A faint, light blue network diagram consisting of numerous small circles of varying sizes connected by thin grey lines, forming a complex web-like structure.

# PathAct

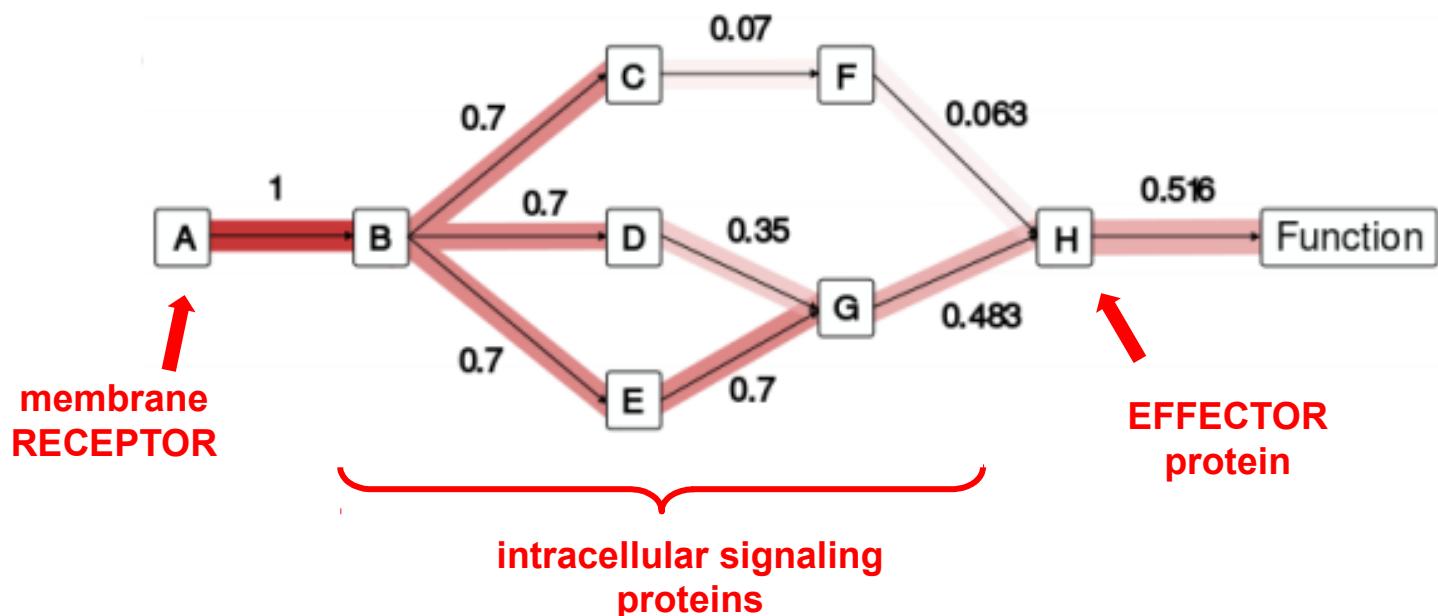
## In silico modulation of signal transduction

Marta R. Hidalgo  
June 22th, 2018



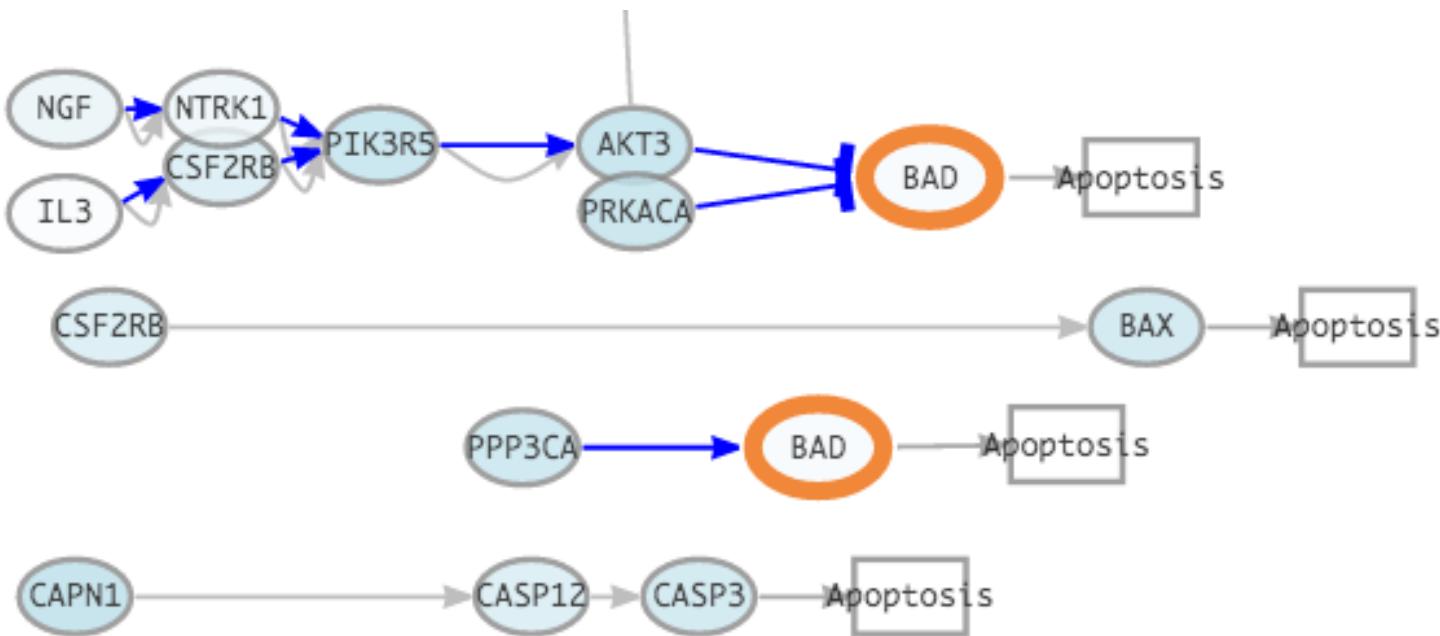
# Signal transduction modelling

In our model, signal transduction is usually modulated through all nodes between a membrane receptor and an effector protein



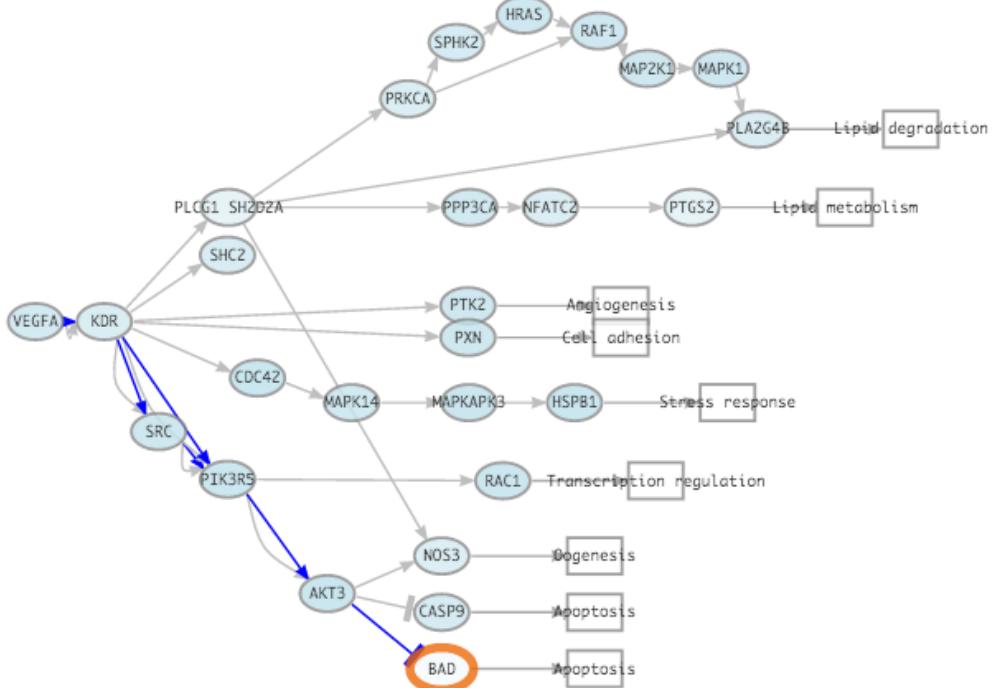
# Signal transduction modelling

We can use the same machinery to virtually explore the consequences of knocking out (or overexpress) a gene in signal transduction.



# Signal transduction modelling

This approach offers a powerful framework to design targeted therapies with minimum resources



# PathAct Web Tool



<http://pathact-course.clinbioinfosspa.es/>

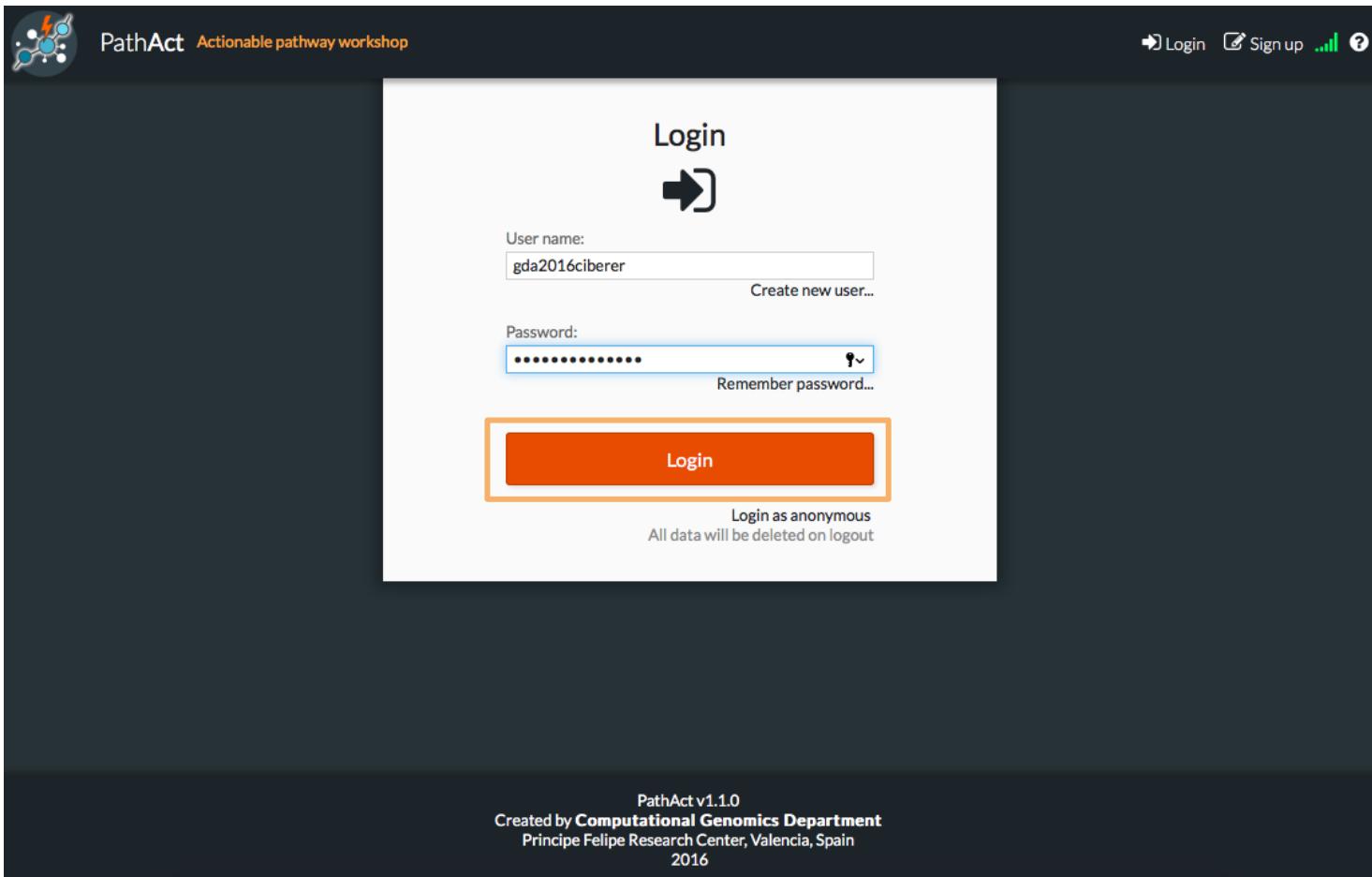


The screenshot shows the homepage of the PathAct web tool. At the top left is the PathAct logo and the text "Actionable pathway workshop". At the top right are "Login" and "Sign up" buttons, along with a search icon. Below the header, there's a large circular graphic featuring a central node with a red lightning bolt symbol, surrounded by smaller nodes and a magnifying glass icon. To the right of this graphic, the word "PathAct" is written in large white letters, with "ACTIONABLE PATHWAY WORKSHOP" in smaller orange text below it. A large orange button labeled "Start" with a white rocket ship icon is positioned next to a numbered circle "1". Numbered circles "2" and "3" are also present. The main text area describes the tool's purpose: "PathAct is a web tool that enables the study of the consequences that Knockouts(KOs) or over-expressions of genes can have over signalling pathways. PathAct implements robust models of signalling pathways within an advanced graphical interface that provide a unique interactive working environment in which actionable genes, that could become potential drug targets, can be easily assayed alone or in combinations. Also the effect of drugs with known targets over the different signalling pathways can be studied. Since signals trigger functions across the pathways, the direct and long-distance functional consequences of interventions over genes can be straightforwardly revealed through this actionable pathway scenario." At the bottom, there's a "Notes" section and copyright information: "PathAct v1.1.0", "Created by Computational Genomics Department", "Principe Felipe Research Center, Valencia, Spain", and "2016".

# PathAct Web Tool



<http://pathact-course.clinbioinfosspa.es/>



The image shows the login interface of the PathAct Web Tool. The header includes the PathAct logo, the text "Actionable pathway workshop", and links for "Login" and "Sign up". Below the header is a "Login" form. It features a large orange "Login" button at the bottom. Above it, there are fields for "User name:" containing "gda2016ciberer" and "Password:" containing a masked password. To the right of the password field is a "Remember password..." link. At the bottom of the form is a link to "Login as anonymous" with the note "All data will be deleted on logout". The footer contains the text "PathAct v1.1.0", "Created by Computational Genomics Department", "Principe Felipe Research Center, Valencia, Spain", and the year "2016".

# PathAct Web Tool

PathAct Actionable pathway workshop

Create a new job

1. In order to create a job, a file must be selected from the server, if the file is not already in the server it should be uploaded first, both actions can be performed using the following button.

Please click [here](#) to read more about the input file format.

1

hcc4006\_mutant\_dmso.txt

2. Now select a sample from your expression matrix file.

Log<sub>e</sub> transform data matrix

hcc4006\_mutant\_dmso

3. To finish, set a name for your job, and press the run button.

Jobs

Settings gda2016ciberer Profile Logout

Use an existing job

Search by name...

<input checked="" type="checkbox"/>	HCC4006 mutant dmso-hcc4006_mutant_dmso.txt Pathact-Init Done 28/9/2016 12:14:59	<input type="button" value="Delete"/> <input type="button" value="Download"/>
<input checked="" type="checkbox"/>	HCC4006_mutant_dmso-hcc4006_mutant_dmso.txt Pathact-Init Done 28/9/2016 12:11:39	<input type="button" value="Delete"/> <input type="button" value="Download"/>
<input checked="" type="checkbox"/>	Example Pathact-Init Done 28/9/2016 11:54:27	<input type="button" value="Delete"/> <input type="button" value="Download"/>

Total: 3

Enable job notifications

# PathAct Web Tool

The screenshot shows the PathAct Web Tool interface. At the top, there is a navigation bar with the PathAct logo, a search bar containing "Actionable pathway workshop", and links for "Jobs", "Settings", "Profile", "Logout", and a help icon. Below the navigation bar, there are two main sections: "Create a new job" on the left and "Use an existing job" on the right. A central modal dialog is open, titled "Select Expression Matrix File...", showing a file browser interface. The browser has a sidebar with a tree view of folders under "/PathAct\_Exercises/", including "gda2016ciberer", "BRCA\_exercise", "KIRC\_exercise", "PathAct\_Exercises", "gse36807\_exercise", and "gse51835\_exercise". The main area shows a single file named "Example" with a size of 81.7 MB and a date of Sep 28, 2016. An "Upload" button is highlighted with a red box. At the bottom of the modal, there are buttons for "All", "Gene", "Sample", "Experiment", and "Search by name...". The status bar at the bottom of the page indicates "Total: 1" and "Enable job notifications".

# PathAct Web Tool

The screenshot shows the PathAct Web Tool interface. At the top, there is a navigation bar with icons for Home, Jobs, Settings, Profile, Logout, and Help. Below the navigation bar, there are two main sections: "Create a new job" and "Use an existing job". A central modal dialog is open, titled "Upload File".  
The modal contains the following steps:

- 1.** File upload: A button labeled "Choose file..." is highlighted with an orange circle.
- 2.** Bioformat: A dropdown menu showing "Data matrix expression" is highlighted with an orange circle.
- 3.** Upload: A large orange button labeled "Upload" is highlighted with an orange circle.

Other visible elements in the modal include:

- A "Selected file:" field containing "hcc4006\_mutant\_dmso.txt".
- A "Revalidate" button.
- A "File validation log" section showing one warning message:

Line	Type	Message
19766	warning	Empty line.
- Statistics at the bottom: "Errors: 0", "Warning: 1", "Info: 0", and "Lines: 19766".

# Select data

gene expression data

<http://bioinfo.cipf.es/gda16ciberer>

## File format

Columns: GeneIDs + Sample

Rows: EntrezGene (id)

## Example

Non-small cell lung cancer (NSCLC)

EGFR mutant

Not treated with Erlotinib (TKIs)

geneID	hcc4006_mutant_dmso
1	5.99830927735415
10	4.26909388237212
100	7.90281107406193
1000	8.46383745767134
10000	5.82801370891263
100009676	5.95028396323201
10001	9.24054483957849
10002	4.50114481512442
10003	2.84739433259492
10004	4.59393709385877
100048912	3.2801596933055
10005	7.61874234203795
10006	8.67399667422145
10007	9.68407263257293
10008	4.72208873889579
10009	8.67753823201646
100093630	9.99164686804014
100093698	2.90650126505663
1001	11.4324736716045
10010	8.27543394593235
100101467	5.19948516713951
100101938	4.20778055144368
10011	9.43505129657583
100113407	3.3861342172626
100124700	4.55907367543182
100125288	5.92518975661431
100126784	5.23839965772242

# Select data

PathAct Actionable pathway workshop

Create a new job

[Run example](#)

1. In order to create a job, a file must be selected from the server, if the file is not already in the server it should be uploaded first, both actions can be performed using the following button.

Please click [here](#) to read more about the input file format.

1  hcc4006\_mutant\_dmso.txt

2. Now select a sample from your expression matrix file.

2  hcc4006\_mutant\_dmso

3. To finish, set a name for your job, and press the run button.

3

4

Jobs

Settings gda2016ciberer Profile Logout

Use an existing job

5

Search by name...

HCC4006 mutant dmso-hcc4006\_mutant\_dmso.txt  
Pathact-Init Done 28/9/2016 12:14:59

HCC4006\_mutant\_dmso-hcc4006\_mutant\_dmso.txt  
Pathact-Init Done 28/9/2016 12:11:39

Example  
Pathact-Init Done 28/9/2016 11:54:27

Total: 3

Enable job notifications

# Overexpression

PathAct Actionable pathway workshop

Jobs Settings gda2016ciberer Profile Logout

6 4 5 2 1 3

ErbB signaling pathway (hsa04012)

Show report

Add genes: Gene search (min 2 char)

Select gene related drugs:

Add drugs: Drug search (min 3 char)

Genes affected by drugs:

Category: Filter... Adherens junction, Adipocytokine signaling pathway, Adrenergic signaling in cardiomyocytes, AMPK signaling pathway, Apoptosis, B cell receptor signaling pathway, Calcium signaling pathway, cAMP signaling pathway, Cell cycle, cGMP-PKG signaling pathway, Chemokine signaling pathway, Choline metabolism in cancer, ErbB signaling pathway, Estrogen signaling pathway, Focal adhesion, G-protein coupled receptor signaling pathway, HIF-1 signaling pathway, Integrin signaling pathway, MAPK signaling pathway, PI3K-Akt signaling pathway, Phagosome, Protein processing in endoplasmic reticulum, RAS signaling pathway, Recepto...

Circuit list: ABL1, BAD, CAMK2A, CBLC, CDKN1A, CDKN1B, EIF4EBP1, ELK1, ERBB3 ERBB3, GSK3B, JUN, MYC, PRKCA

Last update gene list:

The diagram illustrates the ErbB signaling pathway (hsa04012). It starts with EGFR (ErbB1) and ERBB2 (ErbB2), which are activated by EGF and TGFα. These receptors dimerize and recruit Grb2 (GRB2), which then activates SOS1. SOS1 triggers a cascade through HRAS, ARAF, MAP2K1, and MAPK1 (ERK1/2). This leads to the activation of MYC and ELK1, both of which are involved in transcription regulation. The pathway also involves PIK3R5, AKT3, and GAB1, leading to the activation of BAD, GSK3B, and CDKN1B, which regulate apoptosis and neurogenesis. Other components include NCK1, PAK4, MAP2K7, MAPK8, CRK, ABL1, SRC, STAT5A, CBLC, PRKCA, CAMK2A, and PLCG1, each associated with various biological processes like apoptosis, angiogenesis, and transcription regulation.

# Overexpression

PathAct Actionable pathway workshop

Jobs Settings gda2016ciberer Profile Logout

**4** Add genes:  2  
 0,95   
 0,95

**1** Category: 0 altered  
 Adherens junction  
 Adipocytokine signaling pathway  
 Adrenergic signaling in cardiomyocytes  
 AMPK signaling pathway  
 Apoptosis  
 B cell receptor signaling pathway  
 Calcium signaling pathway  
 cAMP signaling pathway  
 Cell cycle  
 EGFR signaling pathway  
 ErbB signaling pathway  
 Estrogen signaling pathway  
 Fatty acid metabolism in cancer  
 G-protein coupled receptor signaling pathway  
 Integrin signaling pathway  
 Insulin signaling pathway  
 MAPK signaling pathway  
 Nervous system development  
 Oncostatin M signaling pathway  
 Phagosome  
 Protein processing in endoplasmic reticulum  
 Receptor tyrosine kinase signaling pathway  
 Retinoblastoma signaling pathway  
 Signaling by tyrosine kinase receptors  
 Small molecule biochemistry  
 T cell receptor signaling pathway  
 Transcription factor activity, sequence-specific DNA binding  
 Wnt signaling pathway

**2** Select gene related drugs:  
 Cetuximab  
 Trastuzumab  
 Lidocaine  
 Gefitinib  
 Erlotinib  
 Lapatinib  
 Panitumumab

**3** Add drugs:

**4** Genes affected by drugs:

**5** Circuit list: 0 altered  
 ABL1  
 BAD  
 CAMK2A  
 CBLC  
 CDKN1A  
 CDKN1B  
 EIF4EBP1  
 ELK1  
 ELK1  
 ERBB3 ERBB3  
 GSK3B  
 JUN  
 MYC  
 PRKCA

**6** Last update gene list:

# Overexpression

**PathAct Actionable pathway workshop**

**ErbB signaling pathway (hsa04012)**

**Category:** 14 altered

**Circuit list:** 16 altered

**Last update gene list:** gene - w - origin  
EGFR - 0.95 - user

1

2

3

4

# Overexpression

**PathAct Actionable pathway workshop**

Jobs Settings gda2016ciberer Profile Logout ?

+ New   Clear  

Add genes: /update

Q: EGF 2  
EGFR 0,95      
EGFR EGFR 0,95    

Select gene related drugs:  
 Cetuximab  
 Trastuzumab  
 Lidocaine  
 Gefitinib  
 Erlotinib  
 Lapatinib  
 Panitumumab

Add drugs:  
 Drug search (min 3 char)

Genes affected by drugs:

**ErbB signaling pathway (hsa04012)**

2

Show report

Category: 14 altered

Filter...  
↑ ↓ Adherens junction  
↑ ↓ Choline metabolism in cancer  
↑ ↓ ErbB signaling pathway  
↑ ↓ Estrogen signaling pathway  
↑ ↓ Focal adhesion  
↑ ↓ Gap junction  
↑ ↓ HIF-1 signaling pathway  
↑ ↓ MAPK signaling pathway  
↑ ↓ Oxytocin signaling pathway  
↑ ↓ Pathways in cancer  
↑ ↓ PI3K-Akt signaling pathway  
↑ ↓ Proteoglycans in cancer  
↑ ↓ Rap1 signaling pathway  
↑ ↓ Ras signaling pathway

Circuit list: 16 altered

1

- ↑ ↓ ABL1
- ↓ BAD
- ↑ ↓ CAMK2A
- ↑ ↓ CBLC
- ↓ CDKN1A
- ↓ CDKN1B
- ↓ EIF4EBP1
- ↑ ↓ ELK1
- ↑ ↓ ERK1
- ↓ GSK3B
- ↑ ↓ JUN
- ↑ ↓ MYC
- ↑ ↓ PRKCA
- ↓ RAK2

Last update gene list:  
 gene - w - origin  
 EGFR - 0.95 - user

# Results interpretation

ge:  |logFC| > log(2) = 0.693

on weight:

or:

relation:

itive:

0,1	Activator:
0,1	Agonist:
0,1	Antagonist:
0,1	Binder:
0,1	Blocker:
0,1	Chelator:
0,1	Cofactor:
0,1	Conversion Inhibitor:
0,1	Desensitize The Target:
0,1	Incorporation Into And Destabilization:
1	Inhibitor:
0,1	Inhibitory Allosteric Modulator:
0,1	Inverse Agonist:
0,1	Metabolizer:
0,1	Multitarget:

# Report

C Report x

5 R 0,9

ne rel  
hab  
umab  
he  
b  
b  
::  
arch (

ected b

Circuit impact  $|logFC| > \log(2) = 0.693$

grid Circuit changes ▼

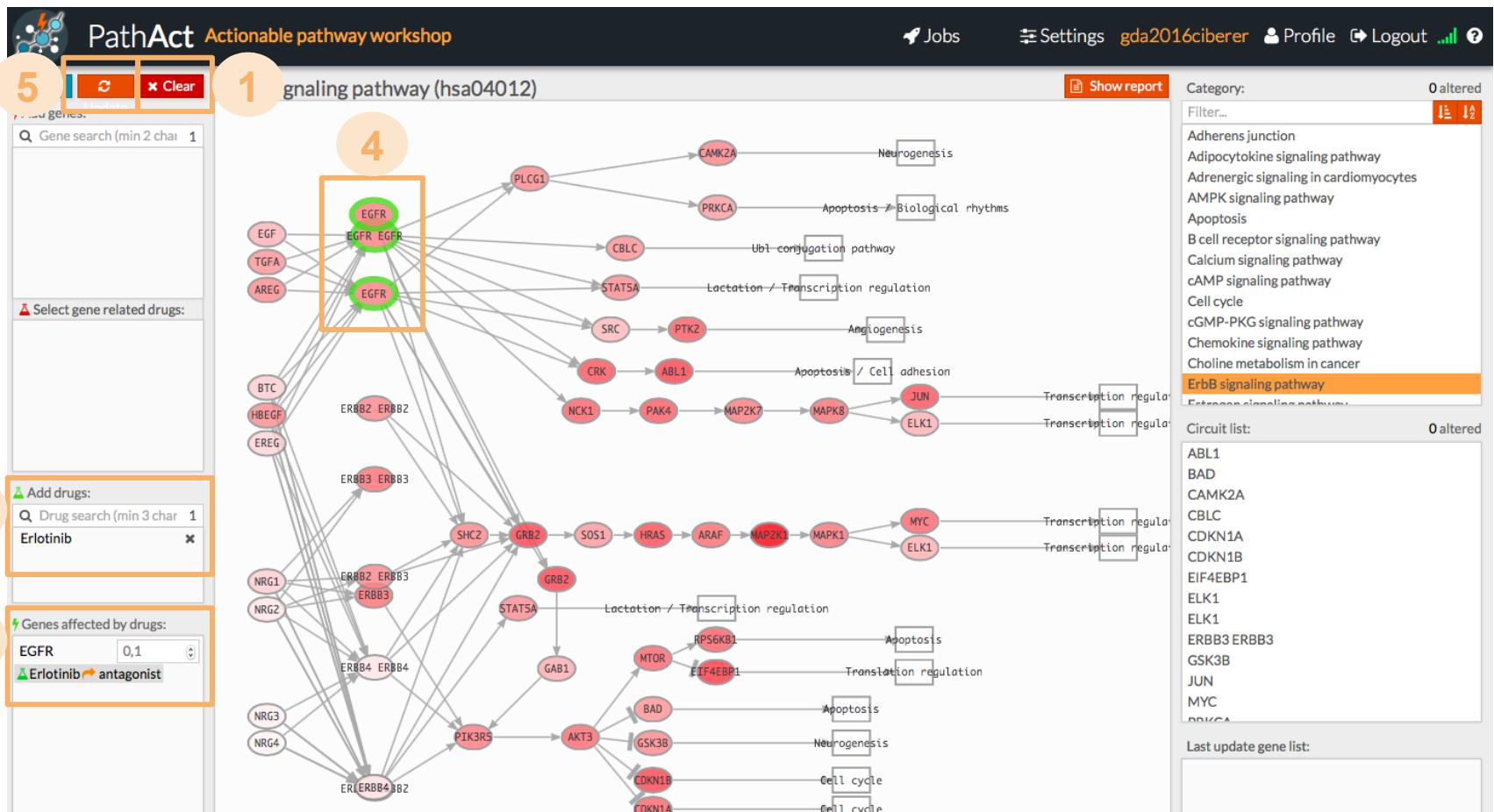
circuit	log_fold_change	sig
Adherens junction: CTNND1	-1.665	TRUE
Adherens junction: LEF1 CTNNB1	-1.665	TRUE
Estrogen signaling pathway: AKT3*	0.708	TRUE
ErbB signaling pathway: JUN	0.708	TRUE
ErbB signaling pathway: ELK1*	0.708	TRUE
ErbB signaling pathway: CBLC	0.708	TRUE
Oxytocin signaling pathway: CDKN1A	0.708	TRUE
Estrogen signaling pathway: ESR1 C00951	0.708	TRUE
Estrogen signaling pathway: ESR1 FOS	0.708	TRUE
Estrogen signaling pathway: ESR1 C00951*	0.708	TRUE

« < Page 1 of 15 > »

Close

cancer  
ray  
way  
hway

# Drug action



# Drug action

**PathAct Actionable pathway workshop**

**ErbB signaling pathway (hsa04012)**

**3**

**Category:** 10 altered

**Filter...**

- ↑ ↓ Adherens junction
- ↑ ↓ Choline metabolism in cancer
- ↑ ↓ ErbB signaling pathway**
- ↑ ↓ Estrogen signaling pathway
- ↑ ↓ Gap junction
- ↑ ↓ HIF-1 signaling pathway
- ↑ ↓ MAPK signaling pathway
- ↑ ↓ Oxytocin signaling pathway
- ↑ ↓ Pathways in cancer
- ↑ ↓ Proteoglycans in cancer

Adipoacytokine signaling in cardiomyocytes  
AMPK signaling pathway  
Apoptosis

**1**

**Circuit list:** 16 altered

- ↓ ABL1**
- ↑ BAD
- ↓ CAMK2A
- ↓ CBLC
- ↑ CDKN1A
- ↑ CDKN1B
- ↑ EIF4EBP1
- ↓ ELK1
- ↓ ELK1
- ↑ GSK3B
- ↓ JUN
- ↓ MYC
- ↓ PRKCA
- ↓ PTK2

**2**

Last update gene list:  
gene - w - origin  
EGFR - 0.1 - drug

**Gene search (min 2 char):** 1

**Select gene related drugs:**

**Add drugs:**

**Drug search (min 3 char):** 1

Erlotinib

**Genes affected by drugs:**

EGFR 0,1

Erlotinib → antagonist



Thanks for your attention

Any questions?