

PathAct

In silico modulation of signal transduction

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September 30th, 2016



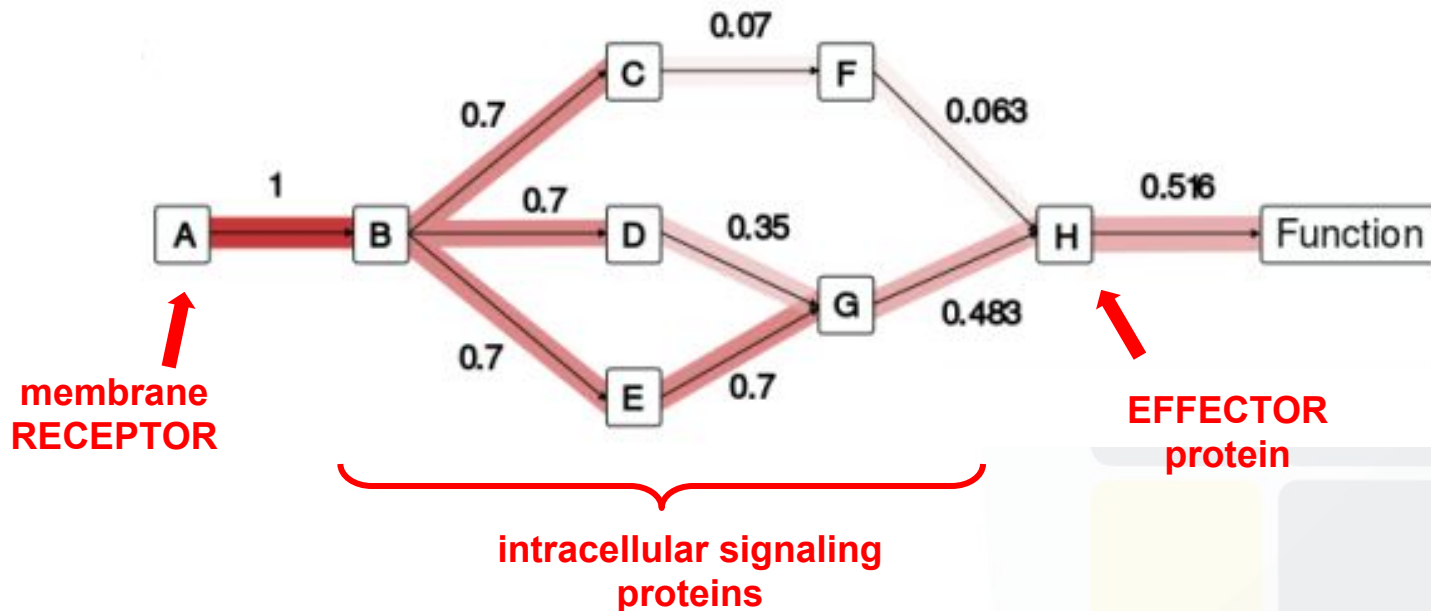
GDA
International Course on
Genomic **D**ata **A**nalysis



PRINCIPE FELIPE
CENTRO DE INVESTIGACION

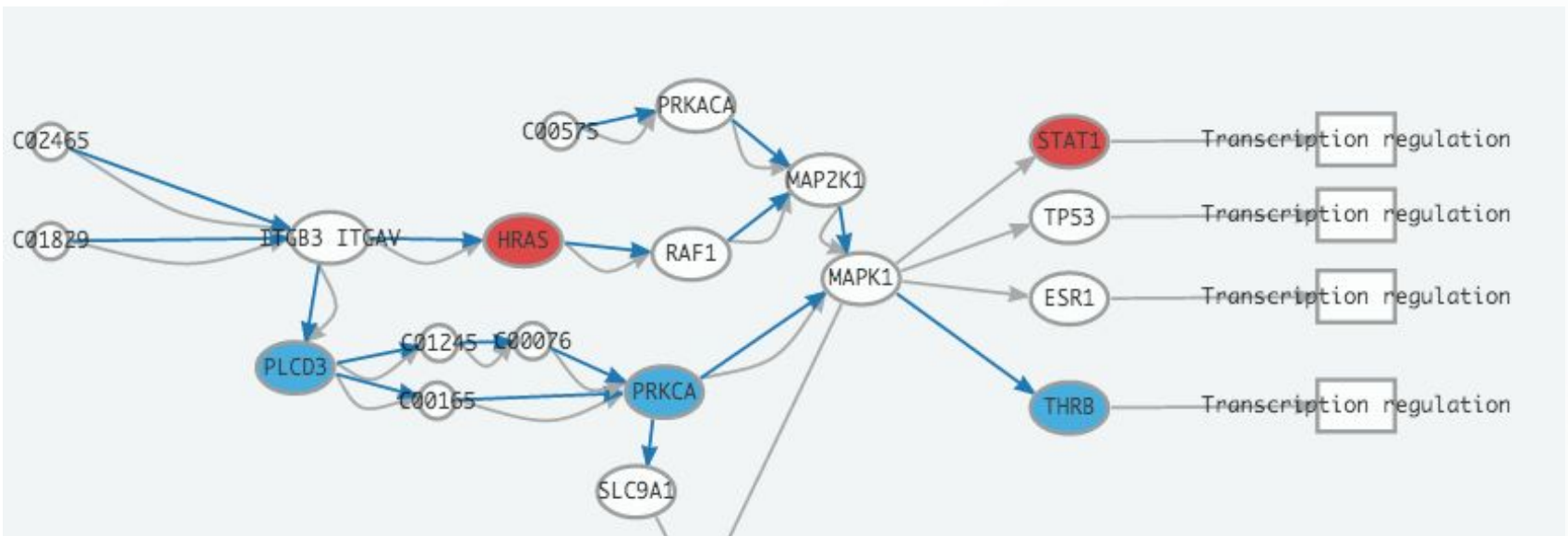
Signal transduction modelling

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



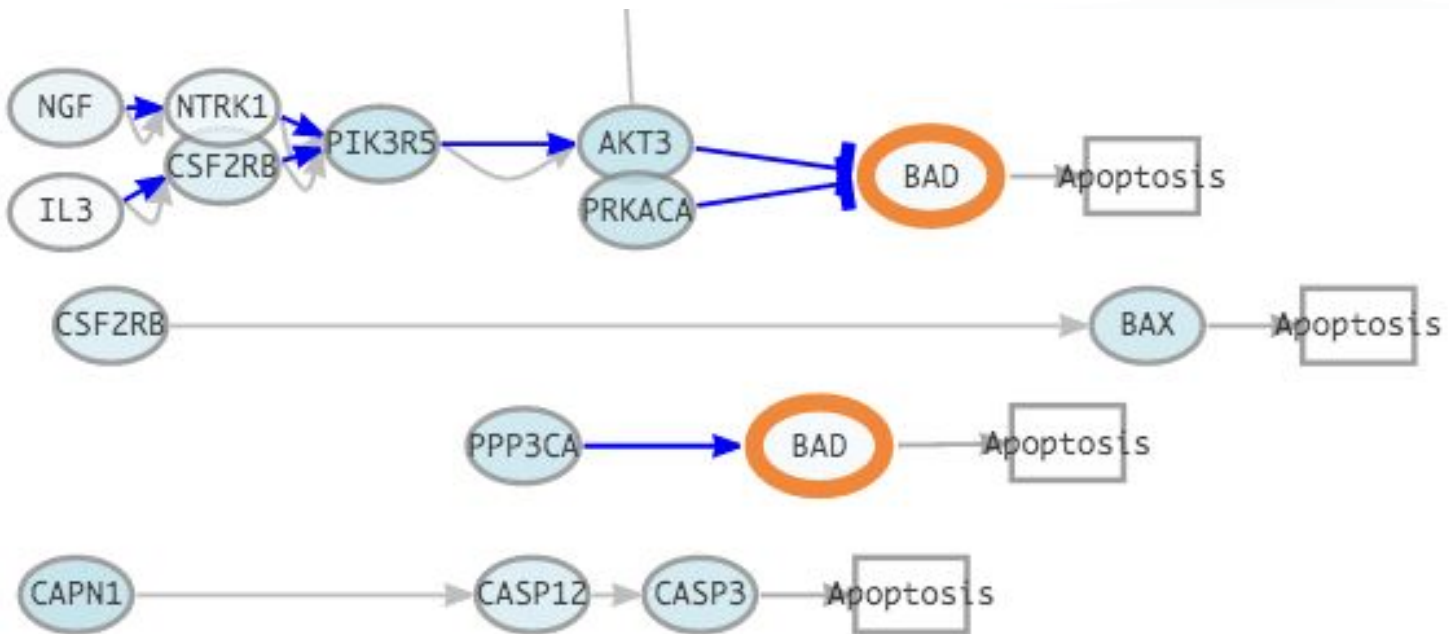
Signal transduction modelling

This **systemic approach** allow us to detect which signaling cascades (or cellular functions) are impaired in a given disease, even when patients are heterogeneous



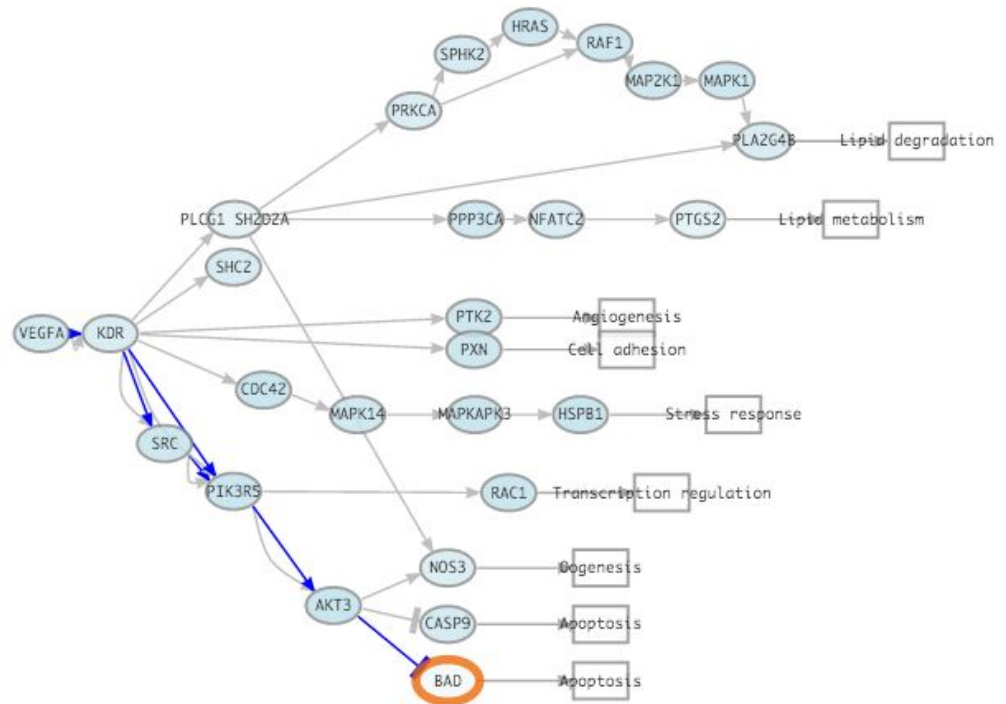
Signal transduction modelling

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.babelomics.org>

PathAct Actionable pathway workshop

Login Sign up

2 3

PathAct

ACTIONABLE PATHWAY WORKSHOP

1 Start

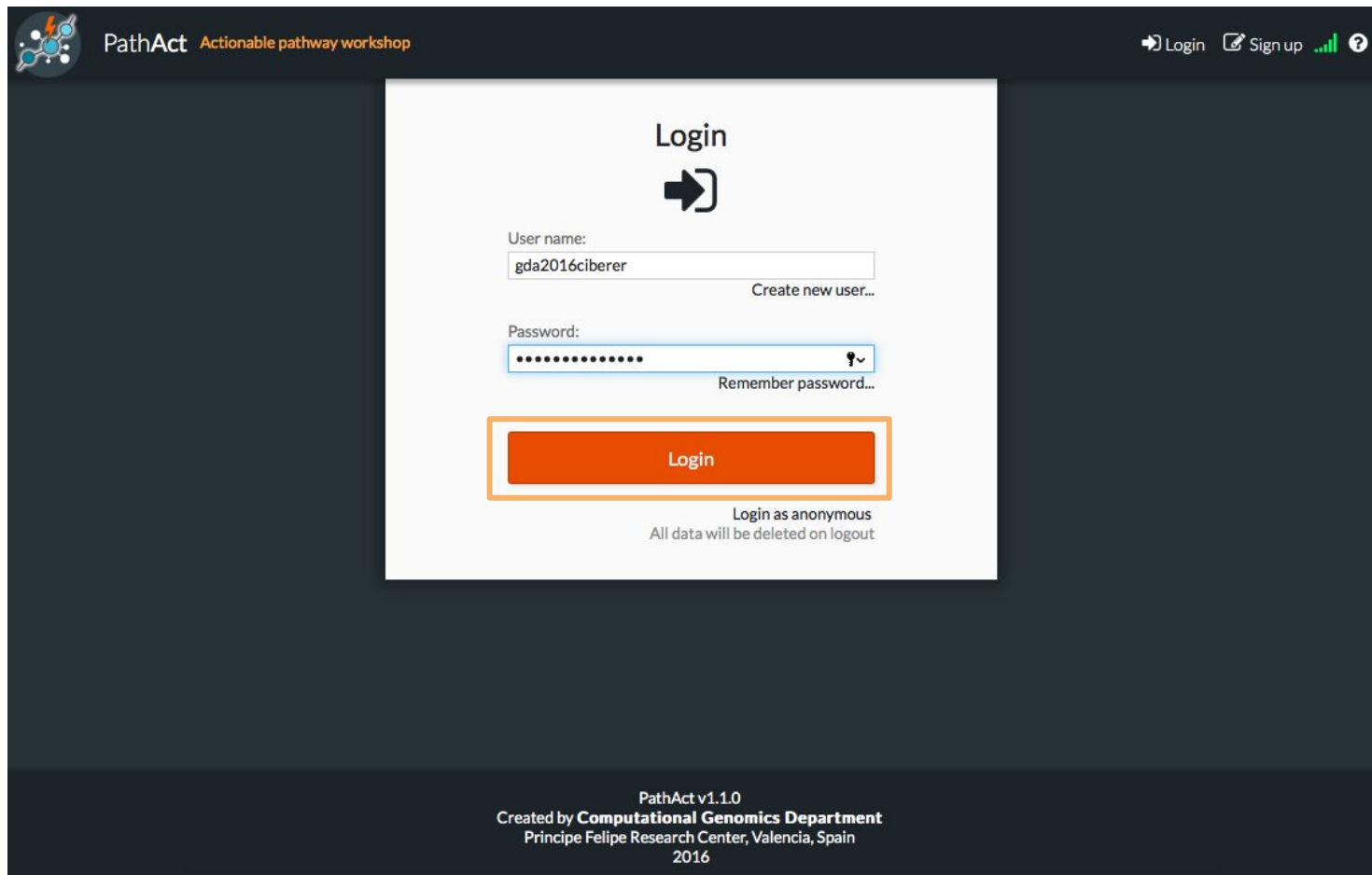
PathAct is a web tool that enables the study of the consequences that Knockouts(KOs) or over-expressions of genes can have over signalling pathways. PathAct implements robust models of signalling pathways within an advanced graphical interface that provide a unique interactive working environment in 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://pathact.babelomics.org>



The screenshot shows the PathAct web tool interface. At the top left, there is a logo and the text "PathAct Actionable pathway workshop". At the top right, there are links for "Login", "Sign up", and a help icon. The main content area is a white box with the title "Login" and a right-pointing arrow icon. Below the title, there are two input fields: "User name:" with the value "gda2016ciberer" and "Password:" with a masked password. There are also links for "Create new user..." and "Remember password...". A large orange "Login" button is highlighted with a red border. Below the button, there is a link for "Login as anonymous" with a note: "All data will be deleted on logout". At the bottom of the page, there is a footer with the text: "PathAct v1.1.0", "Created by Computational Genomics Department", "Principe Felipe Research Center, Valencia, Spain", and "2016".

PathAct Actionable pathway workshop

→ Login Sign up

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

Select data

PathAct Actionable pathway workshop Jobs Settings gda2016ciberer Profile Logout

Create a new job Use an existing 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_e 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

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

Select data

The screenshot shows the PathAct web interface. At the top, there is a navigation bar with the PathAct logo and the text "Actionable pathway workshop". On the right side of the navigation bar, there are links for "Jobs", "Settings", "gda2016ciberer", "Profile", and "Logout". Below the navigation bar, there are two main sections: "Create a new job" and "Use an existing job". A "Run example" button is visible under "Create a new job".

A modal dialog titled "Select Expression Matrix File..." is open in the center. The dialog shows a file browser view for the user "gda2016ciberer". The current directory is "/ PathAct_Exercises /". The file list contains several folders: "BRCA_exercise", "KIRC_exercise", "PathAct_Exercises", "gse36807_exercise", and "gse51835_exercise". An "Upload" button is highlighted with an orange box. Below the file list, there is a table with the following data:

Name	Size	Date
✓ Example	.	Sep 28, 2016

At the bottom of the dialog, it shows "81.7 MB of 1.0 GB" and a search bar with the text "Search by name...".

Select data

The screenshot shows the PathAct interface with a modal dialog titled "Upload File". The dialog is divided into several sections:

- File upload:** Contains a "Choose file..." button, highlighted with a red box and the number 1.
- Selected file:** Displays "hcc4006_mutant_dms0.txt" and a "Revalidate" button.
- Bioformat:** Contains a radio button for "Data matrix expression" with an information icon, highlighted with a red box and the number 2.
- File validation log:** A table with columns "Line", "Type", and "Message". It shows a warning for line 19766: "Empty line.". A "Stop" button is visible to the right of the table.
- Summary:** Shows "Errors: 0", "Warning: 1", "Info: 0", and "Lines: 19766".
- Upload:** Contains an "Upload" button, highlighted with a red box and the number 3.

The background interface includes a navigation bar with "Jobs", "Settings", "Profile", and "Logout" options, and a main area with "Create a new job" and "Use an existing job" tabs.

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 Use an existing job

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hcc4006_mutant_dmso.txt

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

Log_e transform data matrix

2 hcc4006_mutant_dmso

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

3

4

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

PathAct overview

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

Category: 0 alterer

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 alterer

- 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

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
- PTEN

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

2

1

Add genes: Update
Q EGF 2
EGFR 0,95 x
EGFR EGFR 0,95 x

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

Add drugs:
Q Drug search (min 3 char)

Genes affected by drugs:

Results interpretation

Settings

Configure fold change: Reset defaults

$|\log(2)| > 0.693$

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"/>

EGF
TGFA
AREG
BTC
HBEGF
EREG

K2A
11A
11B
BP1
B
te gene lis

Report

Report

Circuit impact

$|\log(2)| > 0.693$

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

1 Signaling pathway (hsa04012)

4

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) Show report

1

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
- Adipocytokine signaling pathway
- Adrenergic signaling in cardiomyocytes
- AMPK signaling pathway
- Apoptosis

2

Circuit list: 16 altered

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

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

3

Left Panel:

- Add genes:** Search for genes (min 2 char).
- Select gene related drugs:** Search for drugs related to selected genes.
- Add drugs:** Search for drugs (min 3 char). **Erlotinib** is added.
- Genes affected by drugs:** EGFR (0,1) is affected. **Erlotinib** is an antagonist.

Thanks for your attention

Any questions?

