



# PathAct

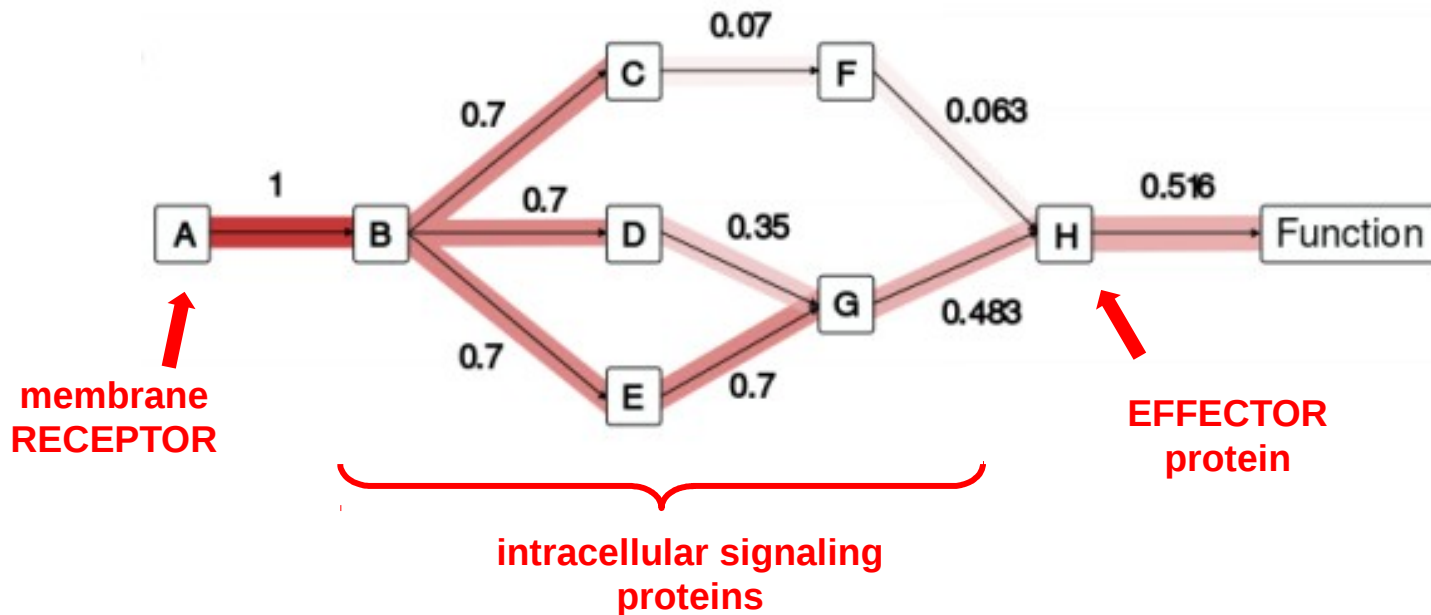
## In silico modulation of signal transduction

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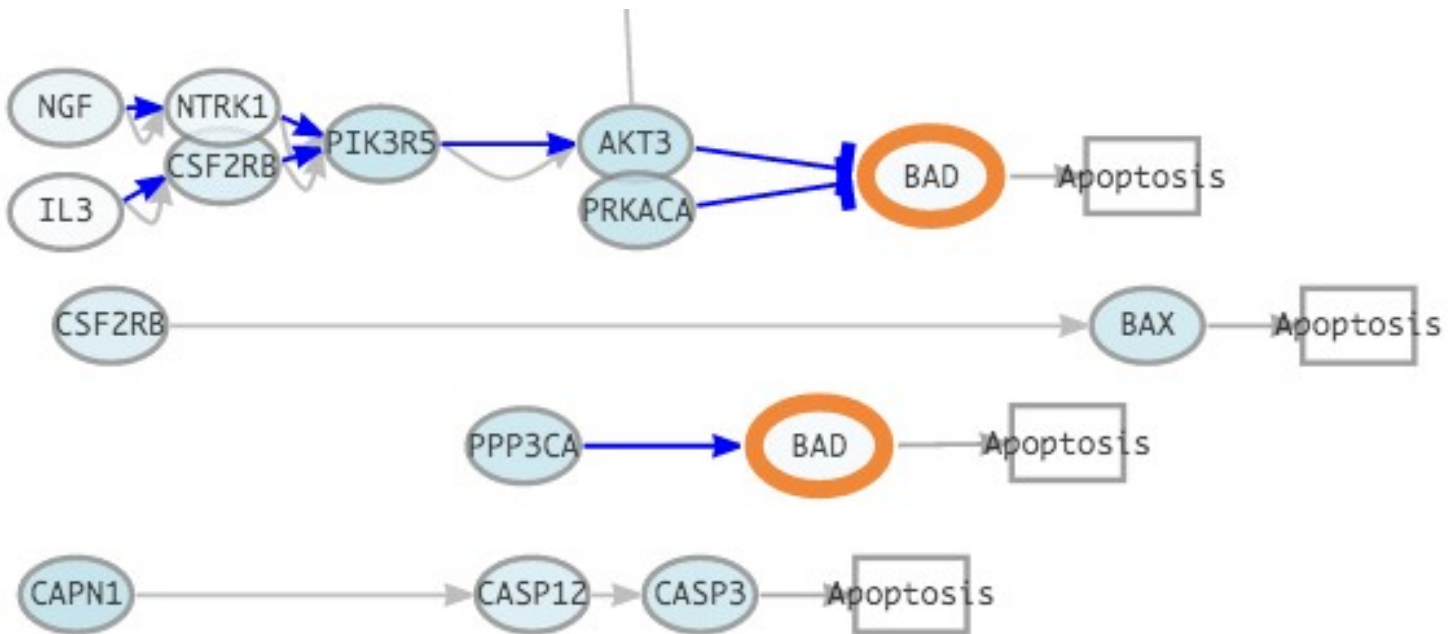
# Signal transduction modelling

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



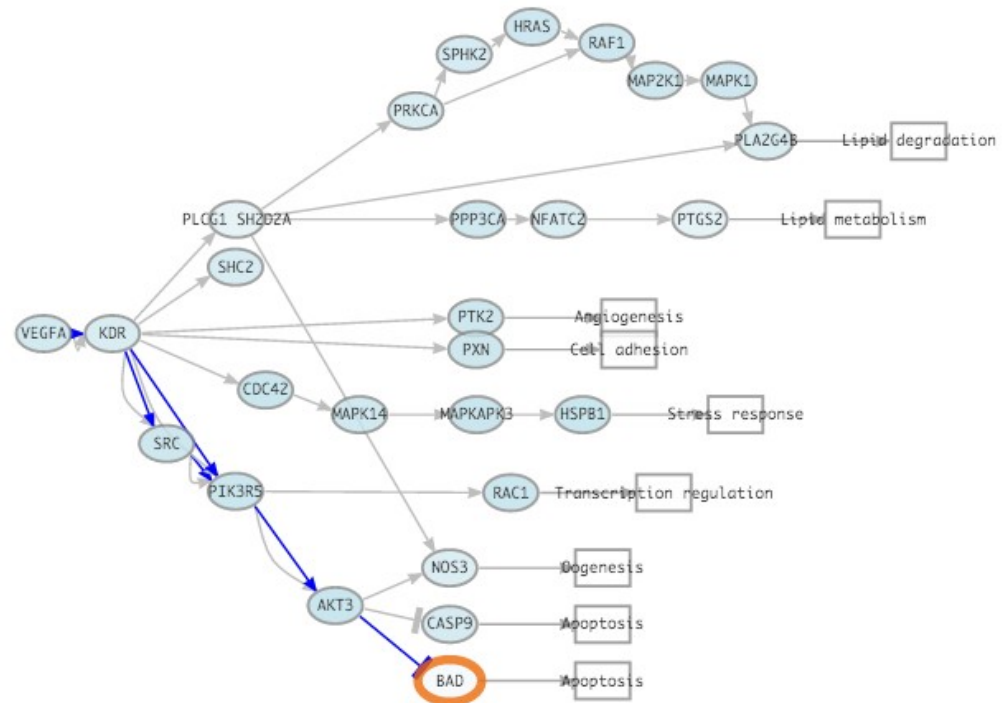
# Signal transduction modelling

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://pathact2.babelomics.org>

PathAct Actionable pathway workshop

Login Sign up

2 3

# PathAct

ACTIONABLE PATHWAY WORKSHOP

1 Start

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.

Note:

PathAct v1.1.0  
Created by Computational Genomics Department  
Principe Felipe Research Center, Valencia, Spain  
2016

# PathAct Web Tool

<http://pathact2.babelomics.org>

PathAct Actionable pathway workshop

Login

User name:  
gda2016ciberer [Create new user...](#)

Password:  
..... [Remember password...](#)

**Login**

[Login as anonymous](#)  
All data will be deleted on logout

PathAct v1.1.0  
Created by **Computational Genomics Department**  
Principe Felipe Research Center, Valencia, Spain  
2016

# PathAct Web Tool

**PathAct** Actionable pathway workshop

Jobs Settings gda2016ciberer Profile Logout

Create a new job Use an existing 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.

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

hcc4006\_mutant\_dmso

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

My HCC4006 mutant dims analysis

Run

Search by name...

✓ HCC4006 mutant dmso-hcc4006_mutant_dmso.txt	Done 28/9/2016 12:14:59	🗑️ ⬇️
✓ HCC4006_mutant_dmso-hcc4006_mutant_dmso.txt	Done 28/9/2016 12:11:39	🗑️ ⬇️
✓ Example	Done 28/9/2016 11:54:27	🗑️ ⬇️

Total: 3  Enable job notifications

# PathAct Web Tool

The screenshot displays the PathAct web tool interface. At the top, the navigation bar includes the PathAct logo, the text "Actionable pathway workshop", and user options: "Jobs", "Settings", "gda2016ciberer", "Profile", "Logout", and a help icon. The main content area is split into two sections: "Create a new job" and "Use an existing job". A "Run example" button is visible under the "Create a new job" section. A modal dialog box titled "Select Expression Matrix File..." is open, showing a file browser view. The browser shows a directory structure under "/ PathAct\_Exercises /" with sub-directories: "gda2016ciberer", "BRCA\_exercise", "KIRC\_exercise", "PathAct\_Exercises", "gse36807\_exercise", and "gse51835\_exercise". An "Upload" button is highlighted with an orange box. A table lists a file named "Example" with a size of "." and a date of "Sep 28, 2016". The dialog also shows "81.7 MB of 1.0 GB" used and a search bar at the bottom.

PathAct Actionable pathway workshop

Jobs Settings gda2016ciberer Profile Logout

Create a new job Use an existing job

Run example

Select Expression Matrix File...

/ PathAct\_Exercises /

gda2016ciberer

- BRCA\_exercise
- KIRC\_exercise
- PathAct\_Exercises
- gse36807\_exercise
- gse51835\_exercise

Upload

Name	Size	Date
Example	.	Sep 28, 2016

81.7 MB of 1.0 GB

All Search by name...

Total: 1  Enable job notifications



# PathAct Web Tool

PathAct Actionable pathway workshop

Jobs Settings gda2016ciberer Profile Logout

Create a new job Use an existing job

Run example

Upload File

File upload: Choose file...

Selected file: hcc4006\_mutant\_dms0.txt Revalidate

Bioformat: Data matrix expression

File validation log:

Line	Type	Message	100%	Stop
19766	warning	Empty line.		

Errors: 0 Warning: 1 Info: 0 Lines: 19766

Upload

- 1
- 2
- 3

# 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_dms0
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

Jobs Settings gda2016ciberer Profile Logout

### 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 Select a expression matrix file...  
hcc4006\_mutant\_dmso.txt

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

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

2 hcc4006\_mutant\_dmso

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

3 My HCC4006 mutant dims analysis

4 Run

### 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 + New Clear

4 Add genes: Gene search (min 2 char)

5 Add drugs: Drug search (min 3 char)

Genes affected by drugs:

2 ErbB signaling pathway (hsa04012)

Show report

1 Category: 0 altere

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

3 Circuit list: 0 altere

- ABL1
- BAD
- CAMK2A
- CBLC
- CDKN1A
- CDKN1B
- EIF4EBP1
- ELK1
- ELK1
- ERBB3 ERBB3
- GSK3B
- JUN
- MYC
- PRKCA

Last update gene list:

```
graph TD
    EGF --> EGFR
    TGFA --> EGFR
    AREG --> EGFR
    BTC --> ERBB2
    HBEGF --> ERBB2
    EREG --> ERBB2
    NRG1 --> ERBB3
    NRG2 --> ERBB3
    NRG3 --> ERBB4
    NRG4 --> ERBB4
    ERBB2 --> EGFR
    ERBB3 --> EGFR
    ERBB4 --> EGFR
    EGFR --> PLCG1
    EGFR --> CBLC
    EGFR --> SHC2
    EGFR --> GRB2
    EGFR --> STAT5A
    EGFR --> SRC
    EGFR --> CRK
    EGFR --> NCK1
    PLCG1 --> CAMK2A
    PLCG1 --> PRKCA
    SHC2 --> GRB2
    GRB2 --> SOS1
    GRB2 --> PIK3R5
    GRB2 --> GAB1
    SOS1 --> HRAS
    HRAS --> ARAF
    ARAF --> MAP2K1
    MAP2K1 --> MAPK1
    MAPK1 --> MYC
    MAPK1 --> ELK1
    PIK3R5 --> AKT3
    GAB1 --> AKT3
    GAB1 --> MTOR
    GAB1 --> EIF4EBP1
    AKT3 --> BAD
    AKT3 --> GSK3B
    AKT3 --> CDKN1B
    AKT3 --> CDKN1A
    SRC --> PTK2
    CRK --> ABL1
    NCK1 --> PAK4
    PAK4 --> MAP2K7
    MAP2K7 --> MAPK8
    MAPK8 --> JUN
    MAPK8 --> ELK1
    CAMK2A --> Neurogenesis
    PRKCA --> Apoptosis
    PRKCA --> Biological_rhythms
    CBLC --> Ubiquitin_pathway
    STAT5A --> Lactation_Transcription_regulation
    SRC --> Angiogenesis
    CRK --> Apoptosis
    CRK --> Cell_adhesion
    ABL1 --> Apoptosis
    ABL1 --> Cell_adhesion
    PAK4 --> MAP2K7
    MAP2K7 --> MAPK8
    MAPK8 --> JUN
    MAPK8 --> ELK1
    MYC --> Transcription_regulation
    ELK1 --> Transcription_regulation
    JUN --> Transcription_regulation
    ELK1 --> Transcription_regulation
    BAD --> Apoptosis
    GSK3B --> Neurogenesis
    CDKN1B --> Cell_cycle
    CDKN1A --> Cell_cycle
    EIF4EBP1 --> Translation_regulation
    RPS6KB1 --> Apoptosis
```

# Overexpression

**4 PathAct** Actionable pathway workshop Jobs Settings gda2016ciberer Profile Logout

**ErBb signaling pathway (hsa04012)** Show report Category: 0 altered

**1** ErbB signaling pathway

**2** **3**

Activity value: 0.95

**Add genes:**

Q EGF 2

EGFR 0.95

EGFR EGFR 0.95

**Select gene related drugs:**

- Cetuximab
- Trastuzumab
- Lidocaine
- Gefitinib
- Erlotinib
- Lapatinib
- Panitumumab

**Add drugs:**

Q Drug search (min 3 char)

**Genes affected by drugs:**

**Circuit list:** 0 altered

- ABL1
- BAD
- CAMK2A
- CBLC
- CDKN1A
- CDKN1B
- EIF4EBP1
- ELK1
- ELK1
- ERBB3 ERBB3
- GSK3B
- JUN
- MYC
- PRKCA

**Last update gene list:**



# Overexpression

**PathAct Actionable pathway workshop** Jobs Settings gda2016ciberer Profile Logout

**ErbB signaling pathway (hsa04012)** Show report

**1**

Category: 14 altered

- 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

**2**

Circuit list: 16 altered

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

**3**

**4**

Last update gene list:

- gene - w - origin
- EGFR - 0.95 - user

# Overexpression

**PathAct** Actionable pathway workshop

Jobs Settings gda2016ciberer Profile Logout

**ErbB signaling pathway (hsa04012)** 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
- Resonance pathway

Circuit list: 16 altered

- ABL1
- BAD
- CAMK2A
- CBLC
- CDKN1A
- CDKN1B
- EIF4EBP1
- ELK1
- ELK2
- JUN**
- MYC
- PRKCA
- PTK2

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

**2**

**1**

Left sidebar: Add genes: 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:

# Results interpretation

Settings

Configure fold change:

Configure drug action weight:

Acetylation:	<input type="text" value="0,1"/>	Activator:	<input type="text" value="1"/>
Adduct:	<input type="text" value="0,1"/>	Agonist:	<input type="text" value="1"/>
Allosteric Modulator:	<input type="text" value="0,1"/>	Antagonist:	<input type="text" value="0,1"/>
Antibody:	<input type="text" value="0,1"/>	Binder:	<input type="text" value="0,1"/>
Binding:	<input type="text" value="0,1"/>	Blocker:	<input type="text" value="0,1"/>
Chaperone:	<input type="text" value="0,1"/>	Chelator:	<input type="text" value="0,1"/>
Cleavage:	<input type="text" value="0,1"/>	Cofactor:	<input type="text" value="0,1"/>
Component Of:	<input type="text" value="0,1"/>	Conversion Inhibitor:	<input type="text" value="0,1"/>
Cross-Linking/Alkylation:	<input type="text" value="0,1"/>	Desensitize The Target:	<input type="text" value="0,1"/>
Inactivator:	<input type="text" value="0,1"/>	Incorporation Into And Destabilization:	<input type="text" value="0,1"/>
Inducer:	<input type="text" value="1"/>	Inhibitor:	<input type="text" value="0,1"/>
Inhibitor, Competitive:	<input type="text" value="0,1"/>	Inhibitory Allosteric Modulator:	<input type="text" value="0,1"/>
Intercalation:	<input type="text" value="0,1"/>	Inverse Agonist:	<input type="text" value="0,1"/>
Ligand:	<input type="text" value="0,1"/>	Metabolizer:	<input type="text" value="0,1"/>
Modulator:	<input type="text" value="0,1"/>	Multitarget:	<input type="text" value="0,1"/>
Negative Modulator:	<input type="text" value="0,1"/>	Neutralizer:	<input type="text" value="0,1"/>
Other:	<input type="text" value="0,1"/>	Other/Unknown:	<input type="text" value="0,1"/>
Partial Agonist:	<input type="text" value="0,5"/>	Partial Antagonist:	<input type="text" value="0,5"/>
Positive Allosteric Modulator:	<input type="text" value="1"/>	Positive Modulator:	<input type="text" value="1"/>

Reset defaults

$|\log FC| > \log(2) = 0.693$



# Report

Report

## Circuit impact

$$|\log FC| > \log(2) = 0.693$$

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

# Drug action

**PathAct** Actionable pathway workshop Jobs Settings gda2016ciberer Profile Logout

**5** Refresh Clear

**1** Signaling pathway (hsa04012) Show report

**4** EGFR EGFR EGFR

**2** Add drugs:  
 Drug search (min 3 char 1)  
 Erlotinib

**3** Genes affected by drugs:  
 EGFR 0,1  
 Erlotinib antagonist

Category: 0 altered

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

Circuit list: 0 altered

- ABL1
- BAD
- CAMK2A
- CBLC
- CDKN1A
- CDKN1B
- EIF4EBP1
- ELK1
- ELK1
- ERBB3 ERBB3
- GSK3B
- JUN
- MYC
- PRKCA

Last update gene list:

# Drug action

PathAct Actionable pathway workshop

Jobs Settings gda2016ciberer Profile Logout

**ErbB signaling pathway (hsa04012)**

3

1

2

10 altered

16 altered

gene - w - origin  
EGFR - 0.1 - drug

The screenshot displays the PathAct software interface for the ErbB signaling pathway (hsa04012). The main window shows a complex network diagram of proteins and their interactions. Key components include EGFR, ERBB2, ERBB3, ERBB4, SHC2, GRB2, SOS1, HRAS, ARAF, MAP2K3, MAPK1, MYC, and ELK1. The diagram is annotated with various biological processes such as Neurogenesis, Apoptosis, and Transcription regulation. On the left, there are search bars for genes and drugs, with Erlotinib listed as a drug affecting EGFR. On the right, a sidebar shows a list of altered pathways, with 'ErbB signaling pathway' highlighted in orange. Below this, a 'Circuit list' shows 16 altered components, including ABL1, BAD, CAMK2A, and others. The top of the interface includes navigation options like 'Jobs', 'Settings', and 'Logout'.

Thanks for your attention

Any questions?