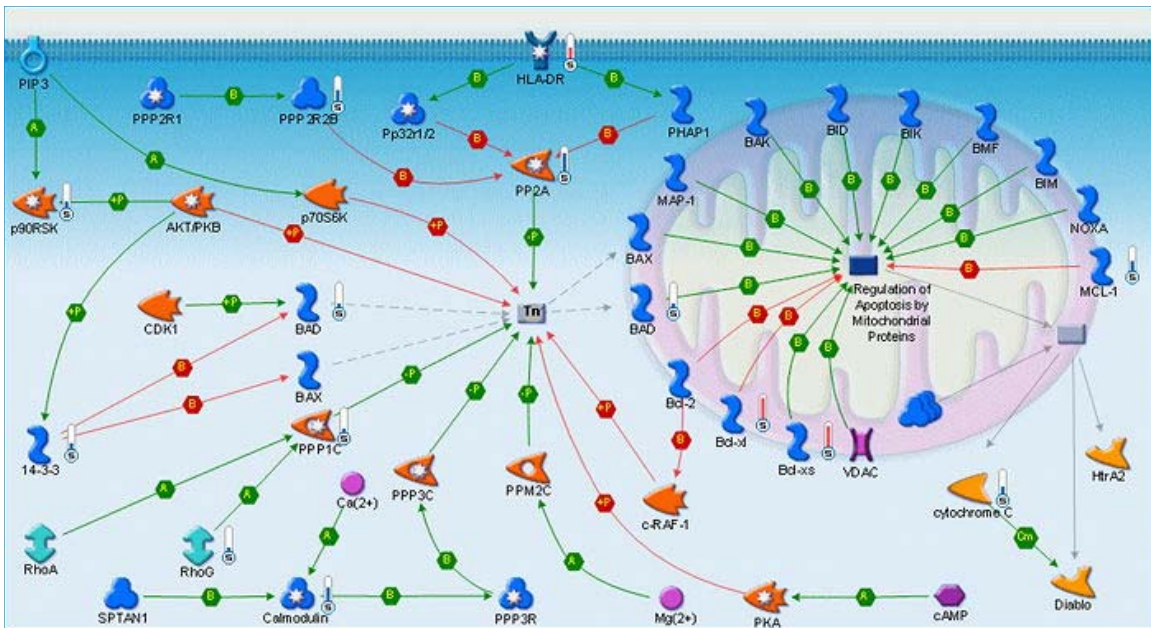




# MetaCore Advanced Training Manual

Version 5.0



GeneGo, Inc. 500 Renaissance Dr., Ste. 106, St. Joseph, MI 49085  
Phone: 888-592-3124, 858 756 7996, 269-983-7869 or +447786150699  
Fax: 269-983-7654  
[customersupport@genego.com](mailto:customersupport@genego.com)  
[www.genego.com](http://www.genego.com)

## Introduction

MetaCore contains many options for network building and manipulation. This manual will go through those options in addition to describing other advanced features of MetaCore such as gene list export and experiment sharing.

## Network Building

### *Algorithms*

MetaCore has four “Analyze” network algorithms. These algorithms are good to use when you have a large number of network objects. They all result in a list of smaller networks, ranked by a p-Value, which can be built separately. Analyze network creates a large network and breaks it up into smaller sub-networks which can be built separately. The resulting networks are ranked by a p-Value. Analyze transcription regulation works similar to analyze network, except the sub-networks created are centered on transcriptional factors.

The other two additional “Analyze” network algorithms (transcription factors and receptors) focus on the presence of either start-nodes or end-nodes of a certain pathway in the submitted list of genes.

The “transcription factors” mechanism favors network construction where the end-nodes / receptor targets of transcriptionally regulated pathways are present in the original gene list. It is irrelevant for this algorithm if the corresponding transcription factors are also present in the original gene list or not.

The “receptors” mechanism favors network construction where the end-point of a pathway leads to a receptor (through “receptor binding”) and the starting point of a pathway (a transcription factor, or ligands, etc...) is present in the original gene list, regardless of the presence of the end-point receptor in the list.

The Shortest paths and Self regulations algorithms are similar. They try to link the original genes with additional objects from the database along a directed path. The difference is that the Self regulations algorithm tries to use transcription factors to link the objects from the original list. For both algorithms the maximum number of steps to use between your objects can be adjusted in the Advanced Options section.

The Direct interactions algorithm creates a network only from the objects in the original list; no other objects from the database will be added. This algorithm is good to start with because it can show if any of the objects in the list “cluster” together by interacting with each other.

The Auto expand algorithm adds objects until it creates a fairly dense network; this is best used to see the neighboring interactions and objects around a few nodes. Finally,

Expand by one interaction simply adds all the one-step interactions around each node from the list.

### *Advanced options*

The Advanced Options section of the Network Options page provides options to specify how a network building algorithm builds a network, by specifying how many and what types of objects to use, for example. The Advanced Options section can be opened by clicking on the Advanced Options header on the Network Options page (**Figure 1**). You can also click on the question mark buttons to see a visual representation for some of the options.

There are many options that are common for all the algorithms. These common options are described below:

**Discard objects** - Checking the boxes in this row will restrict the algorithm so that it uses only those specified. If the Experiments box is checked the algorithm will only use objects from the experiments in the Active Data folder. If the User list box is checked, the algorithm will only use the objects selected just prior to opening the Network Options page (the objects listed in the Network objects section).

**Filter interactions by confidence level** - By default MetaCore uses only highly confident manually curated interactions in network building. The database does contain some low confidence interactions that can be shown or used as specified in this option. If the option is set to Use, then the algorithm will use any low confidence interactions to add additional objects to the network. If it is set to Show, then the algorithm will not use them to add objects, but if both of the low confidence interaction's source and target objects are present on the network, then the interaction will be shown.

**Use unspecified reactions** - An unspecified reaction is an interaction that has both an unspecified effect and mechanism. By default these types of interactions are not used. They can be shown or used with this option.

**Use indirect interactions** - Indirect interactions are denoted by the Influence on Expression interaction mechanism. By default these types of interactions are discarded. With this option you can choose to have the algorithm use them to add additional objects to the network, or you can choose to only have them shown.

**Use binding interactions (special cases)** - By default binding interactions with an unspecified effect are discarded in building networks. As with filtering by confidence level, you can tell the algorithm to simply show the interactions but not use them or you can use unspecified binding interactions. Here also, you can tell the algorithm to treat unspecified binding interactions as being bidirectional.

There are also some options that are only available with certain algorithms:

**Use interaction weights** – This option is available for the Analyze network, Transcription regulation, Shortest paths, Self regulation, Direct interactions, Expand by one interaction, and Auto expand algorithms. If this box is checked the algorithm will take interaction weights into consideration when building the network. Some interaction mechanisms have different weights than others. For example, the Complex Relation (CR) mechanism has a weight close to 0, while the transcription regulation (TR) mechanism has a larger weight. When this option is checked, the weights are used to determine path length. For example, if weights are used on the Expand by one interaction algorithm, it is possible for the algorithm to add an object two steps out. Because of the weights of those two links, they are considered one interaction.

**Number of nodes in a fragment** – This option is available for the Auto-expand, Analyze network, and Transcription regulation. This value is the number of objects that the algorithm will attempt to place into a single cluster of objects. The default value is 50.

**Number of steps in the path** – This option is available for the Shortest paths and Self regulations algorithms. With this drop-down menu you can set the maximum steps the algorithm will use to try and connect the objects from your list. One step is one interaction, so if the maximum number of steps is set to two, then there will be at most one additional object added between two objects from your list. The default maximum value depends on the number of objects in your list. When using one of these algorithms, it is always a good idea to make sure the maximum number of steps is not too high, to avoid creating very large networks.

**Show non-connected root nodes** – This option is available for the Shortest paths, Self regulations, Direct interactions, Expand by one interaction, and Auto-expand algorithms. In some cases the algorithm will not be able to connect a given object to the others from your initial list. By default these objects will be shown as unconnected objects on the network. With this option, you can choose to have these objects hidden.

**Edges weights** – This option is available for the Analyze network (transcription factors) and Analyze network (receptors) algorithms. In these algorithms, the interactions are assigned weight values. These values are:

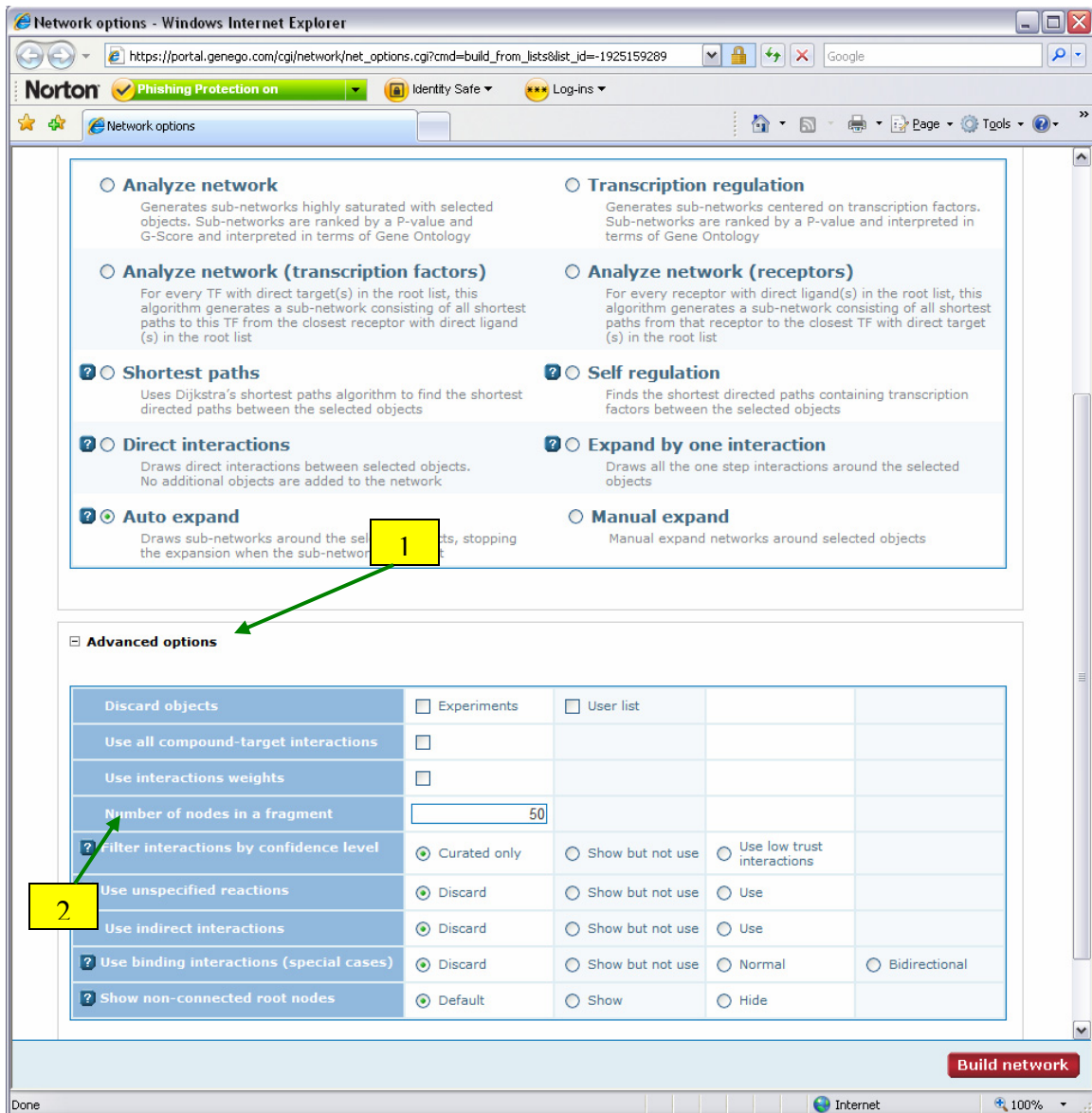
- Inside – edges connecting nodes present in the initial gene list
- Nearest – edges connecting nodes, only one of which is present in the original gene list
- Outside – edges between nodes that do not exist in the original gene list
- Forbidden – those edges that lead to numerous receptors or transcription factors.

The default weight values are pre-selected in such way that preferentially builds network paths through the start- or end-nodes in such a manner that paths would not contain intermediate edges leading to other receptors or transcription factors. Then, the shortest paths from receptors to the corresponding transcription factors are found.



**Add complementary objects** - This option is available for the Analyze network (transcription factors) and Analyze network (receptors) algorithms. Complimentary objects, receptor ligands or transcription targets, from the initial gene list may be added to the resulting networks by checking this box.

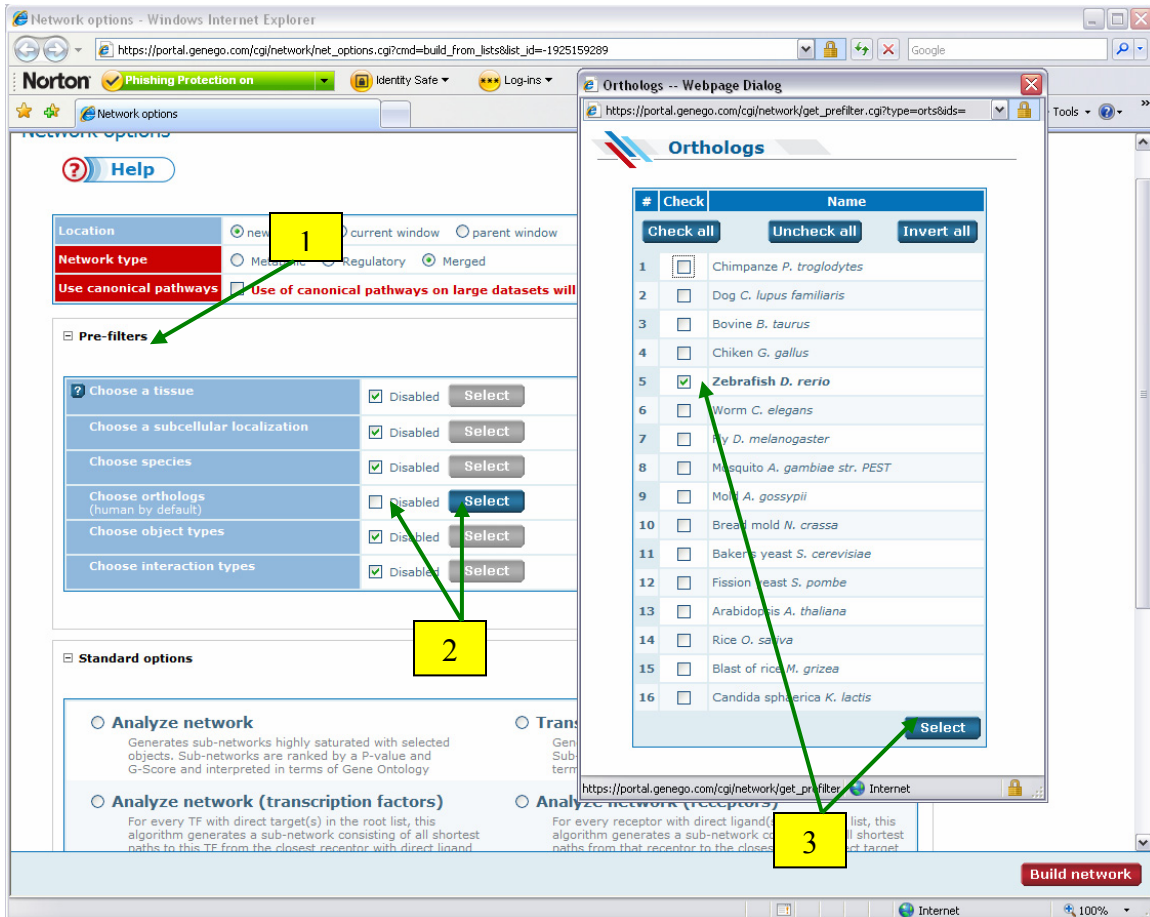
**Group networks** - This option is available for the Analyze network (transcription factors) and Analyze network (receptors) algorithms. This option will group some of the resulting networks together. In the case of the “transcription factors” algorithm, networks are grouped by the targets of given transcription factors. In the case of the “receptors” algorithm, networks are grouped by different transcription factors leading to the given receptors.



**Figure 1:** 1. Click here to open the Advanced Options panel. 2. Click here to see a visual representation of how the algorithm works.

## Pre-filters

Another option available in network building is the ability to pre-filter a network based on tissue, sub-cellular localization, organism, object type, and/or interaction type. The resulting networks then contain only those objects that are known to be expressed in the selected tissue or localization; have an ortholog for the selected organism; are of the selected object type(s); or are connected by the selected interaction type(s). To use the pre-filters, uncheck the 'Disabled' box and click the Select button to choose the pre-filter criteria (**Figure 2**).



**Figure 2:** 1. Click here to open the pre-filter panel. 2. Uncheck the Disabled box and click Select. 3. Choose an option and click Select.

## Adding more objects

Network objects can be added to the list used in network building from the Network Options page. This feature can be useful if, for example, you are building networks around a dataset but wish to add one or more objects not in the dataset to see how the additional objects affect the resulting network.

To add objects from the Network Options page, first click the "Network objects" header. Then click the "Add network objects" button. In the window that appears, search for the

object you wish to add. Then check the box next to the desired result and click the Add selected object button (Figure 3). The object will then be added to the list used for building networks.

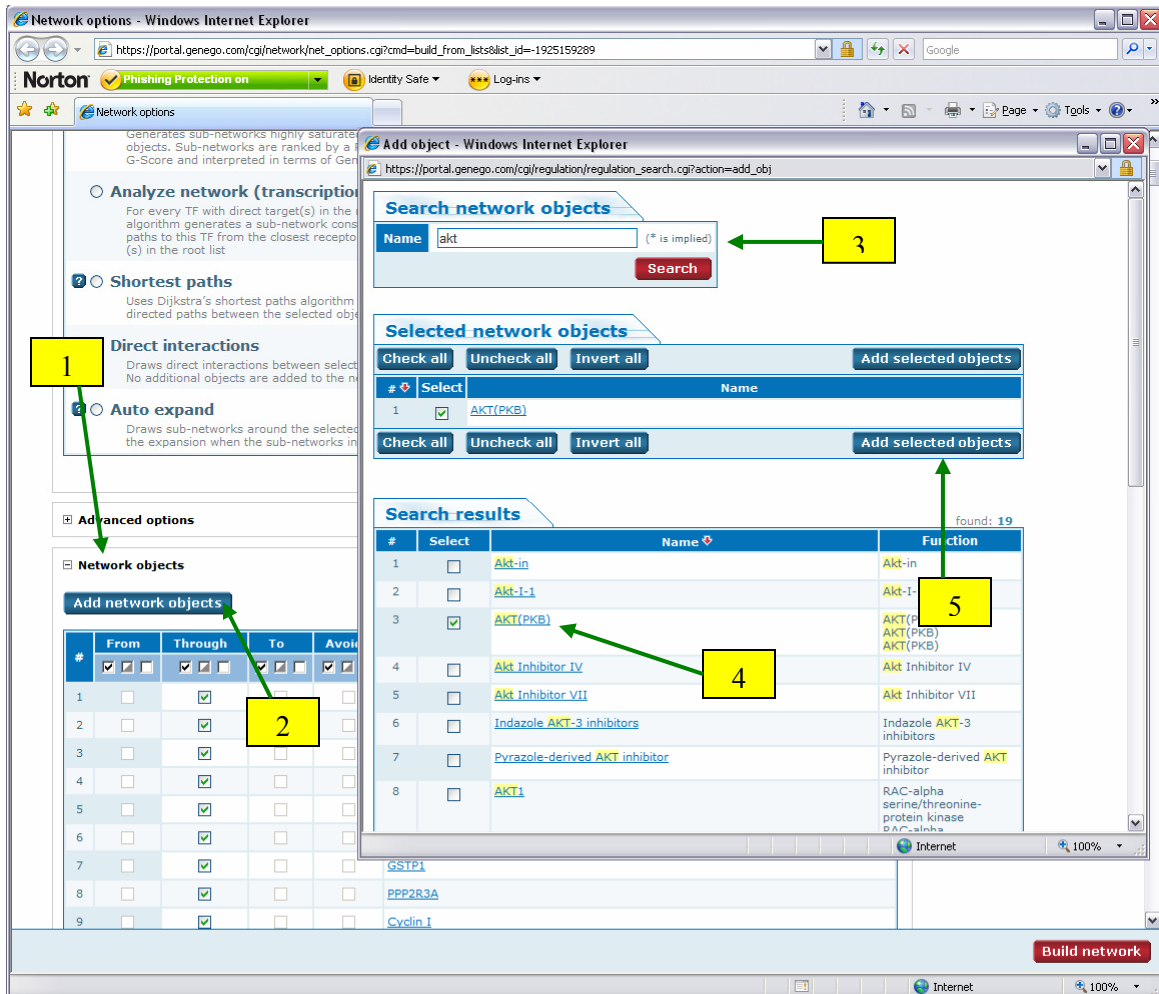
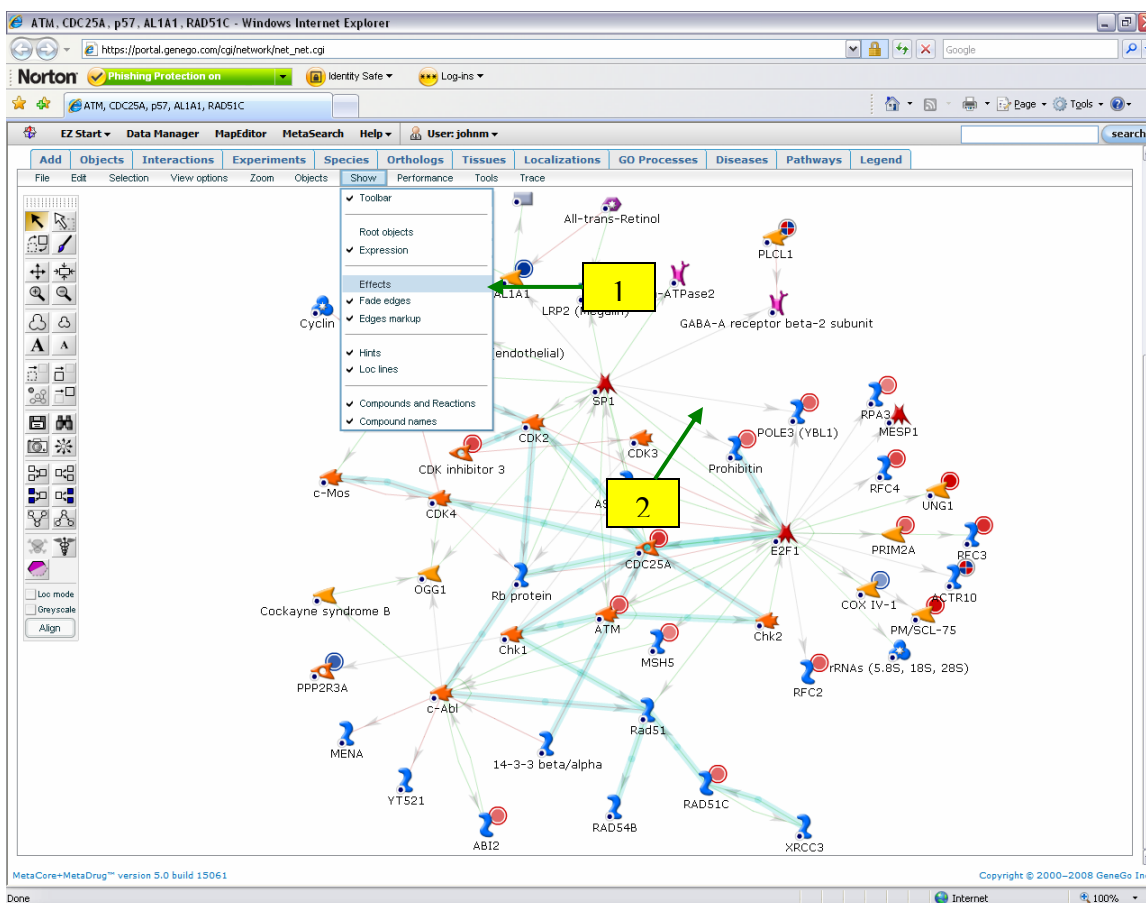


Figure 3: 1. Click here to open the network objects section. 2. Click here to add more objects to the list. 3. Search for the objects to add. 4. Check the desired results. 5. Click here to add selected objects to the list.

## Network Manipulation

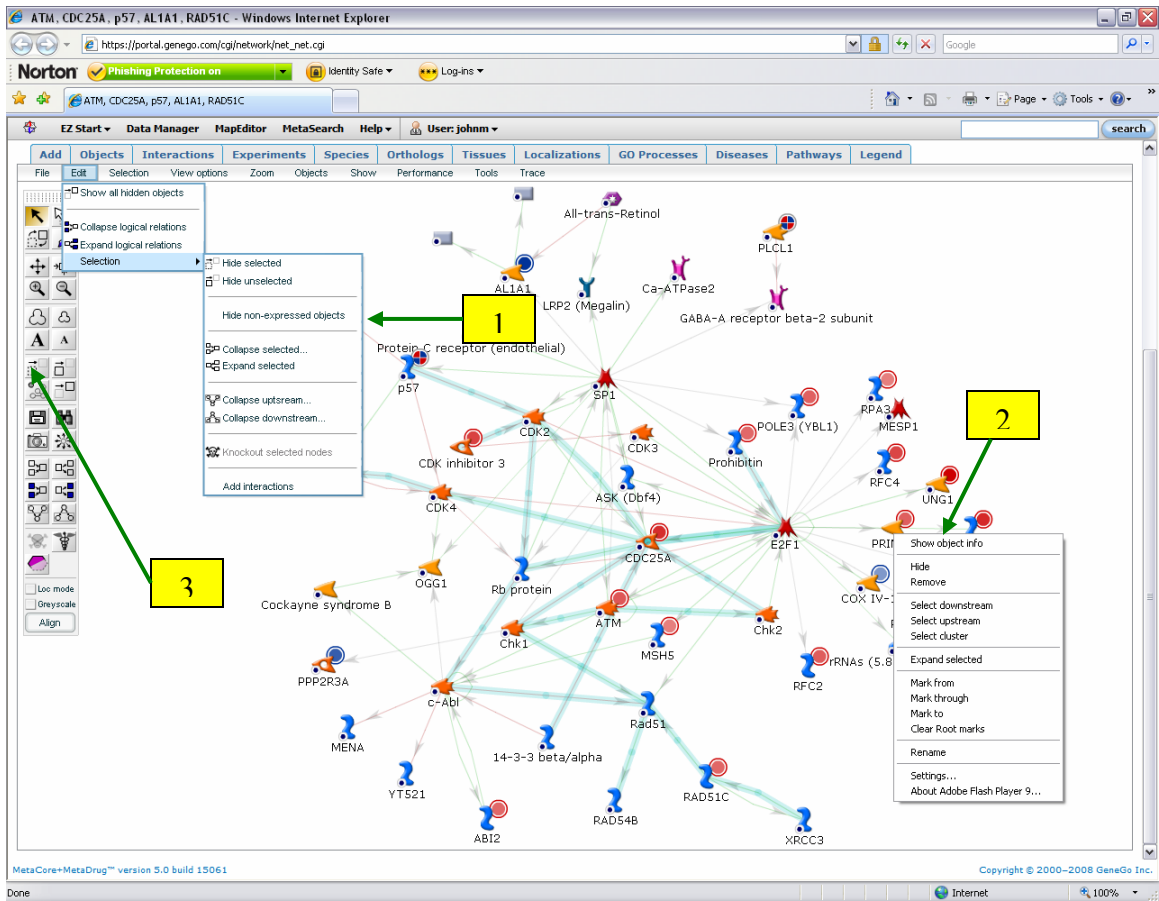
There are many ways to make a network easier to read. You can make all the edges semi-transparent by checking the “Fade edges” option in the Show menu. Fading the edges will cause the nodes to stand out. By doing this a complex network will appear less “cluttered”. Effect hexagons on interaction arrows are hidden by default. They can be shown by checking the “Effects” option in the Show menu (Figure 4).



**Figure 4: 1. Show menu. 2. Edges faded and Effects unchecked.**

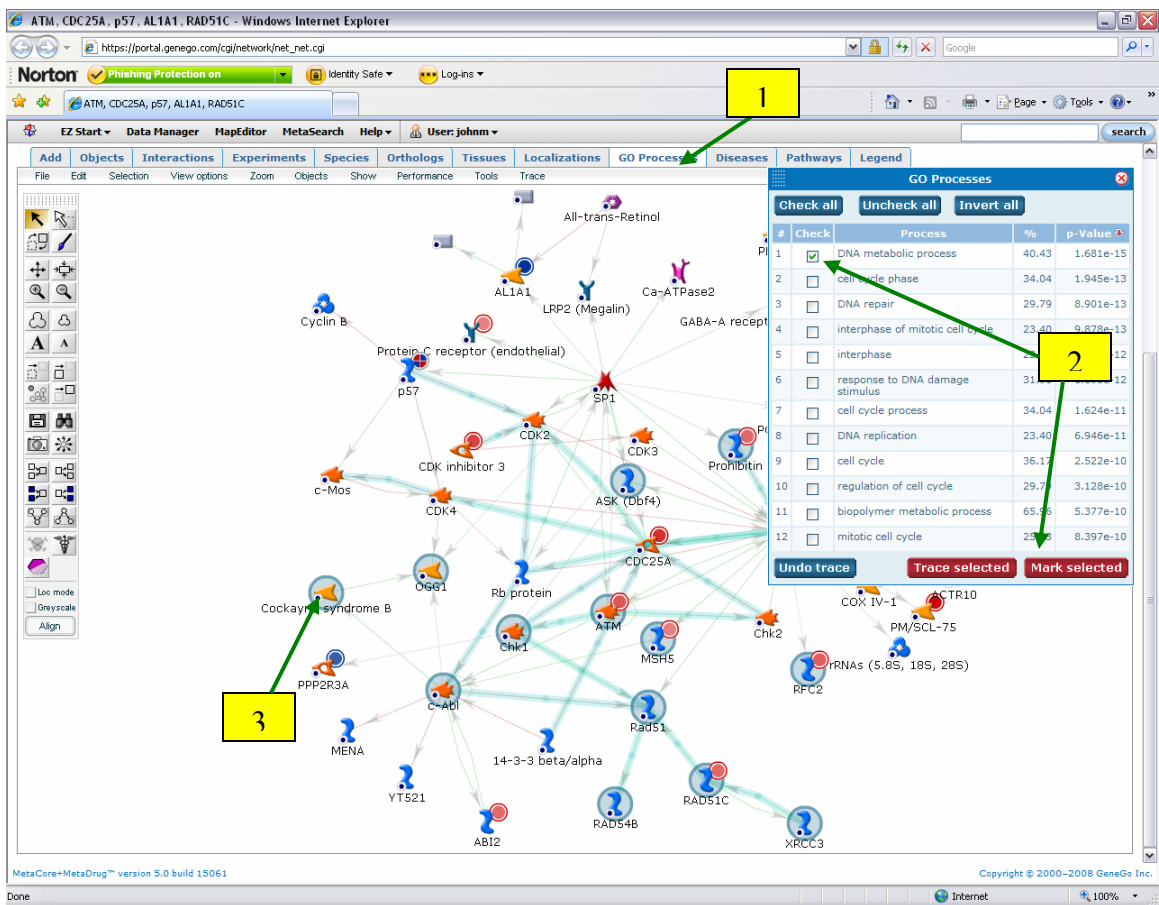
Another way to make a network less complex is to hide objects. You can hide all the objects without expression data by clicking the “Hide non-expressed” option from the Selection sub-menu of the Edit menu. This will leave only those objects that have expression data visible on the network. Additionally, you can hide selected objects by first dragging a box around them or holding CTRL and clicking on them. Then click the “Hide selected objects button” (Figure 5).

Objects and interactions can also be removed from the network. To do this, right-click on the object or interaction hexagon and choose Remove from the context menu (Figure 5). When objects are removed they are then not used in generating Process, Disease, or Tissue lists. Removed objects are also no longer displayed in the network statistics page. Please note that removed objects cannot be returned to the network in the same manner as hidden objects.



**Figure 5: 1. Option to hide non-expressed objects. 2. Right-click context menu where objects can be hidden or removed. 3. Hide selected objects button.**

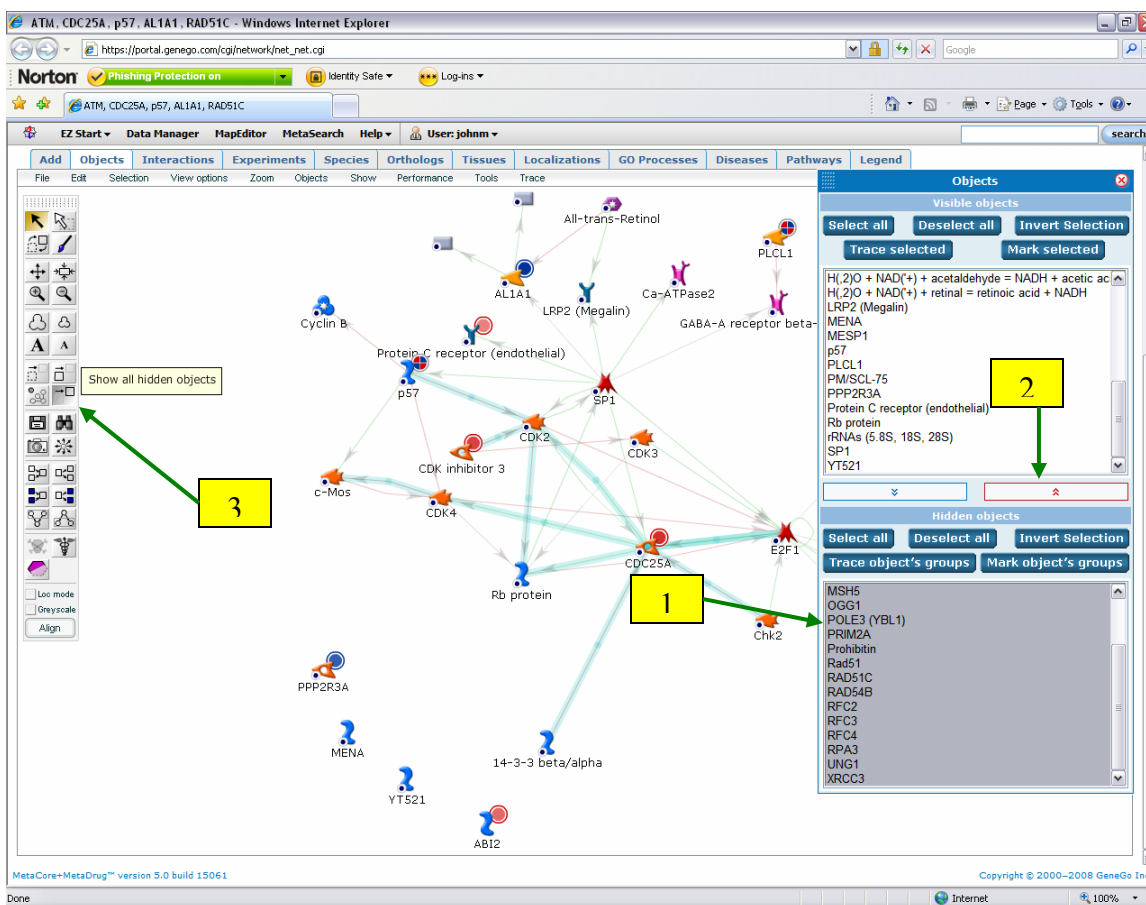
Another way to hide objects is to base your selection on the network filters. First click one of the filter tabs above the network (GO Processes, Diseases, etc.). Then when the list appears, select a category by checking the box next to it. Then click the “Mark selected” button. All the network objects related to that category will then be circled in gray. Now, click the “Hide unselected objects” button (**Figure 6**). The network will now only contain those objects that are related to the selected category.



**Figure 6: 1. GO Processes tab. 2. Choose a process and click Trace selected or Mark selected. 3. Here, objects related to selected process are marked.**

Hidden objects can be returned to the network either by using the Objects tab or by clicking the “Show all hidden objects” button. Clicking the “Show all hidden objects” button will return all the hidden objects to the network. You can use the Objects tab to return individual objects to the network. In the Objects tab, hidden objects are listed in the lower window. To return an object to the network, select it and click the red up arrow button (Figure 7).



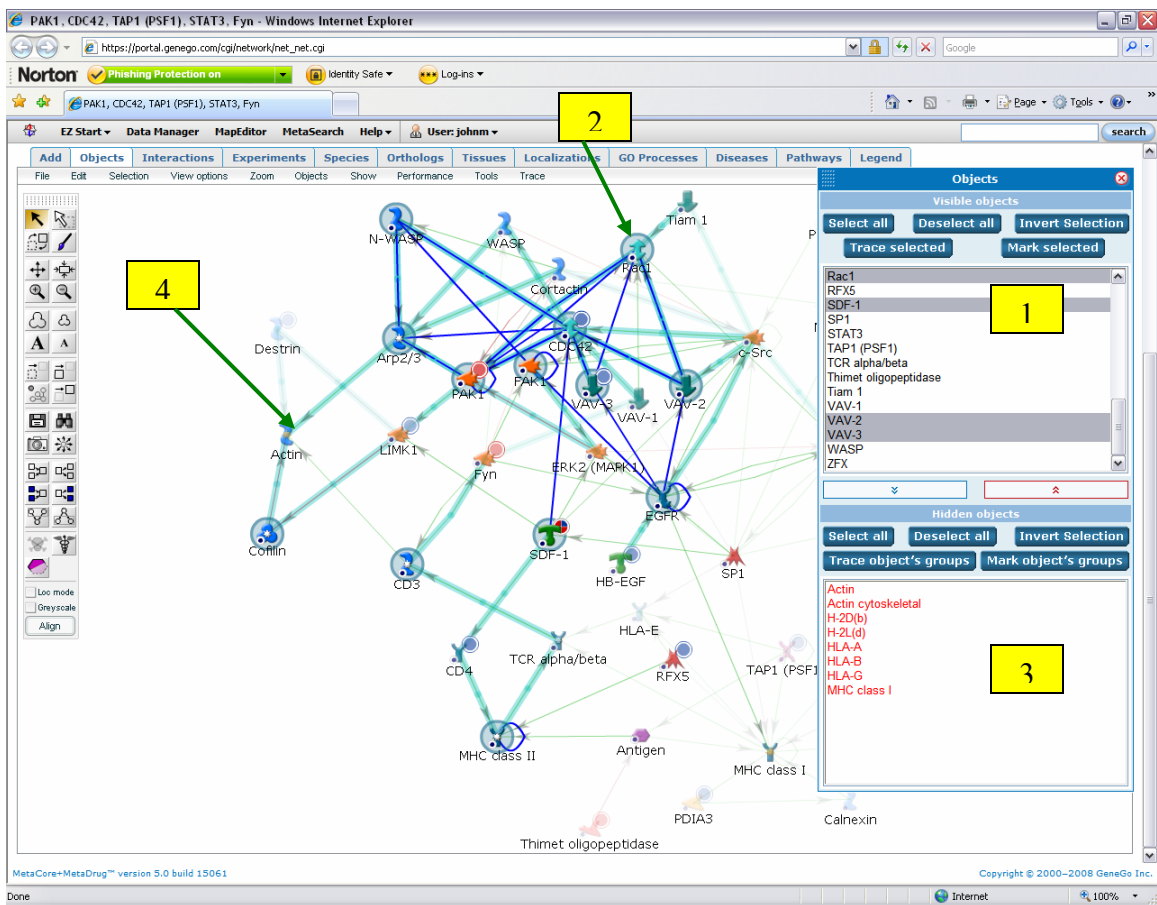


**Figure 7: 1. Select objects to show. 2. Click up arrow to show the selected objects. 3. Click this button to show all hidden objects.**

## Selecting Genes of Interest

Sometimes a large and dense network may be built where it is difficult to find your genes of interest. The quickest way to find your genes of interest is to use the Objects tab. The Objects tab lists all visible network objects in the upper panel and all hidden or grouped objects in the lower panel. To find the object(s) you are looking for on the network select it in the upper panel of the Objects tab. Then you can choose to mark the selected object or trace the selected objects. Tracing the objects will make all unselected objects semi-transparent and highlight any interactions between the selected objects. This makes it easier to pick out your object(s) of interest (**Figure 8**).

Additionally, some objects are part of complex groups. These groups are denoted by a yellow star on the object icon. You can mark or trace the group that your object of interest is a part of by selecting it in the lower panel and clicking “Trace object’s groups” or “Mark object’s groups” (**Figure 8**).



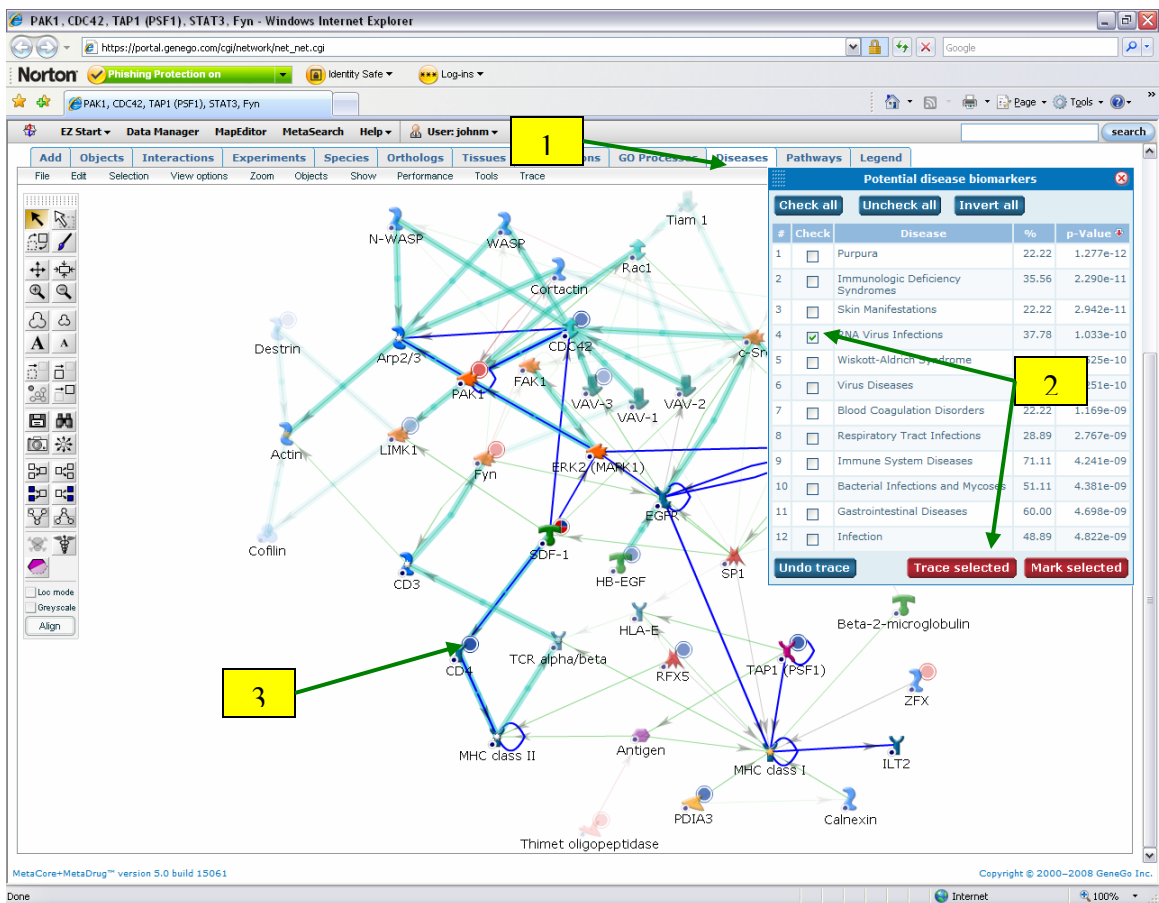
**Figure 8:** 1. Selected objects in Objects tab. 2. Objects traced and marked. 3. Objects in groups are colored red. 4. Complex groups are marked with a yellow star.

## Network post-filters

Another way to see interesting objects is to use the various filter tabs above the network image. Using these tabs you can see the Tissues, the top 12 GO Processes and the top 12 diseases related to the objects on the network. You can also filter the network based on sub-cellular localization and see which objects have orthology with other species.

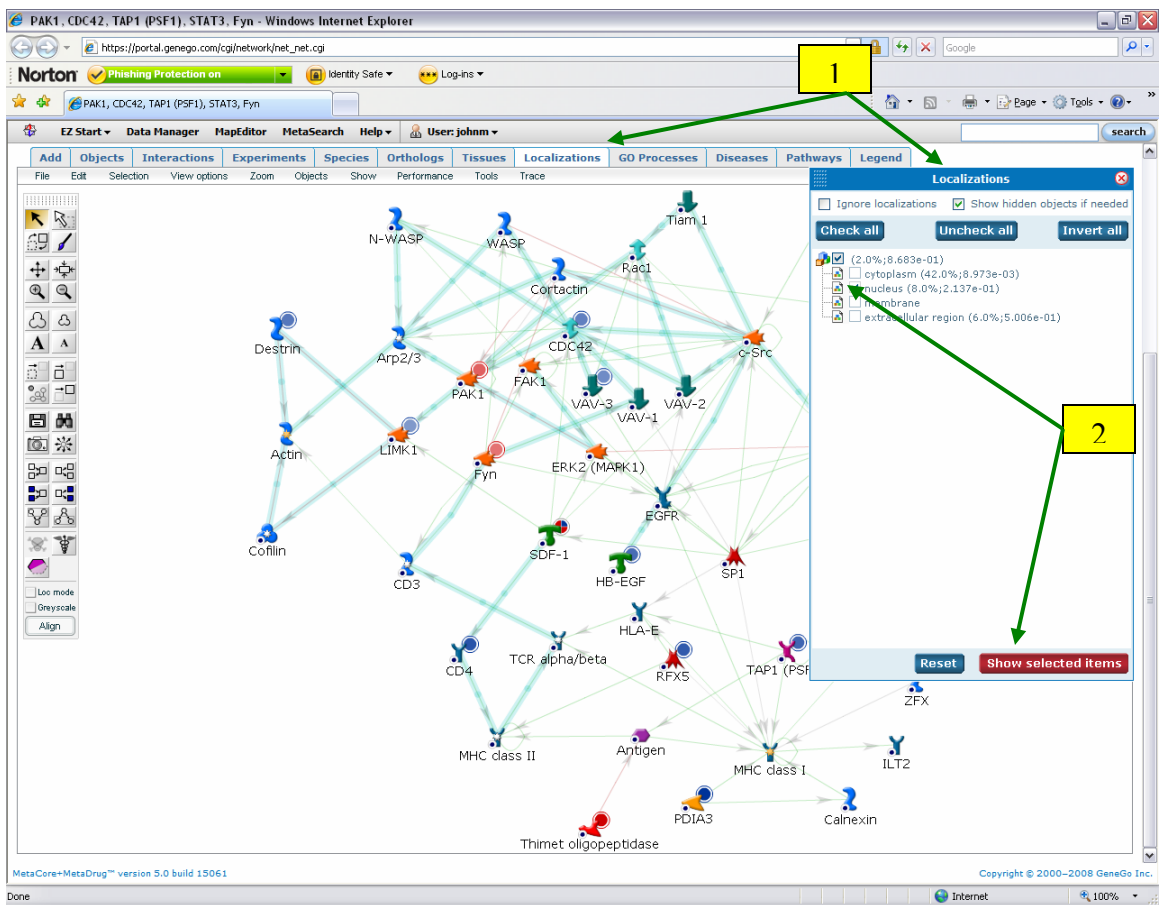
The Tissues, GO Processes and Diseases tabs work in a similar manor. Click the tab to see a list of related tissues, GO processes or diseases. To see which objects on the network are related to a result, select the result by checking the box next to it. Then click either the “Mark selected” or “Trace selected” button. Marking the objects will circle the objects related to the process, tissue or disease in gray. Tracing the objects will make the objects not involved in the process, tissue or disease semi-transparent and highlight any interactions between objects involved in the process, tissue or disease (**Figure 9**).





**Figure 9:** 1. Diseases tab. 2. Select a disease and click Trace selected or Mark selected. 3. Here, objects in the selected disease are traced.

With the Localizations tab you can hide objects not involved in the selected localization. To do so, check the box next to the desired localization and click the “Show selected items” button. Objects not in the selected localization will be hidden (Figure 10).



**Figure 10: 1. Localizations tab. 2. Select a localization and click “Show selected items” to see objects in that localization.**

Using the Orthologs tab you can mark the objects that have an ortholog for the selected species. To do so, click the Orthologs tab. Then check the box next to the desired species and click the “Select” button. The objects with orthologs will be circled in gray (**Figure 11**). From here you can also click the “Hide unselected objects” button as described above to see only the objects with an ortholog in the selected species.

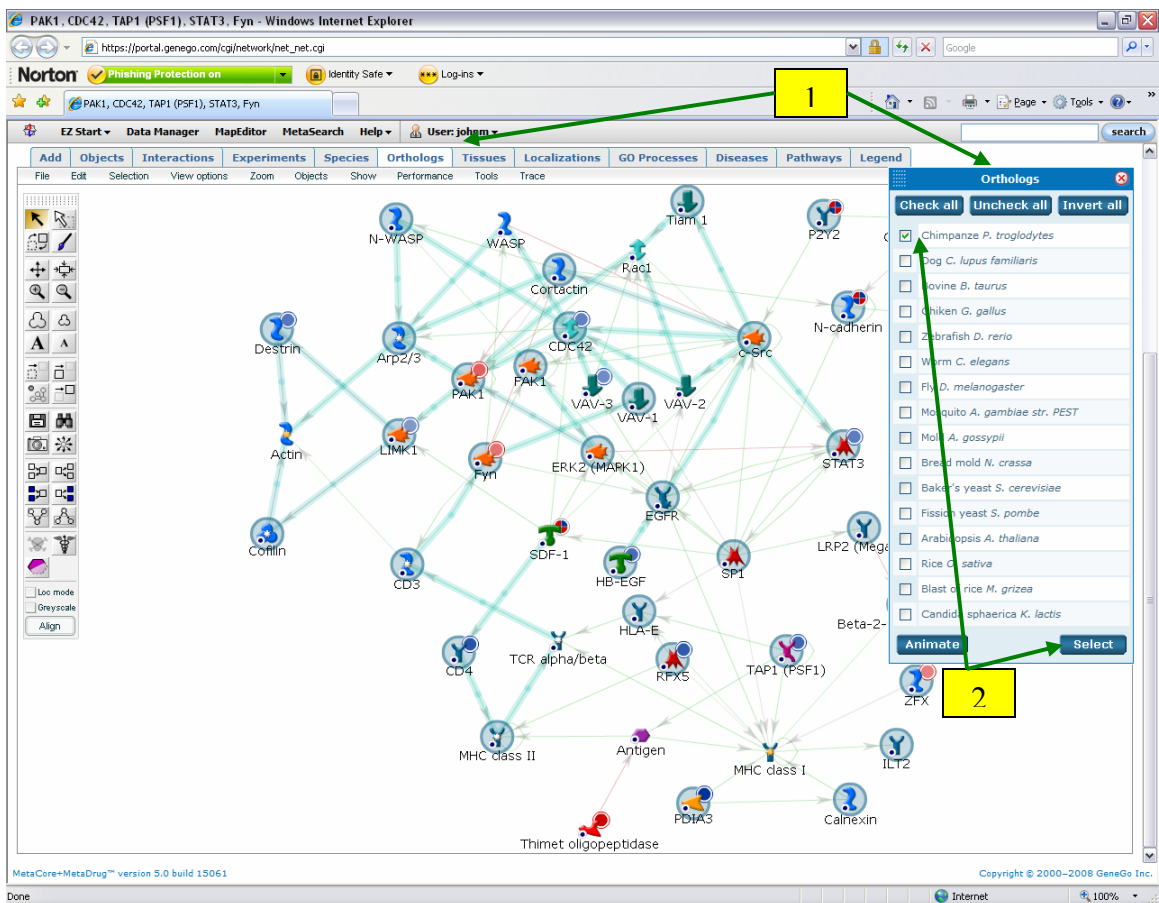


Figure 11: 1. Orthologs tab. 2. Check a species and click Select to mark objects.

### Pathways tab

The Pathways tab contains the list of all the canonical pathways on the network. When building a network, if the “Use canonical pathways” option was checked in Network Options and canonical pathways are present on the network (turquoise colored interaction arrows) you can use the Pathways tab to automatically trace the individual canonical pathways present on the network. Click on a pathway to highlight its interactions in green. Clicking the “Animate” button will cycle through all the pathways on the network. You can also click the “View source” button to see the map or pre-built network that the selected pathway is from (**Figure 12**). Alternatively, you can select an object on the network and click the “Mark pathways for selected node” button to highlight all the pathways on the network that involve the selected object.

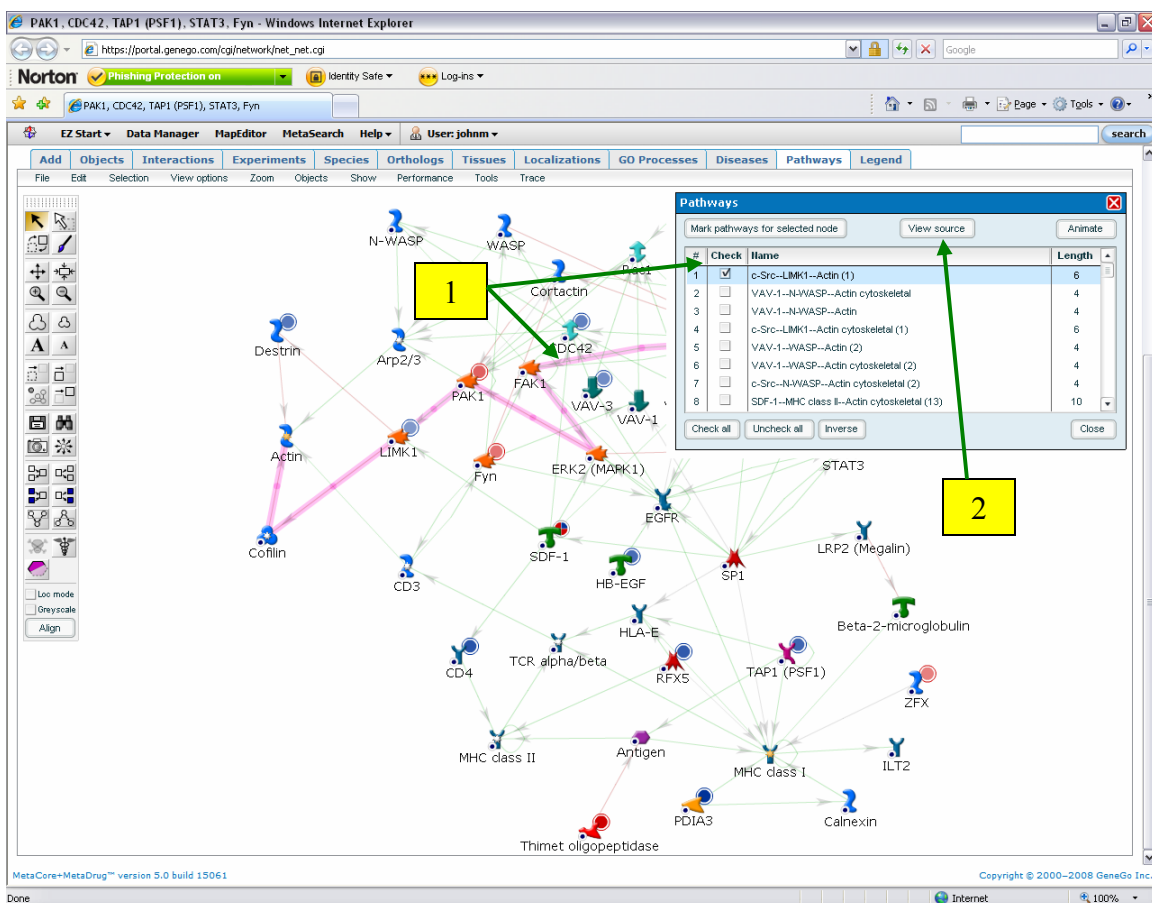
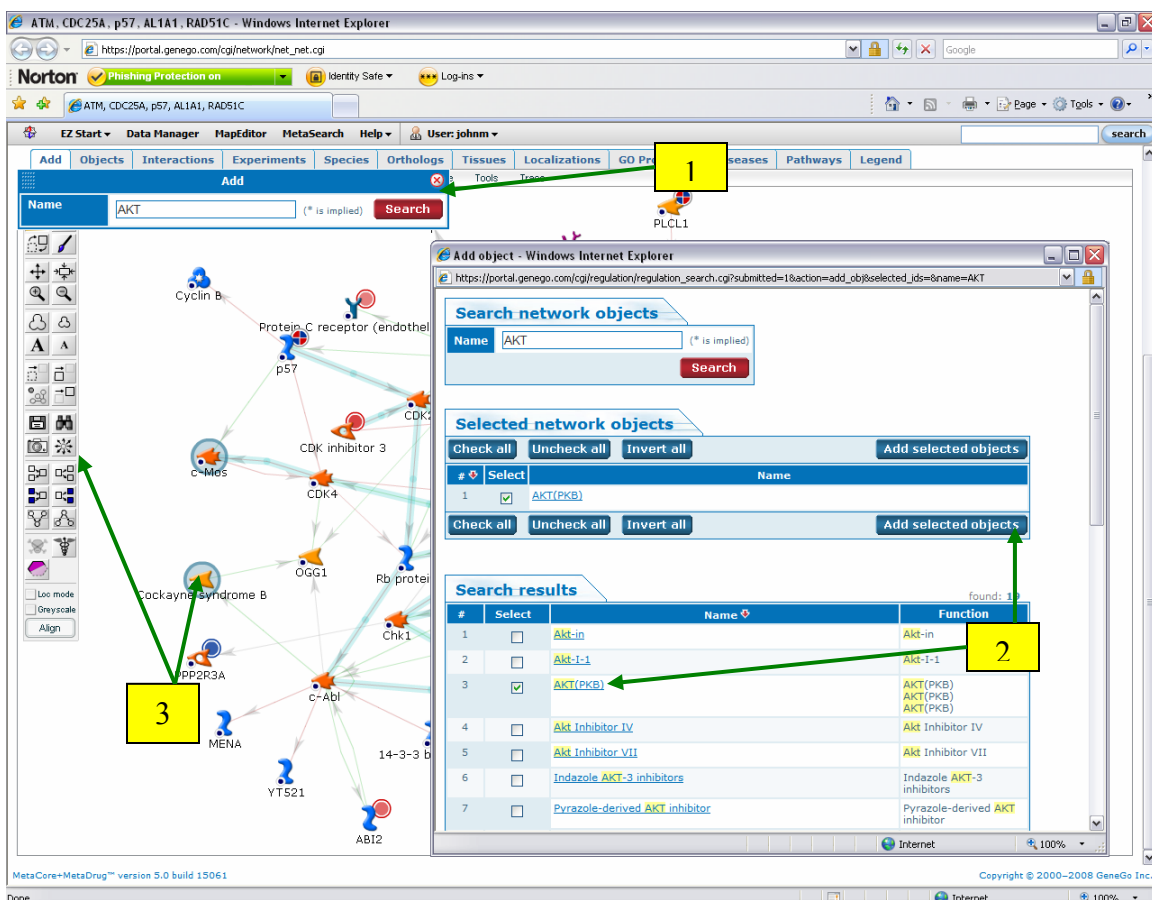


Figure 12: 1. Selected pathway is highlighted in green. 2. Click here to see the source map or pre-built network.

## Adding Genes of Interest

Additional objects can also be added to an already built network. This is done by using the Add tab. With this tab, you can search for new objects to add to the network. To add new objects to the network, enter a search term in the Add tab and click Search. Then in the window that appears check the box to the left of the desired result(s). Then click the “Add selected objects” button. The “Add object” window will then close and the network page will refresh with the selected object added to the network. Objects added in this way are connected to the existing network using the shortest paths algorithm.

To expand around objects already on the network, first select the objects by holding CTRL and clicking on them. Then click the “Expand selected nodes” button in the toolbar. In the box that appears there are two expansion options. You can also choose to expand around the chosen object(s) by either the Auto-expand algorithm or by a selected number of steps (Figure 13). After choosing an expansion option, click OK. The network page will then reload.



**Figure 13:** 1. Search for an object to add from the Add tab. 2. Select the desired object and click “Add selected objects”. 3. Pre-existing objects can be expanded by selecting them on the network and clicking the “Expand selected nodes” button in the toolbar.

## Database information pages

From the network you can see the database information pages for the objects’ associated gene, protein, compound, or reaction by clicking on the object itself. One such example of finding this information is to look for the drugs that target objects on a network. To see which objects on a network are drug targets, click the “Select drug targets” button. Any drug targets present on the network will then be circled in gray (**Figure 14**). At this point, to make the network easier to work with, you can also click the “Hide unselected objects” button to hide all the object that are not drug targets. To see more information about a drug target, click on it. The Network object info page will open (**Figure 15**). This page contains many links to more information about the network object; including the database information for its associated gene or protein, links to any maps the object appears on, links to any corresponding GO processes and diseases, links to known drugs for the object and a list of the object’s network interactions. Click on the “Known drugs for this object” header to see the therapeutic and secondary drugs. After clicking one of the drug links, the compound details page will open.

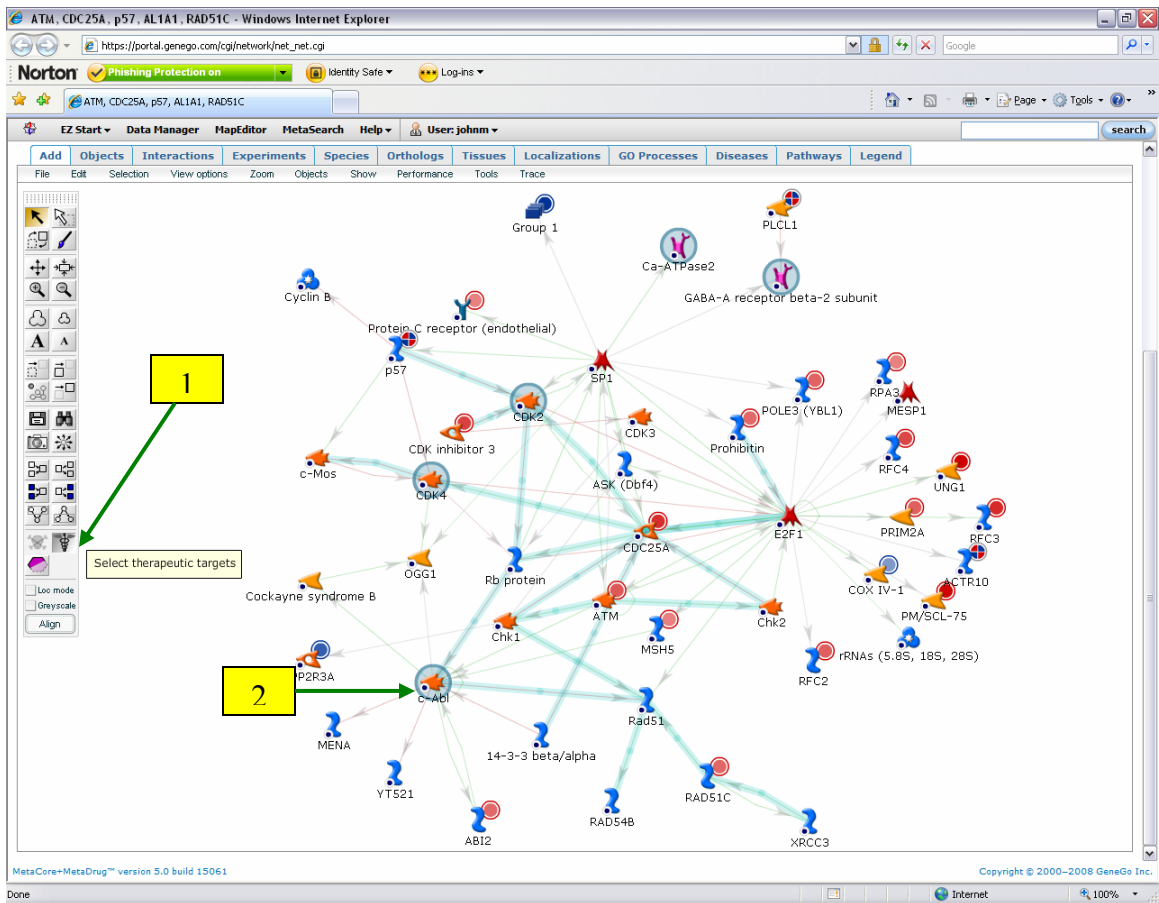


Figure 14: 1. Click here to mark drug targets. 2. Drug targets circled in gray.

Network objects details

Expand Collapse

Network object: c-Abl

Name c-Abl

- Corresponding DB objects
- GeneGo maps
- Drugs for this object
- GO processes
- Diseases
- Interactions

Corresponding DB objects

#	Species	Type	Description
1	Homo sapiens	protein	<a href="#">Proto-oncogene tyrosine-protein kinase ABL1</a>
2	Mus musculus	protein	<a href="#">Proto-oncogene tyrosine-protein kinase ABL1</a>
3	Rattus norvegicus	protein	<a href="#">y-abl Abelson murine leukemia viral oncogene homolog 1 (mapped)</a>

GeneGo maps

Drugs for this object

Therapeutic drugs	
#	
1	<a href="#">Imatinib</a>
2	<a href="#">XL228</a>

Secondary drugs	
#	
1	<a href="#">AZD2171</a>
2	<a href="#">Genistein</a>
3	<a href="#">PD153035</a>
4	<a href="#">Vandetanib</a>
5	<a href="#">Vatalanib</a>

**Figure 15: Network objects info page.**

The compound details page contains the compound structure which can be downloaded as a MOL file by clicking the “Download structure” button. The details page also lists what other genes the drug targets. This information can tell how specific or broad the drug action may be. From the details page you can also build a network around the compound in order to further explore the compounds interactions with other objects (**Figure 16**).

A final tool accessible from the compound details page is the ability search MDL DiscoveryGate for the compound. To do so, first select a search method from the drop-down menu, then click the “Search in DiscoveryGate” button (**Figure 16**). A new window will then open with the DiscoveryGate software. After logging in the search will be automatically performed.



The screenshot displays the 'Drug details' page for Imatinib on the GeneGo portal. The browser window shows the URL <https://portal.genego.com/cgi/chem.cgi?id=70468881>. The page content includes:

- Generic Name:** Imatinib
- Drug Status:** FDA approved, EU approved, Clinical trial drug
- Synonyms/Brand Names:** 4-(4-METHYL-PIPERAZIN-1-YLMETHYL)-N-[4-METHYL-3-(4-PYRIDIN-3-YL-PYRIMIDIN-2-YLAMINO)-PHENYL]-BENZAMIDE, 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-ylpyrimidin-2-ylamino)-phenyl]-benzamide, 4-[[4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridyl)-2-pyrimidinyl]amino]phenyl]benzamide, 4-[[4-methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[[4-(3-pyridin-3-ylpyrimidin-2-yl)amino]-phenyl]-benzamide, 4-[[4-methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[[4-(3-pyridyl)pyrimidin-2-yl]amino]phenyl]benzamide, 4-[[4-methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[[4-(3-pyridyl)pyrimidin-2-yl]amino]phenyl]benzamide, APRD01028, Benzamide, 4-[[4-methyl-1-piperazinyl)methyl]-N-(4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl)-, CGP 57148B, CGP57148B, Cgp 57148, Gleevec, Glivec, Imatinib, Imatinib Methansulfonate, Imatinib mesylate, N-(4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide, NCGC00159456-02, NCGC00159456-03, STI, STI 571, STI-571, STI571, STOCK6S-47743, alpha-(4-methyl-1-piperazinyl)-3'-((4-(3-pyridyl)-2-pyrimidinyl)amino)-p-toluidide, benzamide, 4-[[4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-, chembank665, component of Gleevec, sti-571
- Chemical IUPAC Name:** 4-[[4-methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[[4-(3-pyridin-3-yl)pyrimidin-2-yl]amino]
- Compound Category:** Xenobiotic
- Chemical Formula:** C29H31N7O
- Chemical Structure:** A 2D ball-and-stick model of the Imatinib molecule is shown.
- MOL File:** A button labeled 'Download structure' is highlighted with a yellow box and a green arrow labeled '1'.
- MDL databases:** A button labeled 'Search in DiscoveryGate' is highlighted with a yellow box and a green arrow labeled '2'. A dropdown menu next to it is set to 'Automatic'.

Figure 16: 1. Click here to download structure MOL file. 2. Select a search method and click here to search in DiscoveryGate.

## Network Statistics

Various statistics about a network can be seen by clicking the Network Statistics button or by choosing Network Statistics from the File menu. This allows you to see a tabular overview of the network including information about how the network was built; any experimental data on the network; how active different objects are in the network; and the GO processes, diseases and tissues related to the network (**Figure 17**).

The top section of the statistics page displays basic information about the network including its name and description (a description can be added by clicking the "Rename" button on the network page). Click on a section hyperlink to go directly to that section or click a section header to open the information panel. The first section shows what options were used when building the network including the algorithm used, any chosen pre-filters



and the advanced options used. All the nodes with experimental data are listed as well. The table includes the network object, its related genes, the gene description, and the data value (**Figure 18**). All of the objects on the network are listed in the Hubs and Nodes sections. A Hub is a node that has five or more edges on the network. Two numbers are listed in the edges column. The first number is the total number of edges for that node and the second number is the number of hidden edges for that node on the network. An edge is hidden if one or more of the nodes connected to it is hidden or if the nodes connected by the edge are in a group.

The screenshot shows a web browser window titled "Network statistics - Windows Internet Explorer". The address bar shows the URL "https://portal.genego.com/cgi/network/network\_stats.cgi". The browser interface includes a Norton toolbar with "Phishing Protection on", "Identity Safe", and "Log-ins" buttons. The main content area is titled "Network statistics:" and features an "Export" button. A table displays the following statistics:

MetaCore™ version	5.0 build 15061
Name	ATM, CDC25A, p57, AL1A1, RAD51C
Description	
Total Nodes	51
Total Edges	89
Low Trust Edges	0

Below the table, there is a list of options and experiments:

- Options
  - Advanced options
- Experiments
  - General parser
    - (1) MCF-7 estrogen tamoxifen minmax tx max
    - (2) MCF-7 estrogen tamoxifen minmax tx min
    - (3) MCF-7 estrogen tamoxifen minmax e max
    - (4) MCF-7 estrogen tamoxifen minmax e min
- Hubs
- Divergence hubs
- Convergence hubs
- Nodes
- Transcription factors
- Membrane receptors
- GO processes
- Diseases
- Tissues

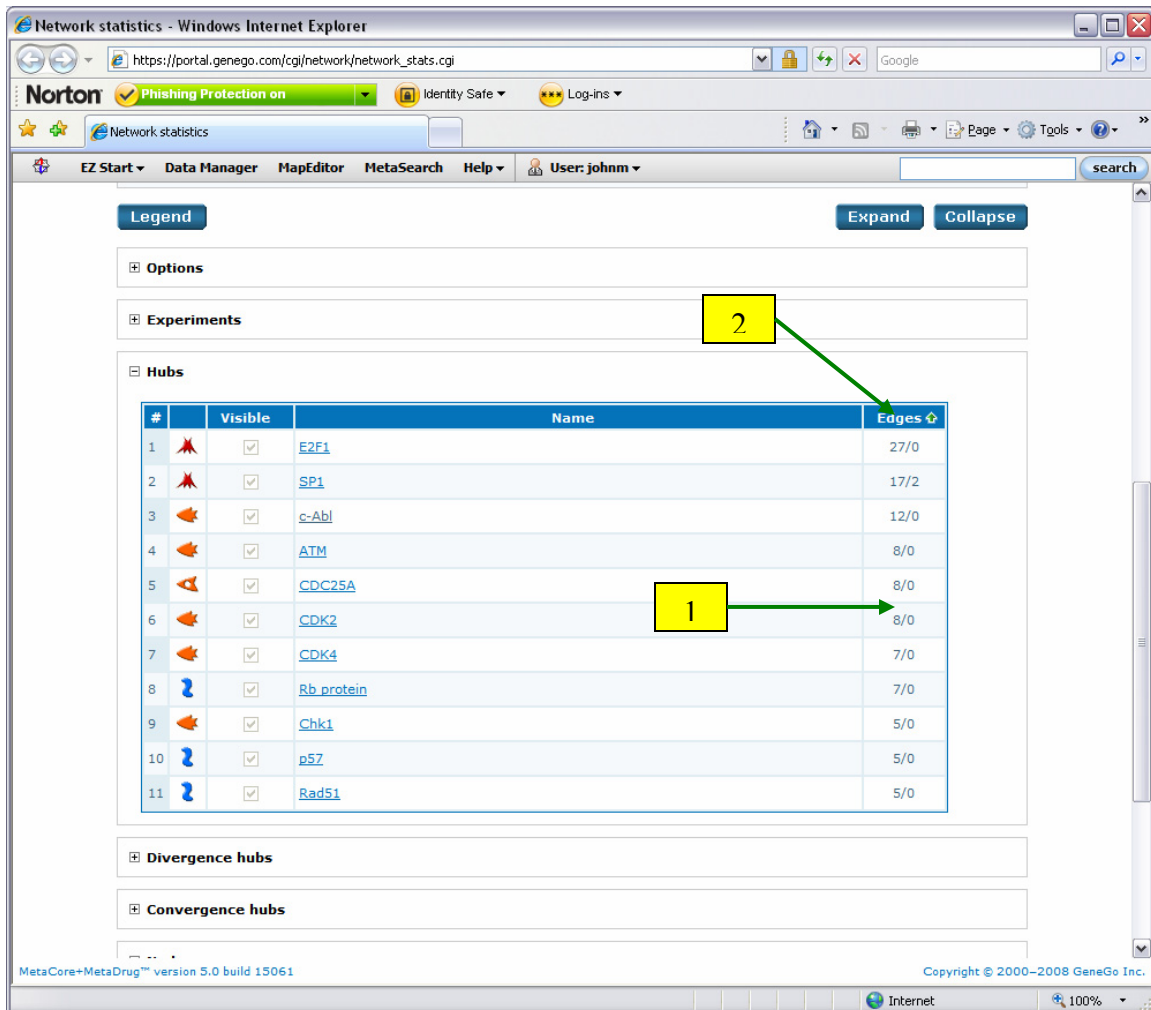
A yellow box with the number "1" and a green arrow points to the link "(1) MCF-7 estrogen tamoxifen minmax tx max". Below the list, there is a legend section with "Expand" and "Collapse" buttons. The legend is currently collapsed, showing only the "Options", "Experiments", and "Hubs" sections. The footer of the page includes "MetaCore+MetaDrug™ version 5.0 build 15061" and "Copyright © 2000–2008 GeneGo Inc.".

Figure 17: 1. Click a link to jump to that section.

The screenshot shows a web browser window titled "Network statistics - Windows Internet Explorer". The address bar shows the URL "https://portal.genego.com/cgi/network/network\_stats.cgi". The browser has Norton security software installed. The page content includes a navigation bar with "Options", "Experiments", and "General parser" sections. A table lists network objects with columns for "#", "Visible", "Network object", "Name", "Description", and "Signal". A yellow box with the number "1" points to the "Options" header, and another yellow box with the number "2" points to the first row of the table.

#	Visible	Network object	Name	Description	Signal
1	<input checked="" type="checkbox"/>	<a href="#">ABI2</a>	<a href="#">ABI2_HUMAN</a>	May act in regulation of cell growth and transformation by interacting with nonreceptor tyrosine kinases ABL1 and/or ABL2. May be involved in cytoskeletal reorganization. Regulates ABL1/c- Abl-mediated phosphorylation of MENA.	0.1022
2	<input checked="" type="checkbox"/>	<a href="#">ACTR10</a>	<a href="#">ARP10_HUMAN</a>		0.1044
3	<input checked="" type="checkbox"/>	<a href="#">CDC25A</a>	<a href="#">MPIP1_HUMAN</a>	Tyrosine protein phosphatase which functions as a dosage-dependent inducer of mitotic progression. Directly dephosphorylates CDC2 and stimulates its kinase activity. Also dephosphorylates CDK2 in complex with cyclin E, in vitro.	0.128
4	<input checked="" type="checkbox"/>	<a href="#">p57</a>	<a href="#">CDN1C_HUMAN</a>	Potent tight-binding inhibitor of several G1 cyclin/CDK complexes (cyclin E-CDK2, cyclin D2-CDK4, and cyclin A-CDK2) and, to lesser extent, of the mitotic cyclin B-CDK2. Negative regulator of cell proliferation. May play a role in maintenance of the non-proliferative state throughout life.	0.1247
5	<input checked="" type="checkbox"/>	<a href="#">PLCL1</a>	<a href="#">PLCL1_HUMAN</a>	Involved in an inositol phospholipid-based intracellular signaling cascade. Shows no PLC activity to phosphatidylinositol 4,5-bisphosphate and phosphatidylinositol. Component in the phospho-dependent endocytosis process of GABA A receptor (By similarity). Regulates the turnover of receptors and thus contributes to the maintenance of GABA-mediated synaptic inhibition. Its aberrant expression could contribute to the genesis and progression of lung carcinoma. Acts as a inhibitor of PPP1C.	0.3105

**Figure 18: 1. Click the headers to open each section. 2. The Experiments section lists the objects with data. A description of the object and the data value are listed as well.**



**Figure 19: 1. Visible edges / Hidden edges are listed for each Node and Hub. 2. Click the “Edges” header to sort the table.**

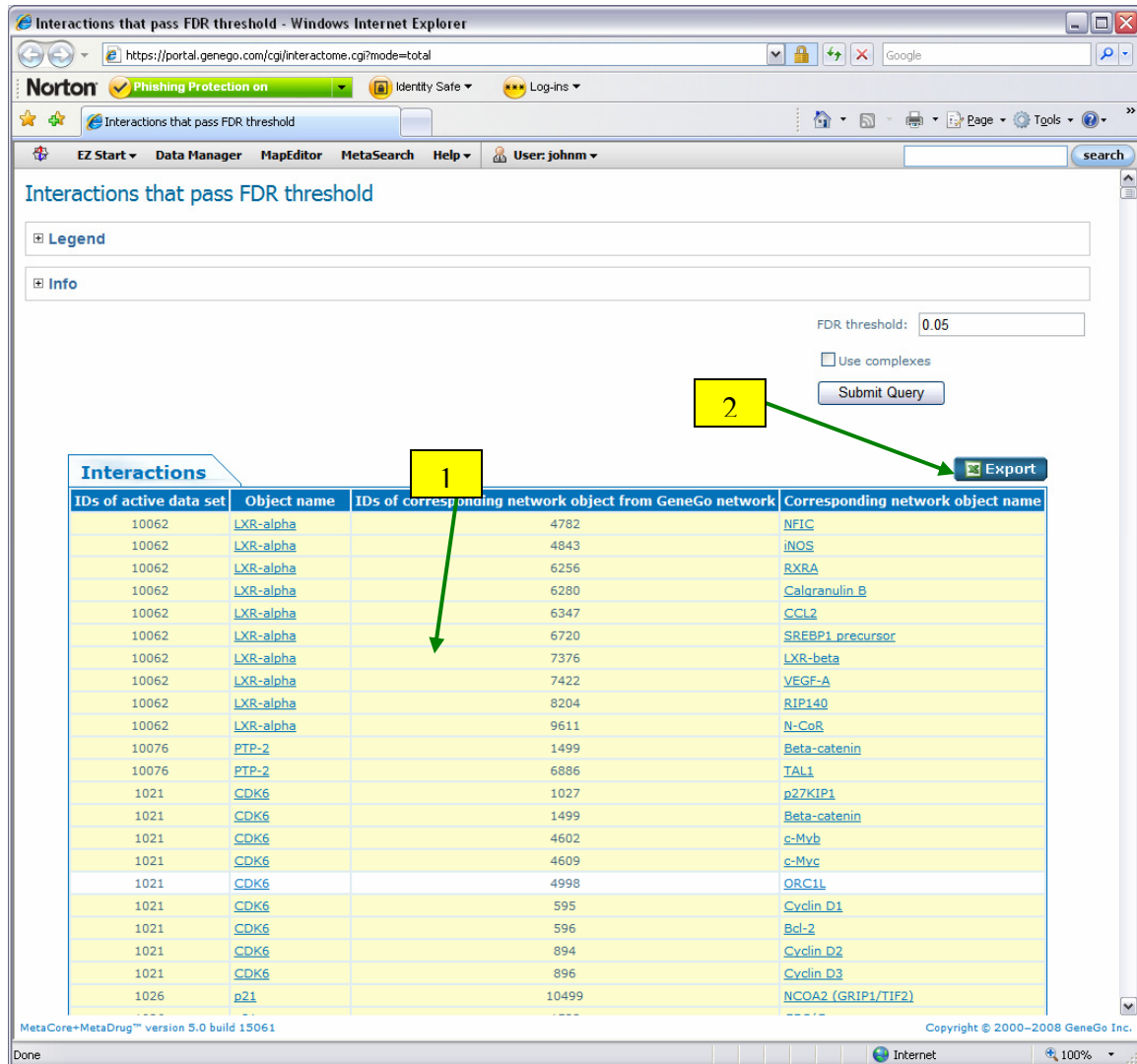
## Experiment Interactome

Similar to the network statistics for a network, the Interactome feature can show network connection information for an uploaded experiment as a whole. With this feature you can see a list of proteins that interact with the proteins from the active experiment. You can also obtain a list of how many interaction an object from your list has in total. To use this feature, first activate an experiment or gene list. Then select the desired option from the “View->Interactome for experiment” sub-menu. There are four options available, described below.

### *Interactions total*

After selecting this option, specify a p-Value threshold in the box that appears. A p-Value is calculated for each object in the active experiment based on the number of interactions it has. The threshold set here is used to filter the proteins based on this calculated p-Value.

After specifying the threshold, a window will open with a table listing the proteins from the active experiment on the left and the proteins that they interact with on the left. If both interacting proteins pass the FDR threshold, the row in the table will be colored yellow (Figure 20). The table can be exported to an Excel file by clicking the “Export” button in the upper right (Figure 20).



**Figure 20: 1. Interactions between two genes that pass the FDR threshold are highlighted. 2. Click here to export the table as an Excel file.**

### *Interactions by protein class*

This tool will generate a table listing the objects from the active experiment and the objects that they interact with. Check the “Show all columns” box to see all the values that have been calculated. The table lists the number of interactions the object has with objects in the active experiment ( $r$ ), the number of network objects in the active experiment ( $n$ ), the total number of network objects that interact with the object ( $R$ ), and the total number of network objects in the database ( $N$ ). The objects in each section are

ranked by a p-Value representing the probability that the object will have a number of interactions greater than or equal to its r value in a network created by a given number of objects. The table also lists the mean value for the hypergeometric distribution. A z-score is also calculated for each object. The z-score is  $(r - \text{mean}) / \sqrt{\text{variance}}$  (Figure 21).

Here again, you can export the information in the table to an Excel file by clicking the “Export” button in the upper right (Figure 21).

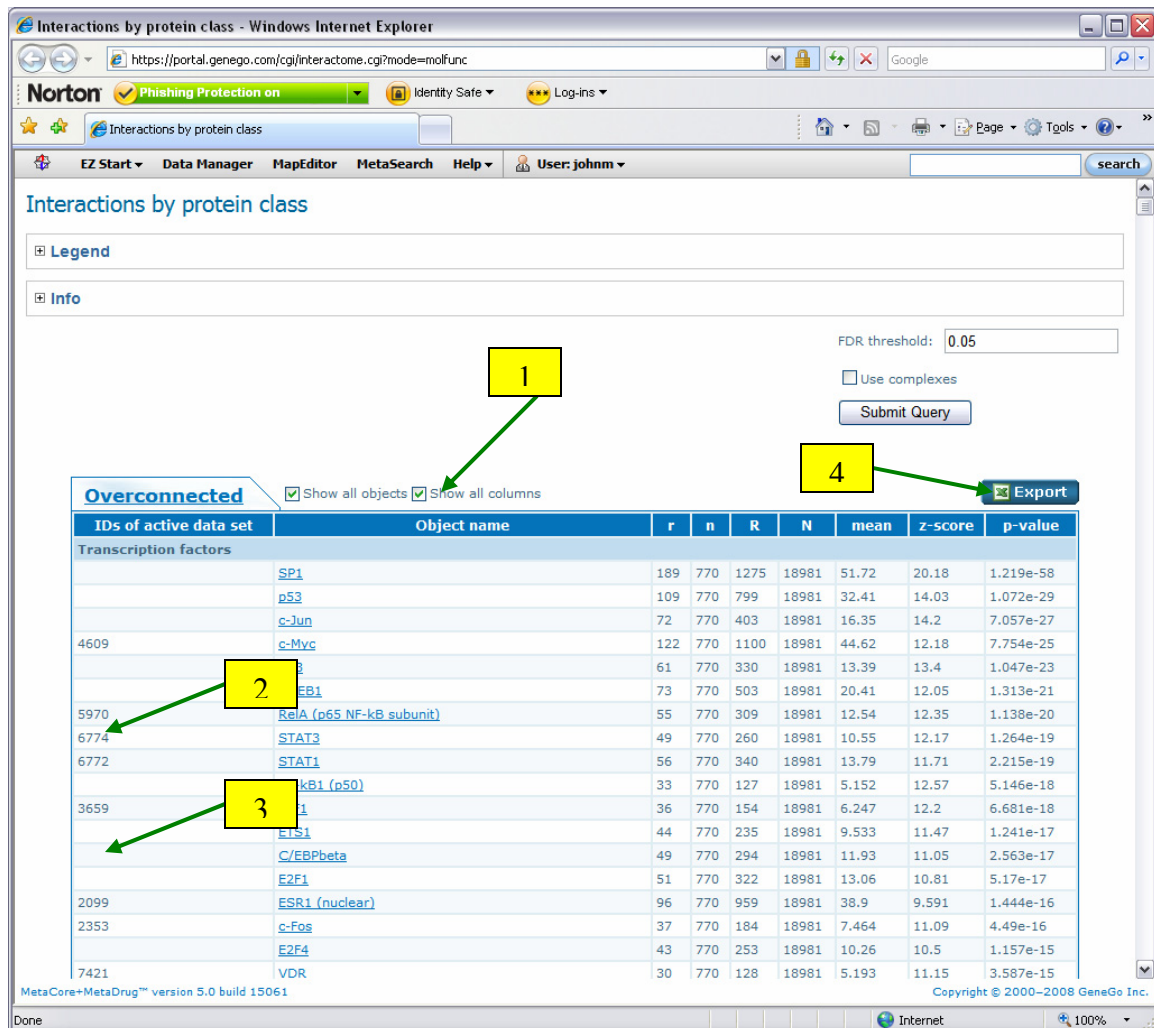


Figure 21: 1. Click here to see all the data columns. 2. Rows with a symbol are from the active experiment. 3. Rows without a symbol are objects from the database that interact with objects from the active experiment. 4. Click here to export the table as an Excel file.

### Transcription factors

This tool functions in a similar manner as the “Interactions by protein class” tool. However, this tool only lists transcription factors.

## Interactome topology

The tool calculates average degree, degree in, degree out, and clustering coefficient for the whole database, for the experiment (node calculations based on the whole database and averages based on the experiment), and for only the experiment (all calculations based only on the experiment). Similarly, this table can also be exported as an Excel file by clicking the “Export” button (**Figure 22**).

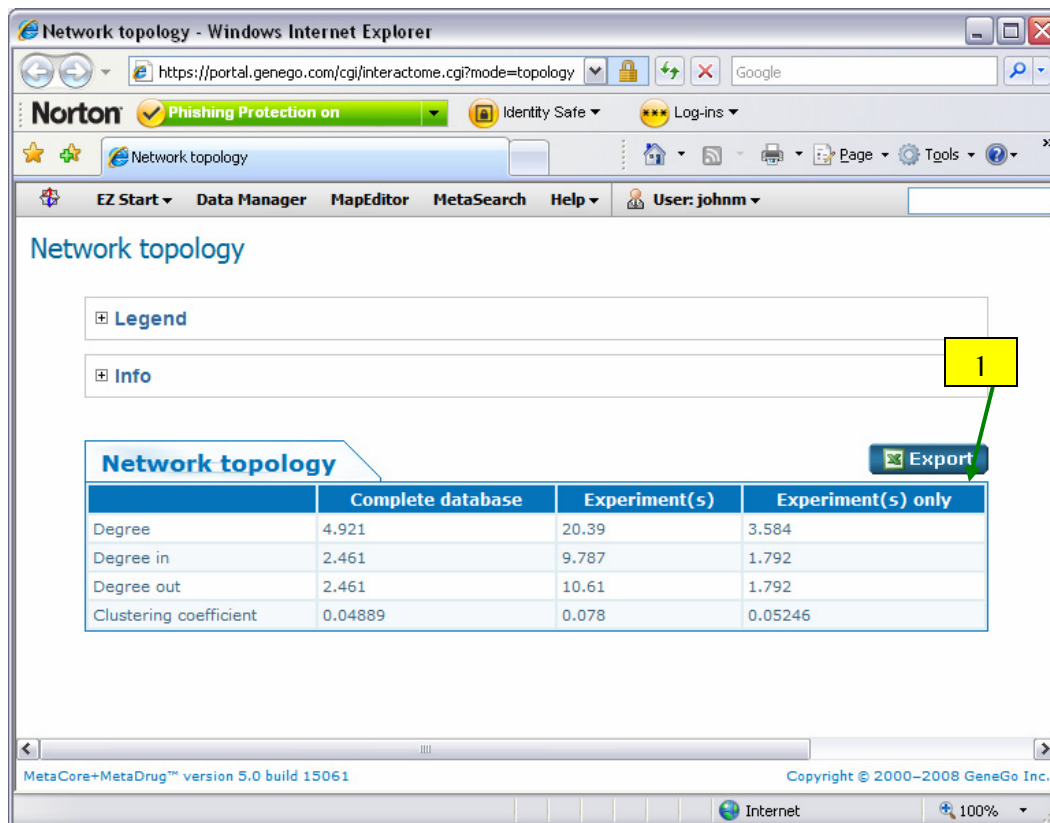


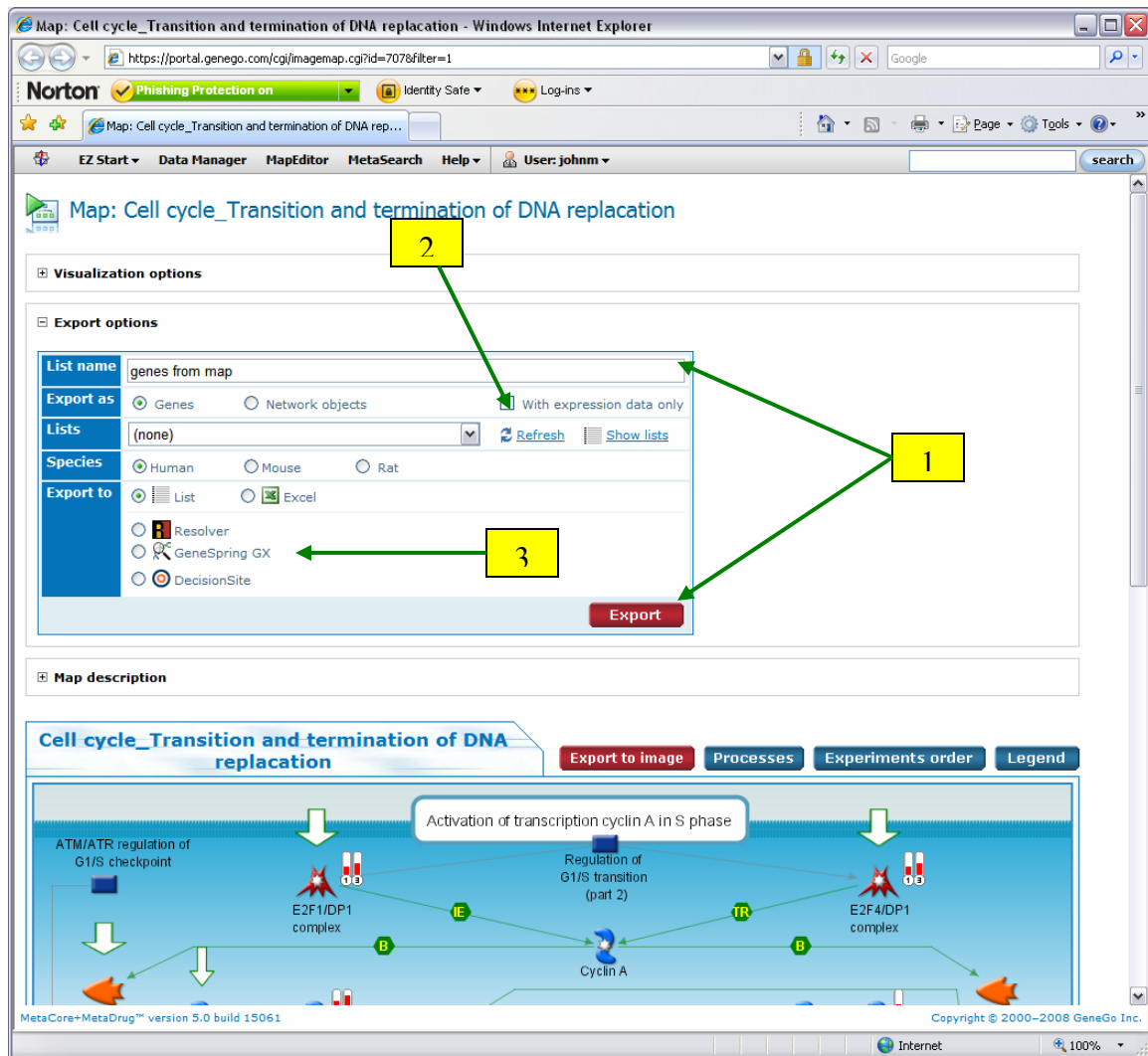
Figure 22: 1. Click here to export the table as an Excel file.

## Working with Gene Lists

There are many locations throughout MetaCore where gene lists can be exported. Most of the export panels contain various options as well. To export genes from a map, first click the “Export options” header. Then enter a name for the list. If you wish to only export those genes that have expression data, check the “With expression data only” box. Then click the Export button (**Figure 23**). Gene lists can also be exported directly to an Excel file by choosing the “Excel” option in the “Export to” row of the Export panel.

In addition, genes can be exported to the third-party analysis tools Rosetta Resolver, GeneSpring GX, and Spotfire DecisionSite. To export a gene list to one of these tools, select one of the tools in the “Export to” row, give the list a name and click Export (**Figure 23**). When exporting to Resolver a .broadcast file will be created. When exporting to GeneSpring GX a zip file will be created. The zip file can then be dragged-

and-dropped into GeneSpring GX. When exporting to Spotfire a new window will appear from which you can either load the list into a running DecisionSite window or mark the genes from the map in an already open file in DecisionSite.



**Figure 23:** 1. Enter a name and click Export to save the gene list. 2. Check this box to only export the expressed genes. 3. Select a tool to export to.

Gene lists can also be exported from the intersection groups of the Enrichment Analysis Workflow and Compare Experiments Workflow tools. To do so, right-click on the intersection bar and choose “Export genes” (**Figure 24**). In the box that pops up, give the list a name and click OK. The list will then be saved to the MetaCore Gene lists tool. The option to export the genes directly to an Excel file is also available from the right-click menu.



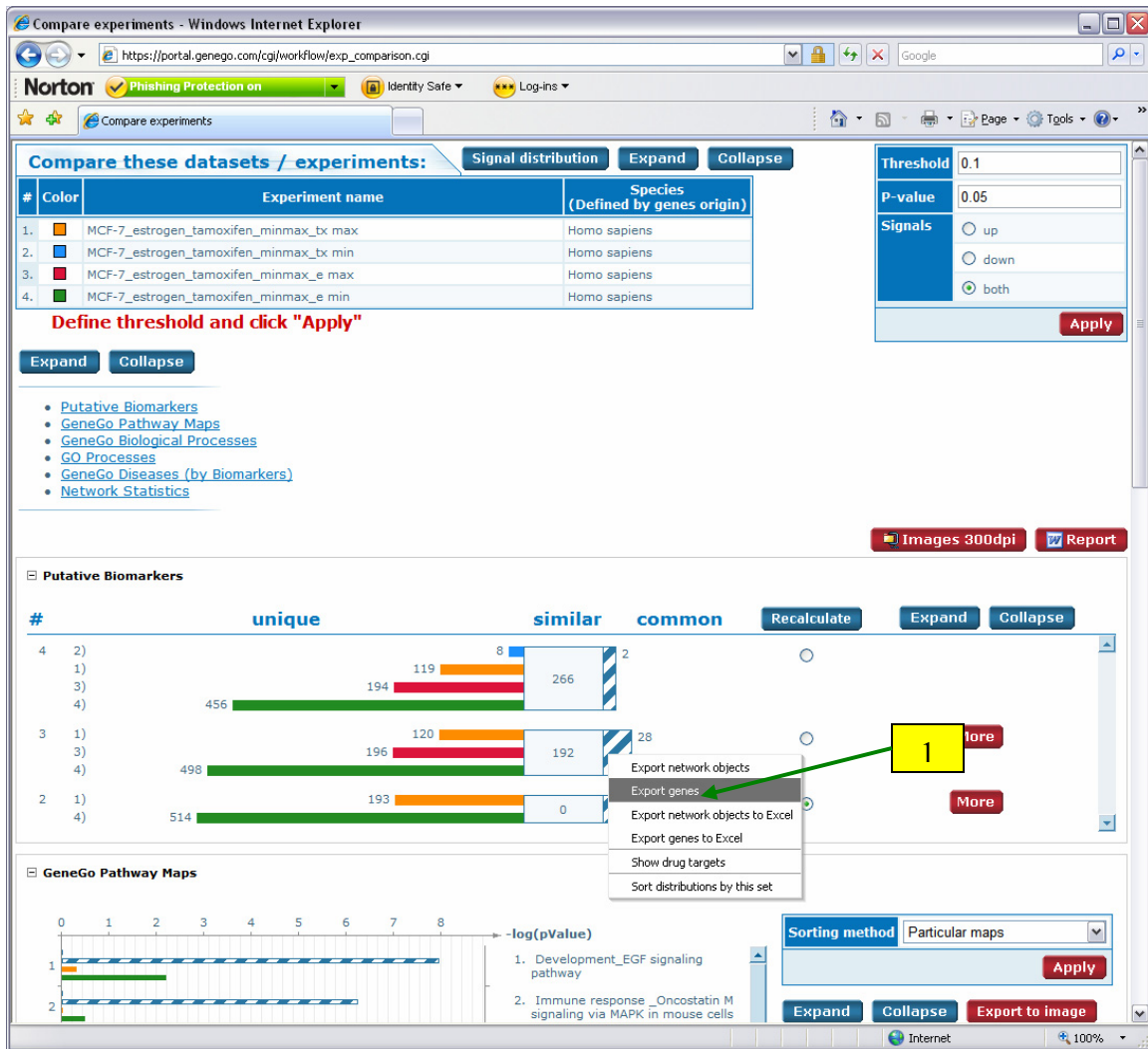
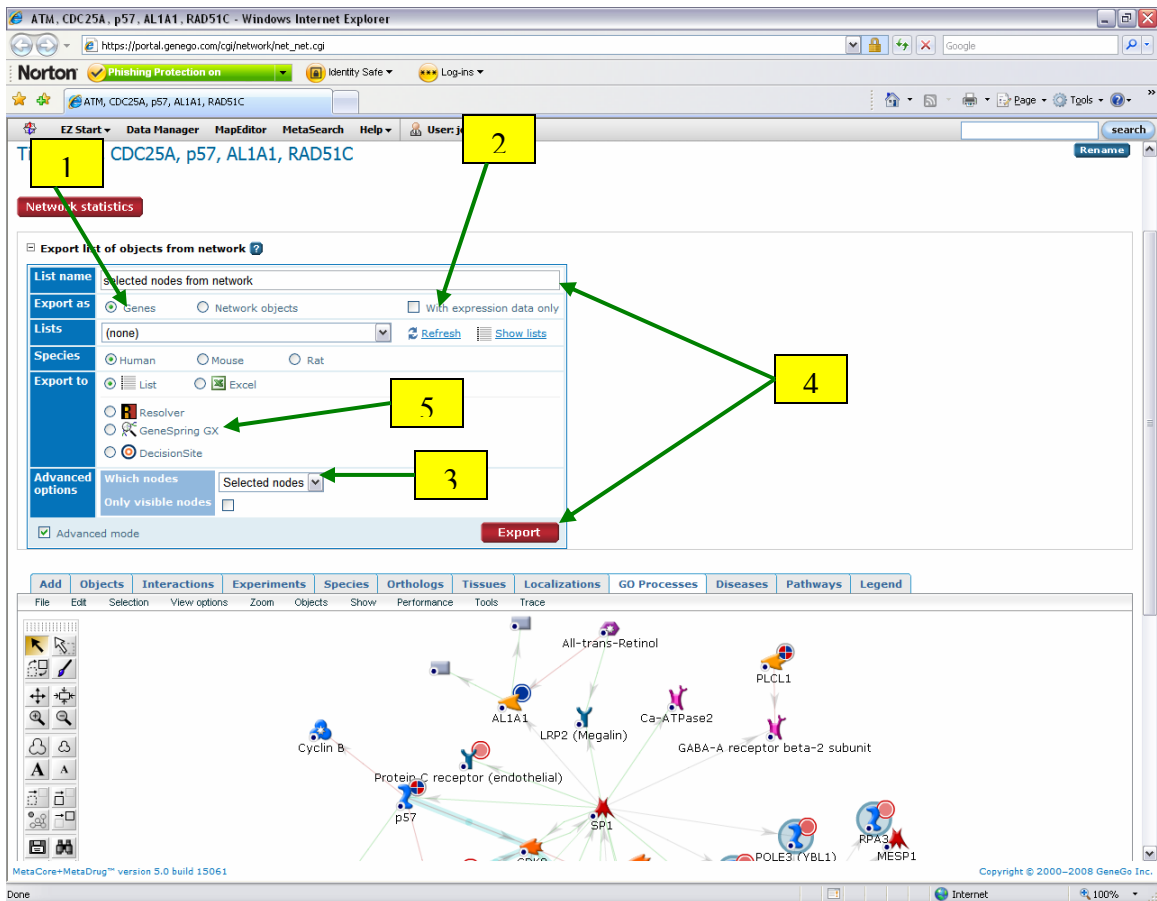


Figure 24: 1. Right-click on an intersection group to export the genes in that group.

Gene lists can also be exported from a network. Click the “Export lists of objects from network” header to open the export panel. There are multiple options for exporting genes. Not only can you choose to export all genes or only expressed genes; but you can also export only root nodes (those objects used to initially build the network), selected nodes, and visible nodes. The additional options are accessible after checking the “Advanced mode” box. For example, to export only the visible selected nodes with expression data, choose “Selected nodes” in the “Which nodes” drop-down menu, check the “Only visible nodes” box, check the “With expression data only box”, give the list a name and click Export (**Figure 25**).

Gene lists can also be exported to an Excel file or to the third-party tools Rosetta Resolver, GeneSpring GX and Spotfire DecisionSite from networks by selecting the desired option in the “Export to” row and clicking the Export button.

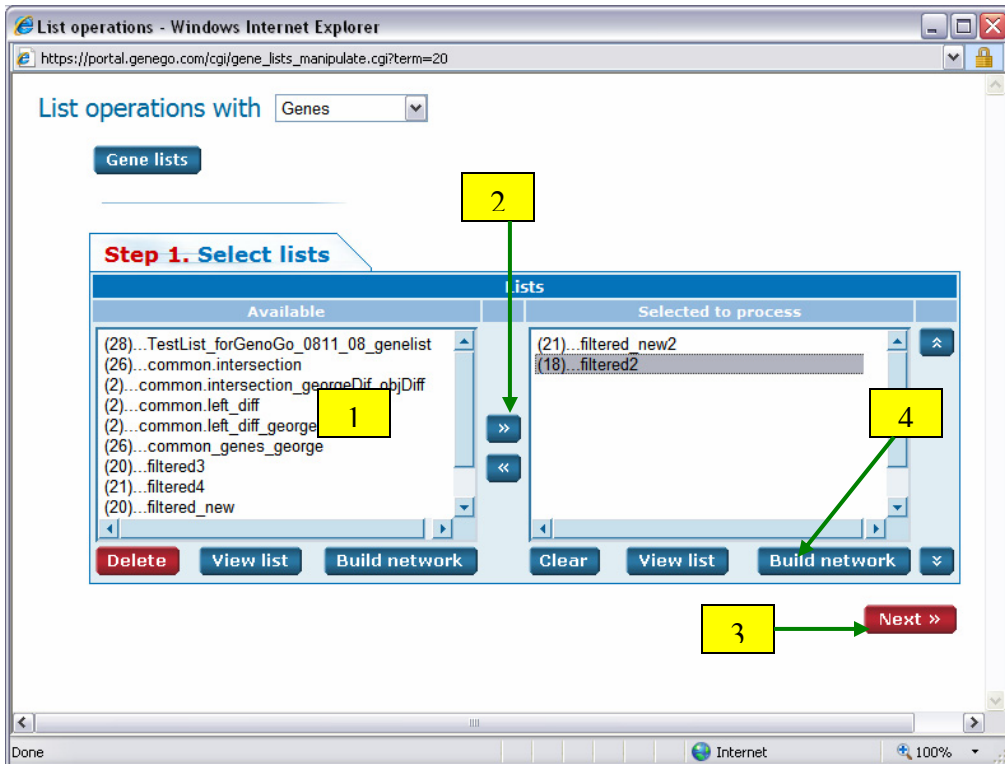




**Figure 25:** 1. Choose Genes. 2. Check this box to export only expressed genes. 3. Choose to export All, Root, or Selected nodes here. 4. Give the list a name and click Export to save the list. 5. Genes can be exported to third-part tools here.

## Logical operations

The Logical Operations tool can be used to combine and compare gene lists. The tool is accessible from the Tools menu of the Data Manager. In the first step of using the tool select the gene lists you wish to work with from the left window and click the “>>” button to move them to the right window. Then click Next (**Figure 26**).



**Figure 26:** 1. Select lists in the left window. 2. Click here to move them to the right. 3. Click Next. 4. Additionally, you can click the “Build network” button to build a network from the two selected lists without having to combine them into one.

In Step 2, choose the operation to use. The operations are Union (combine multiple lists into one), Intersection (create a list of all common genes), Exclusive OR (create a list of genes in one list, but not two), Left difference (subtract the genes in subsequent lists from the first list), List difference (create a list of the Union minus the Intersection), and Right difference (similar to Left difference except that the subtraction starts with the final list instead of the second). You can also create a list based on how many lists a gene appears in using the Index section. For example, if you chose four lists and want to see how many genes appear in three or more of them, select the “>=” option and choose ‘3’ in the Index box. After making your choice, click Next (**Figure 27**).

In step 3, give the list a name and click “Create list”. This new list will then be added to the Gene Lists tool.

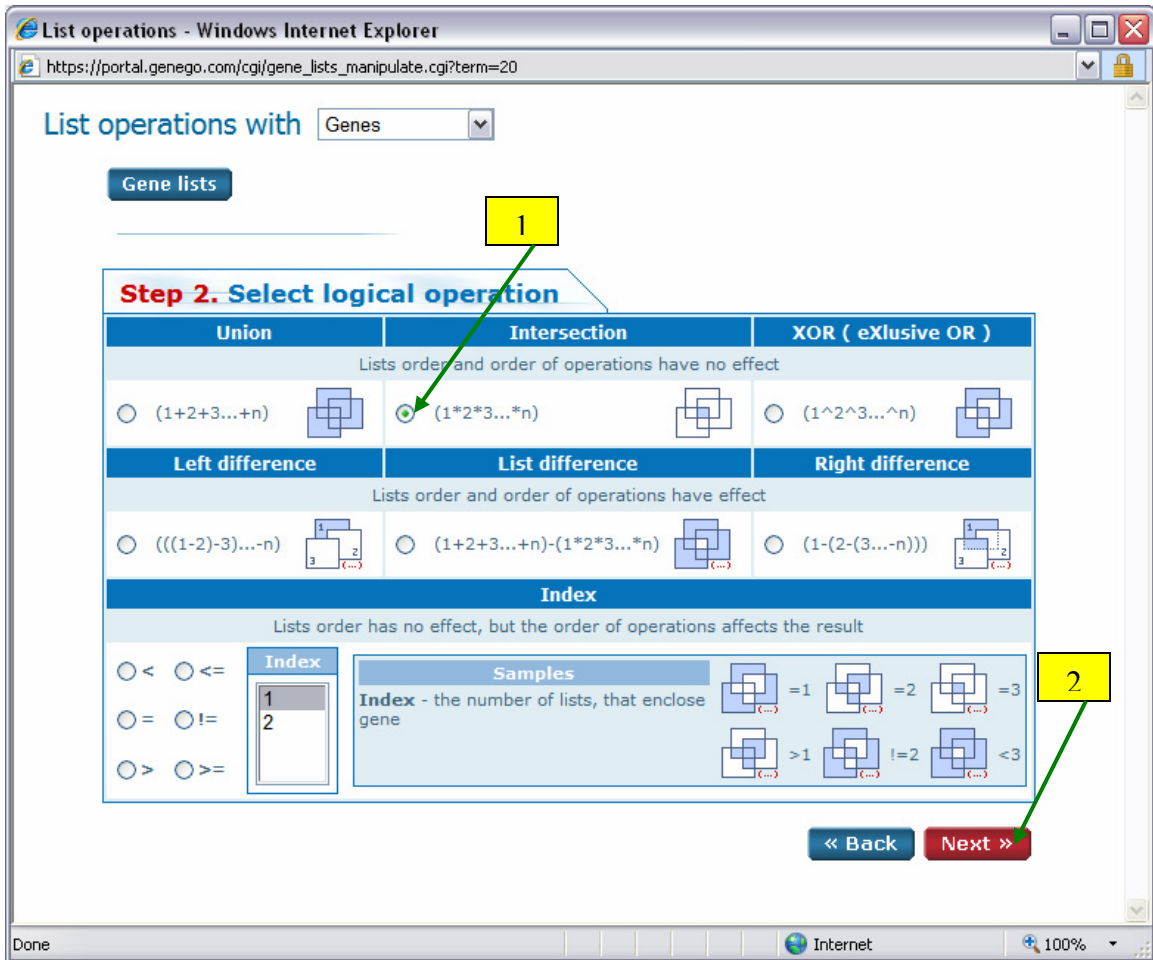
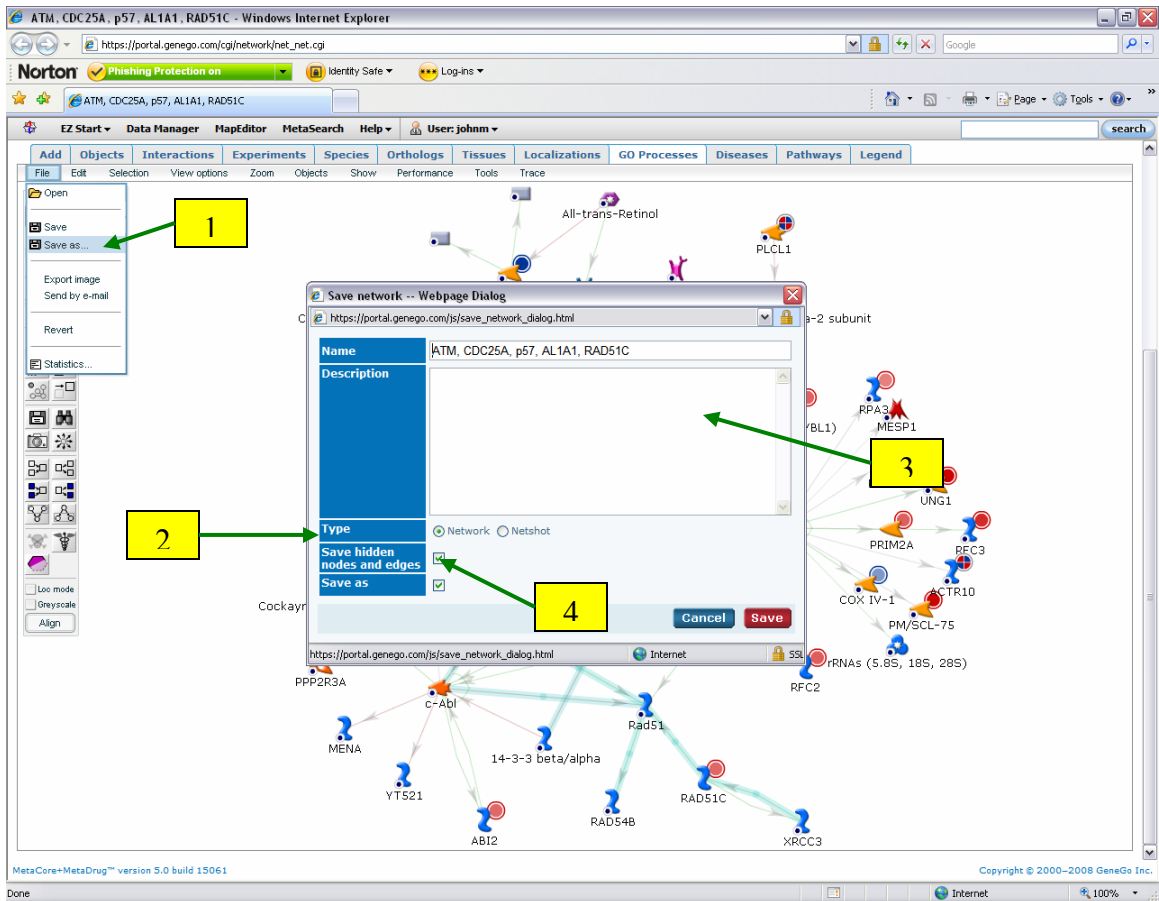


Figure 27: 1. Select an operation. 2. Click Next.

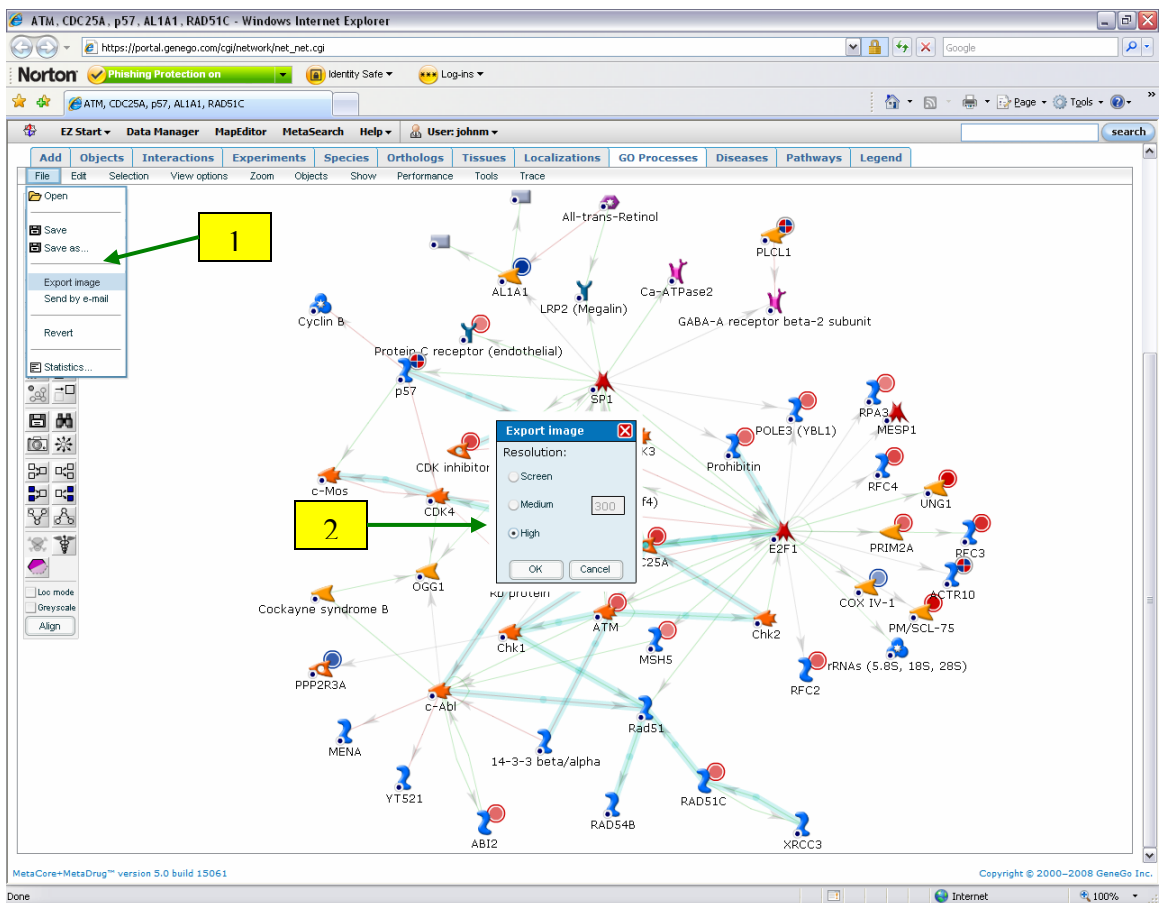
## Saving Networks and Images

Networks can be saved in two formats, Networks and Netshots. Netshots retain the network exactly as it is with any expression data mapped. Saved Networks, however, do not retain the expression data and will reflect any subsequent changes to the objects or interactions on the network as the MetaCore database is updated. So, if you save a network as both a Network and a Netshot you can see exactly how it looked when it was created (with the Netshot) and how it may have changed with subsequent MetaCore updates (with the Network). To save a network, choose “Save” or “Save as” from the File menu. Then, in the window that appears, enter a name and optional description; choose whether to save it as a Network or a Netshot; and then click “Save”. From this window you can also choose to retain or discard any hidden objects by checking or unchecking the “Save hidden nodes and edges” box (Figure 28).



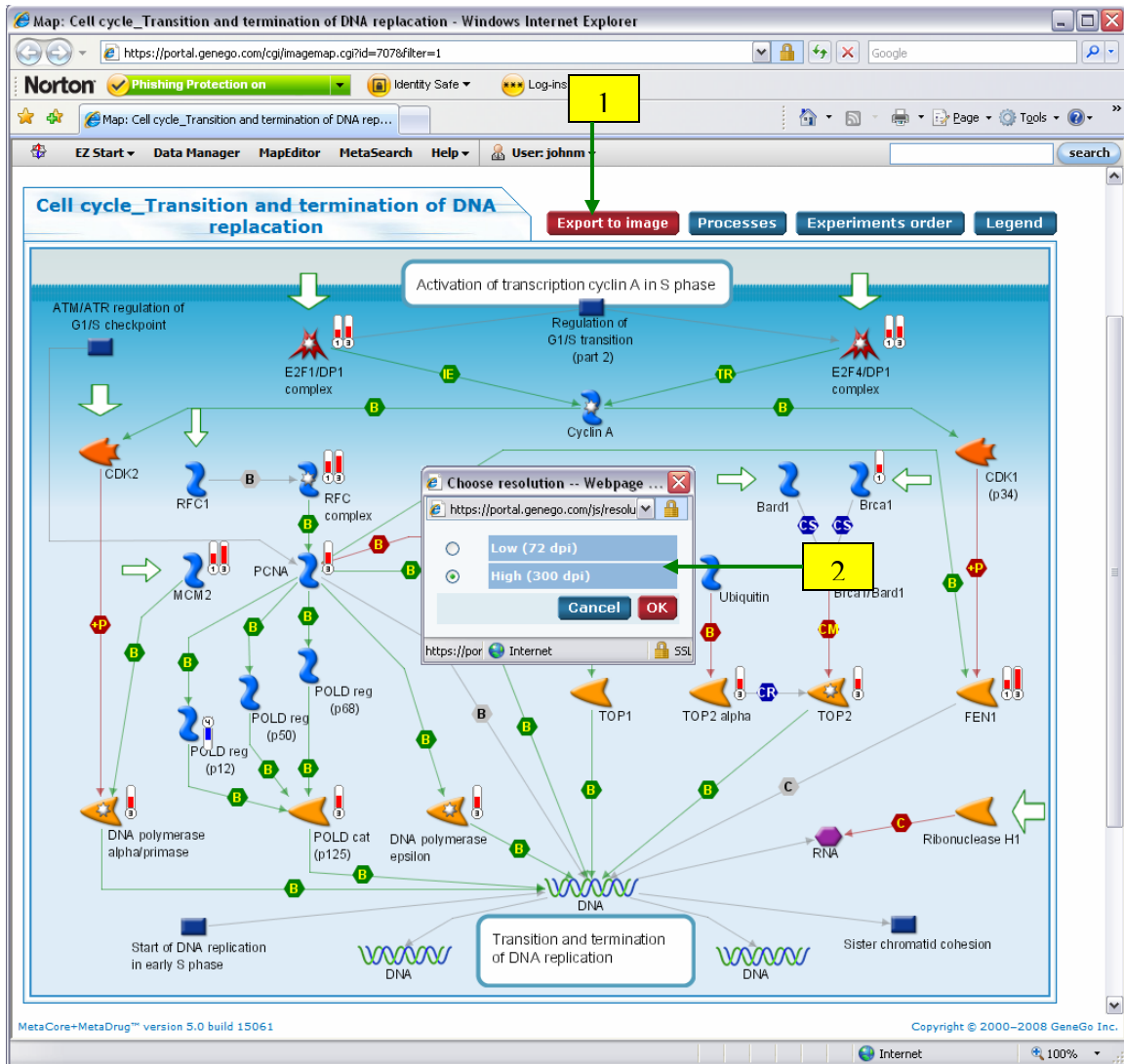
**Figure 28: 1. Click here to save the network. 2. Choose Network or Netshot here. 3. Enter a name and optional description. 4. Choose to save or discard hidden objects here.**

High quality images (300dpi) of networks and maps can be saved as well. To save an image of a network choose the “Export image” option from the file menu. In the box that appears, choose a resolution and click OK (**Figure 29**). Then browse for a location on your computer to save the file. The image file type is PNG.



**Figure 29:** 1. Click here to export an image file. 2. Choose a resolution and click OK.

An image of a map with data thermometers can also be exported to a PNG file. To do so, click the “Export to image” button. In the window that appears, select a resolution and click OK (**Figure 30**). Then browse for a location on your computer to save the file.



**Figure 30: 1.** Click here to save an image of the map with data thermometers. **2.** Choose a resolution and click OK.

## Data Sharing

With the Data Manager, you can share experiments, gene lists, and saved networks with other users or groups. There are two ways to access the share tool. You can either click Share from the File menu after selecting an experiment by Left-Clicking on it, or you can Right-Click on an experiment and select Share in the context menu. The window that comes up will display some information about the experiment and a field to search for users to share it with. Enter a username in the search field and click Search. Select a user in the results field and click "Add selected to list". The user will appear in the "Shared with" section (**Figure 31**).

There are six share levels available. The most permissive level is on the left and the least permissive level is on the right. The different levels are:



**Allow**

- OW - Owner Rights. This level will allow the user it is shared with to share it to others and to delete it.
- WA - Write Access. This level will allow the user it is shared with to rename it and to overwrite it.
- RA - Read Access. This level will only allow the user it is shared with to view the experiment(s) and related maps, networks, etc.

**Deny**

- OW - Owner Rights. Choose this level if you have, for example, allowed ownership rights to an entire folder, but would like to deny ownership right to some individual experiments within the shared folder.
- WA - Write Access. Choose this level to deny write access to individual experiments with a shared folder.
- RA - Read Access. Choose this level to totally restrict all access to a file within a shared folder.

Additionally, if you wish to completely give up your ownership of a file to another user, first select to Allow Owner Rights (OW) of the file to the other user and then check the box next to "Refuse from ownership" and click OK. You will then no longer have ownership rights to the file.

Experiments you own that are shared with other users will be marked with a blue hand icon in the Data Manager (). Experiments owned by another user that are shared with you, can be found in the Shared Data folder and they will be marked with a green hand icon (.

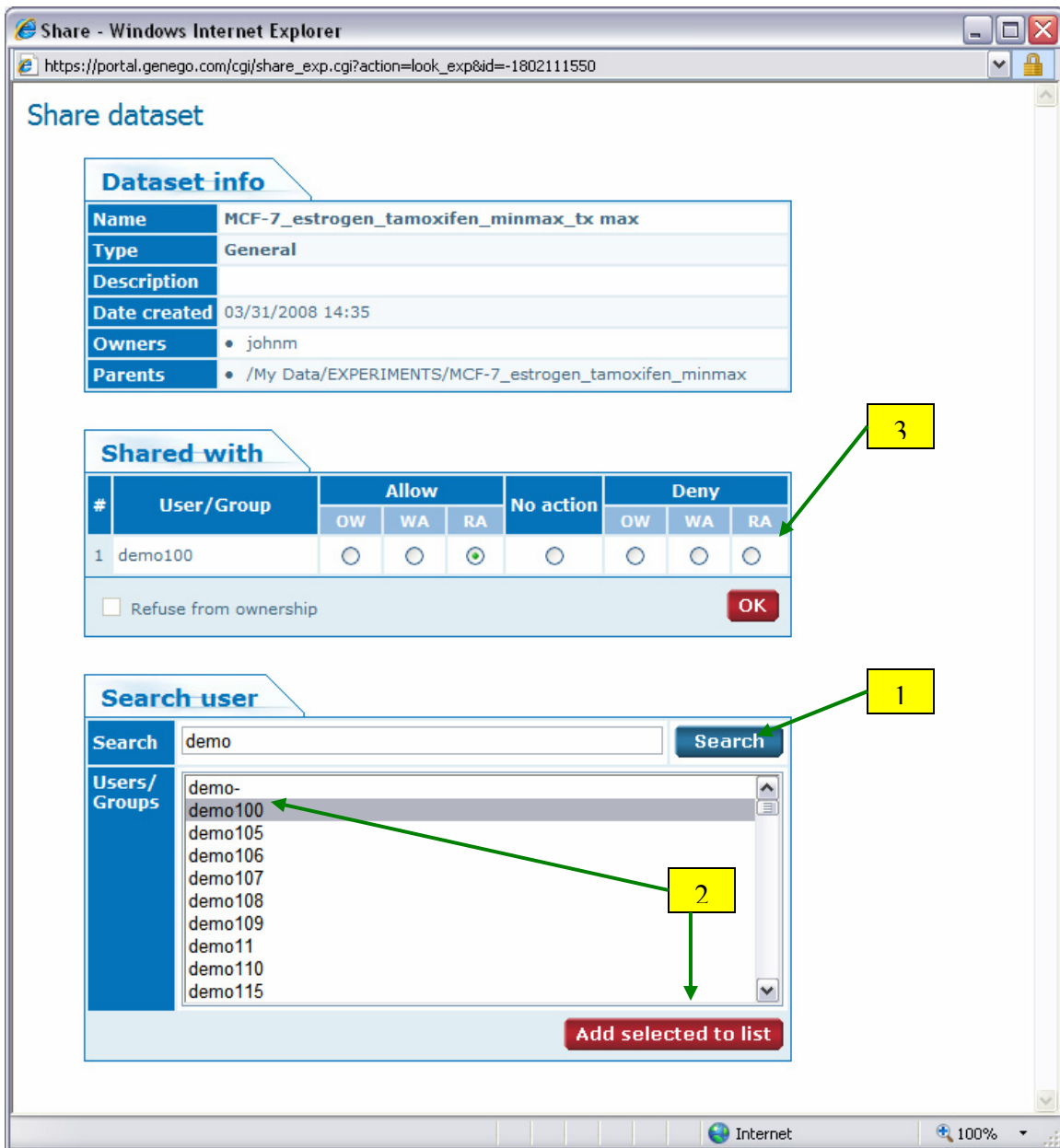
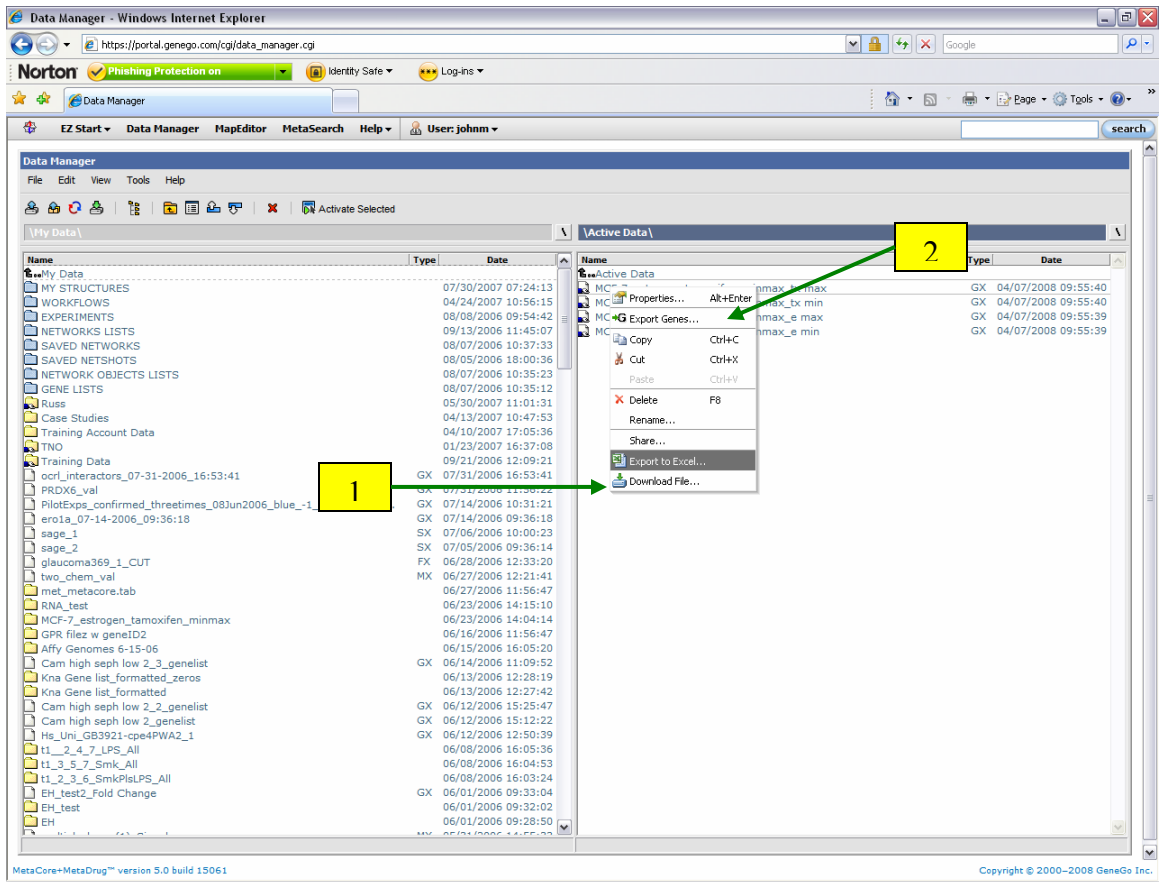


Figure 31: 1. Search for the user to share with here. 2. Select a user and click “Add selected to list”. 3. Set the sharing level and click OK.

In addition to sharing experiments, you can download the original uploaded file by right-clicking on the experiment in the Data Manager and choosing “Download file”. You can also export the experiment to Excel by choosing the “Export to Excel” option from the right-click menu (Figure 32). This option will create an Excel file containing the gene symbols and names for all the recognized genes, along with the uploaded expression data.





**Figure 32: 1. Right-click on the experiment to download the original uploaded file (“Download file”) or to “Export to Excel”. 2. This “Export genes” option will create a gene list within MetaCore containing the genes in the experiment.**