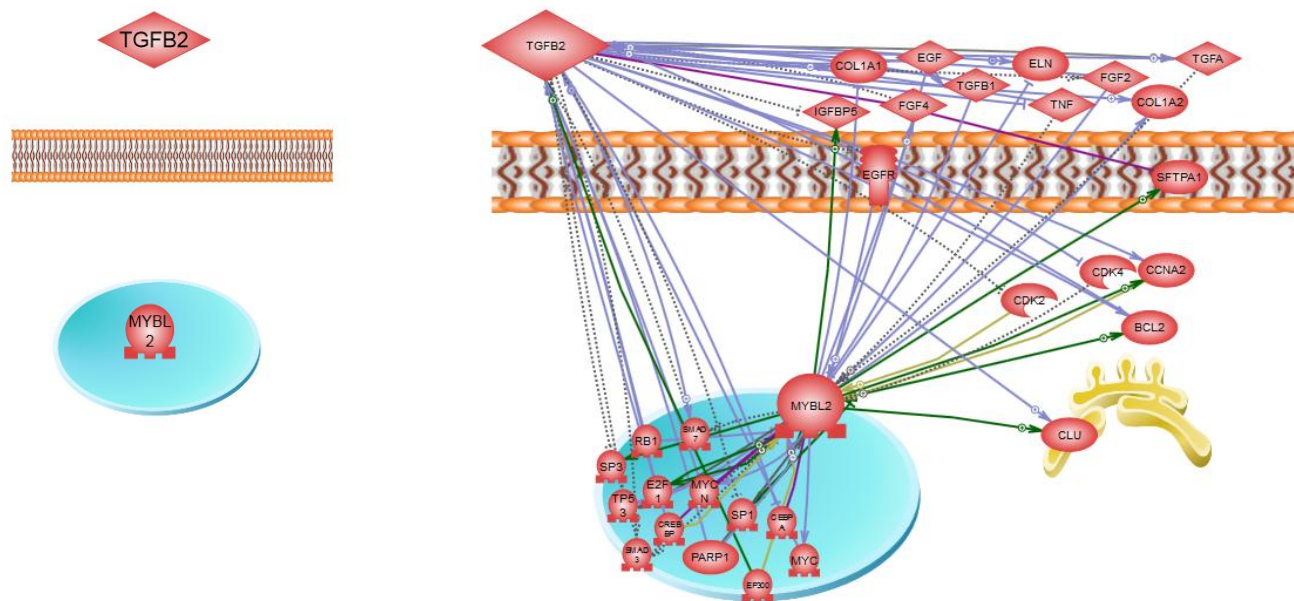

DirectRegulation relations only shown here.

H. If my proteins have no direct interactions, can I connect them through other proteins?

Add two proteins (or more) to a new pathway view and select both (all) proteins.
Wizard settings: **algorithm**: Add Shortest Path; **directionality**: all; **entity type**: proteins; **relation type**: select all

If "Find Shortest Path" is applied to a large number of selected entities, the calculation may take a long time to run.

Filters can be more specific to identify only connections through specific entity types or through specific relations

This guide provides an introduction to pathway building using Pathway Studio and ResNet. For more detailed information on how to use Pathway Studio please visit our website at:
http://www.elsevier.com/online-tools/pathway-studio/customer-support#guides-and-manuals

If you have any questions about Pathway Studio please contact Customer Care:

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