PathAct
In silico modulation of signal transduction

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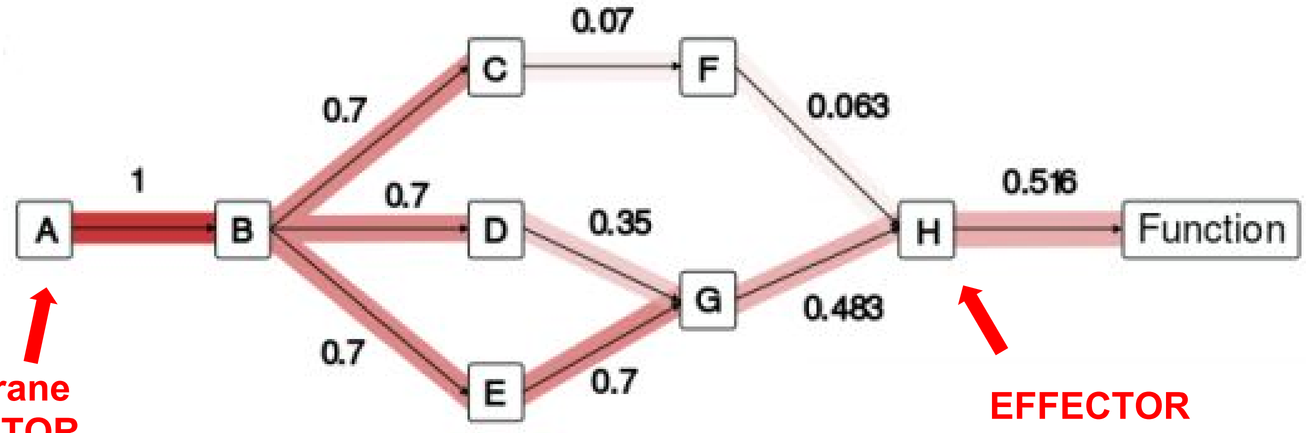
September 30th, 2016

GDA
International Course on
Genomic Data Analysis

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



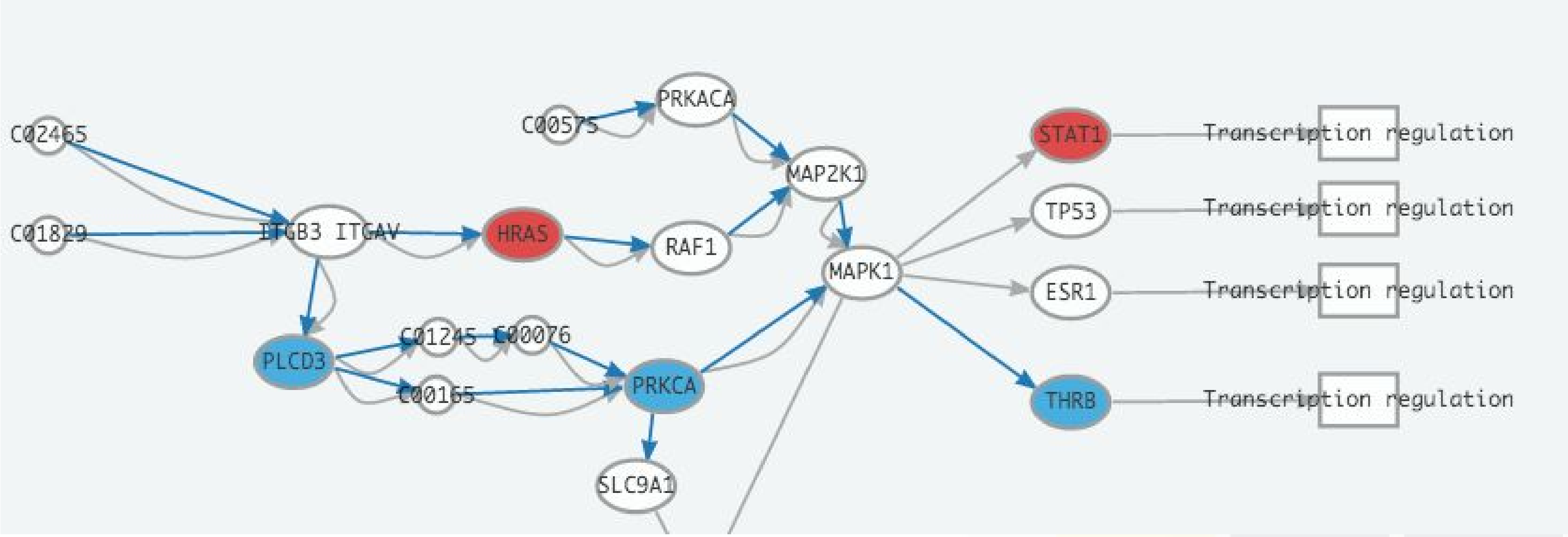
membrane RECEPTOR

EFFECTOR protein

intracellular signaling proteins

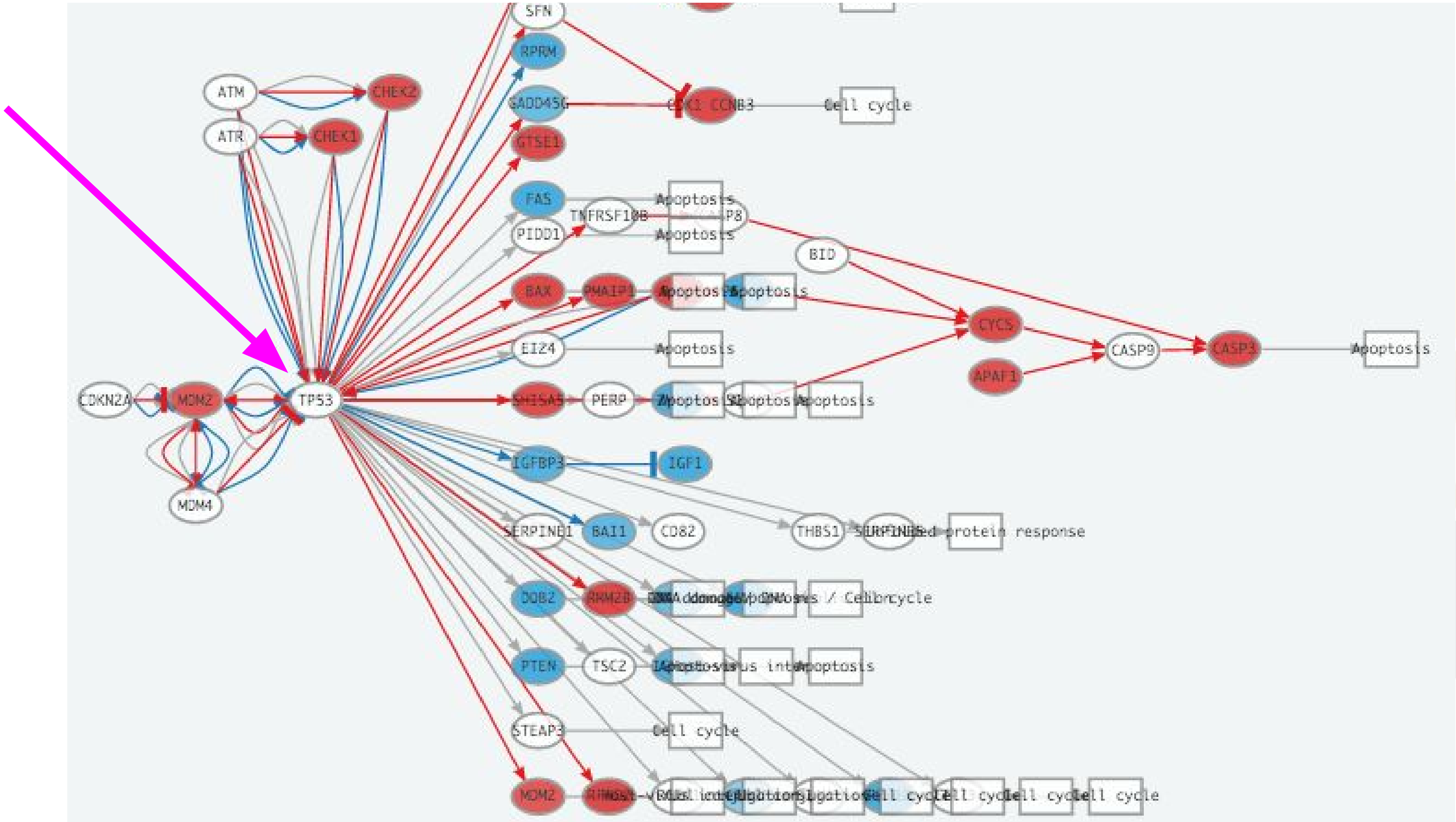
Signal transduction modelling

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



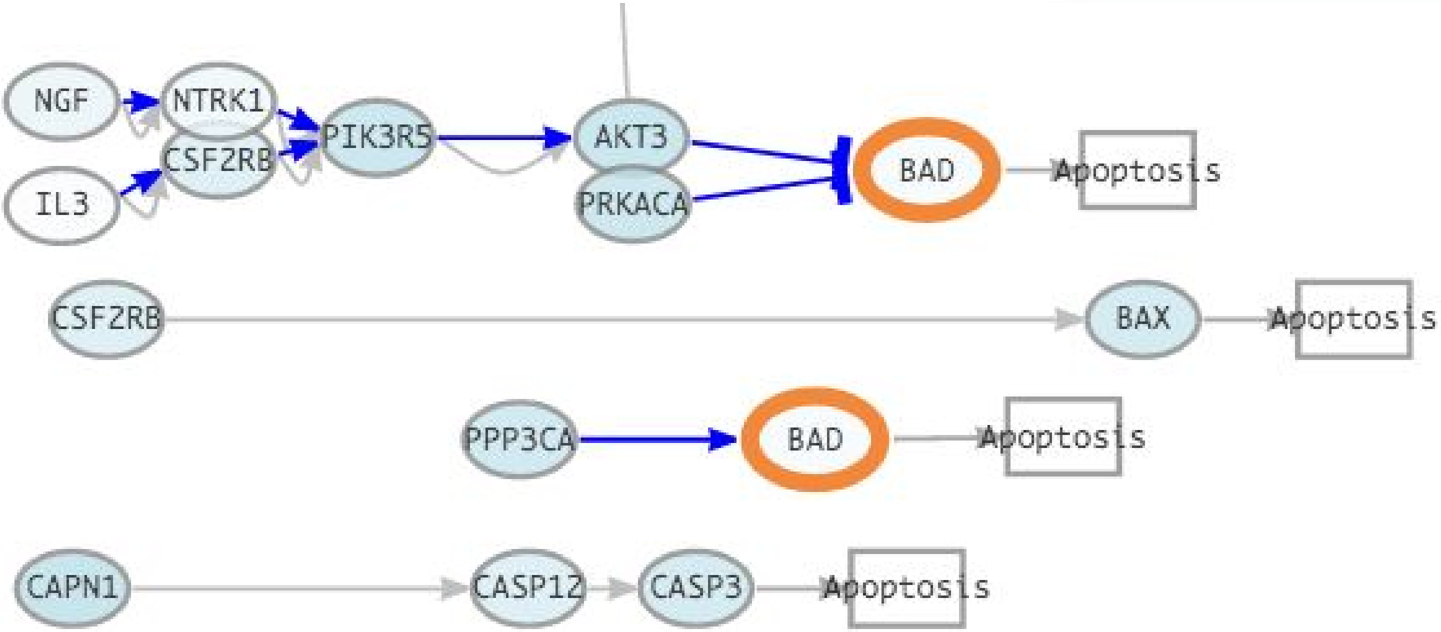
Signal transduction modelling

In a single signaling cascade not all genes weight the same (essential vs non-essential genes)



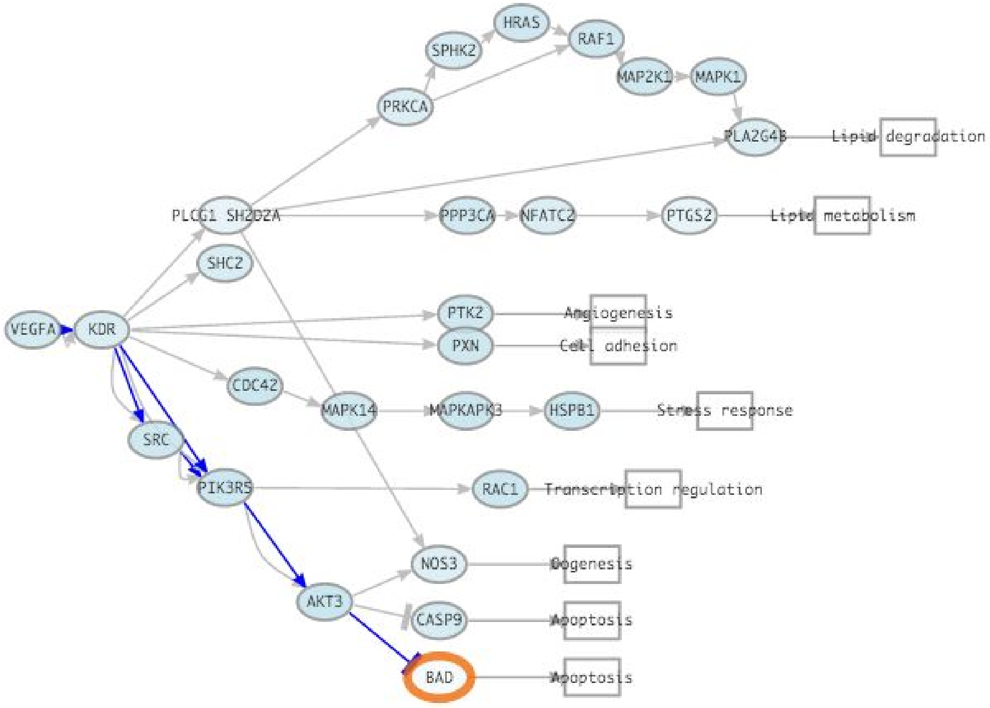
Signal transduction modelling

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

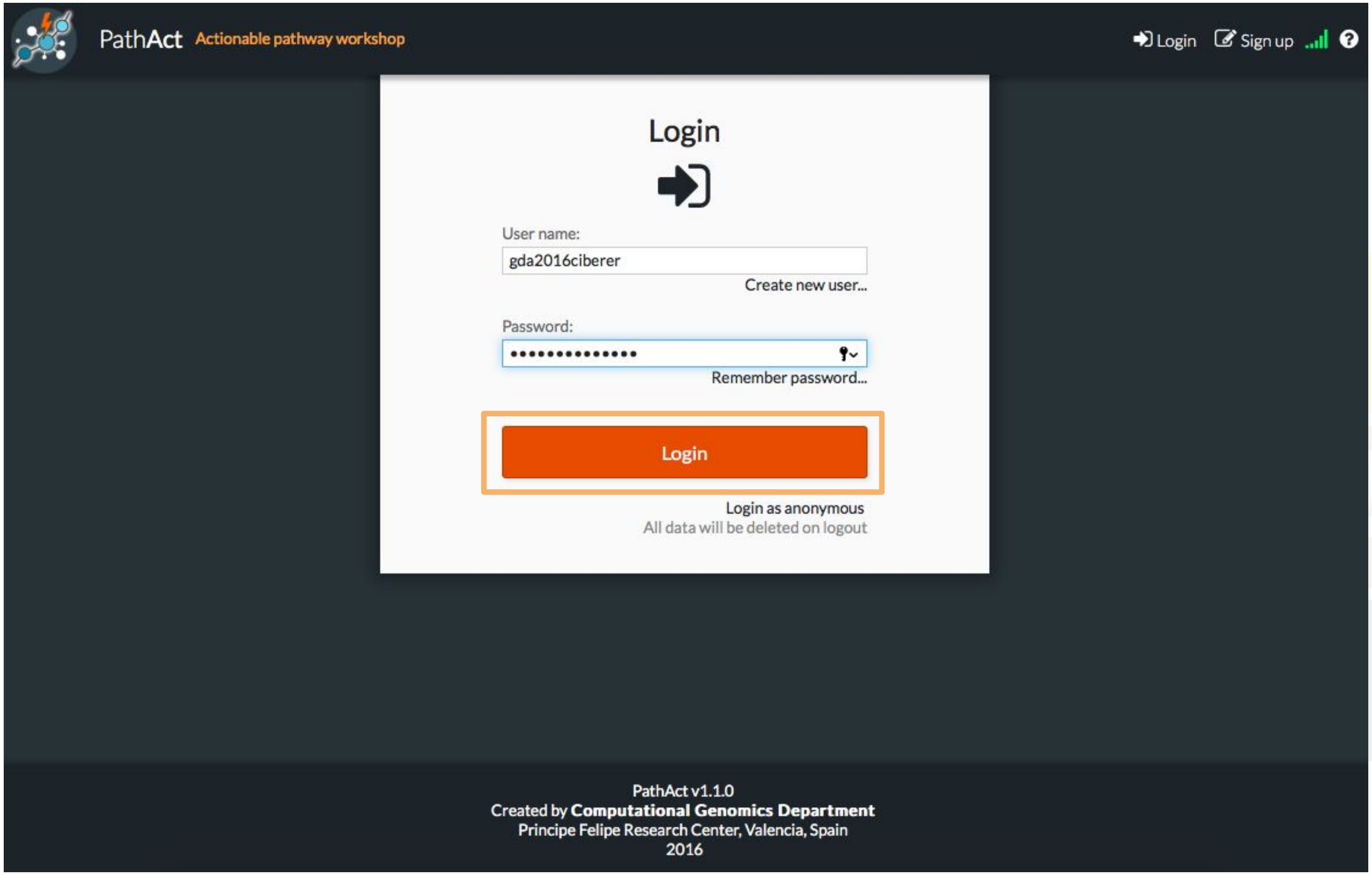
PathAct is a web tool that enables the study of the consequences that Knockouts(KOs) or over-expressions of genes can have over signalling pathways. PathAct implements robust models of signalling pathways within an advanced graphical interface that provide a unique interactive working environment in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



Login

User name:

gda2016ciberer

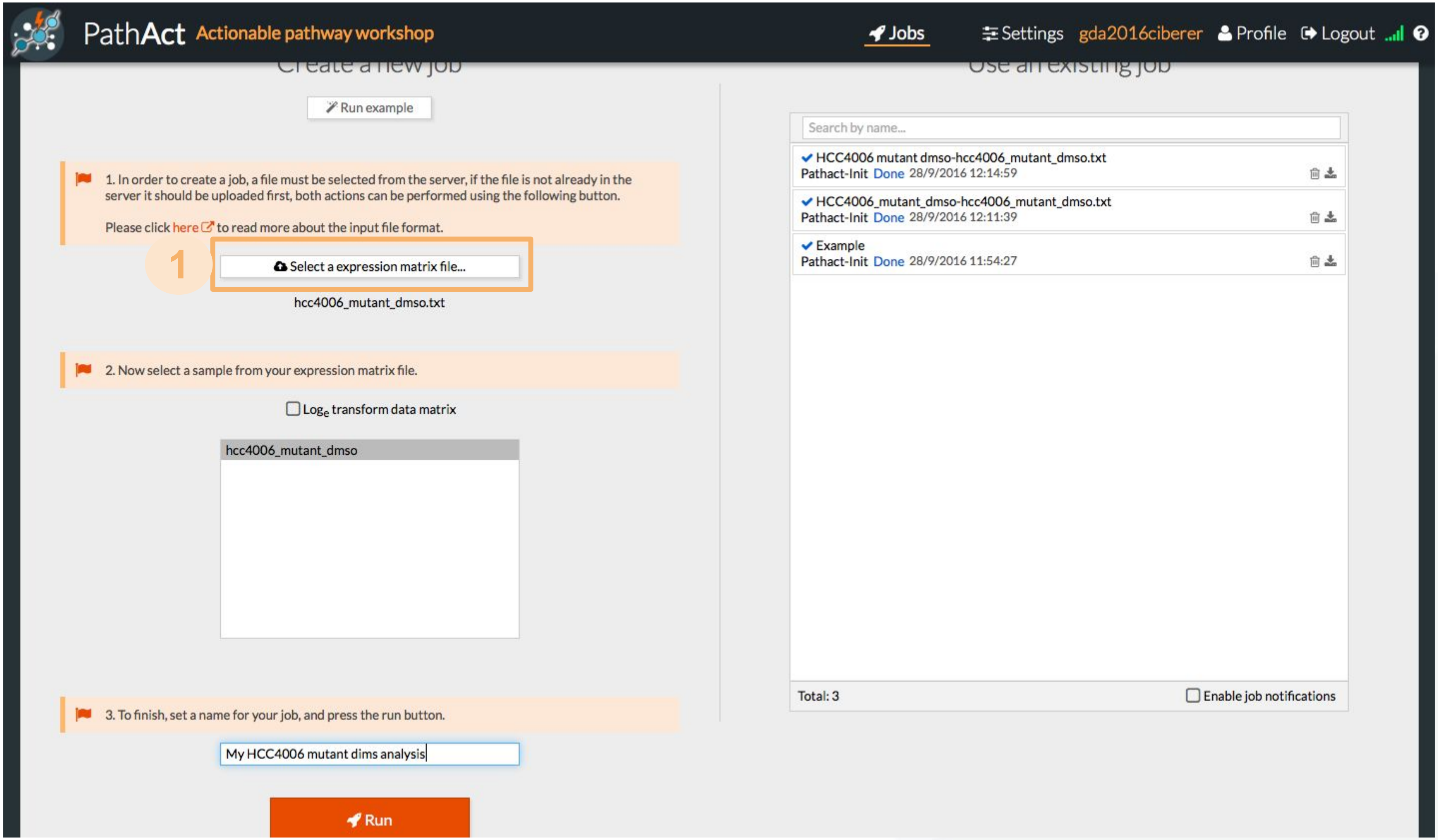
Password:

•••••••••••••••

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



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.

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

✓ HCC4006 mutant dmso-hcc4006_mutant_dmso.txt
Pathact-Init Done 28/9/2016 12:14:59

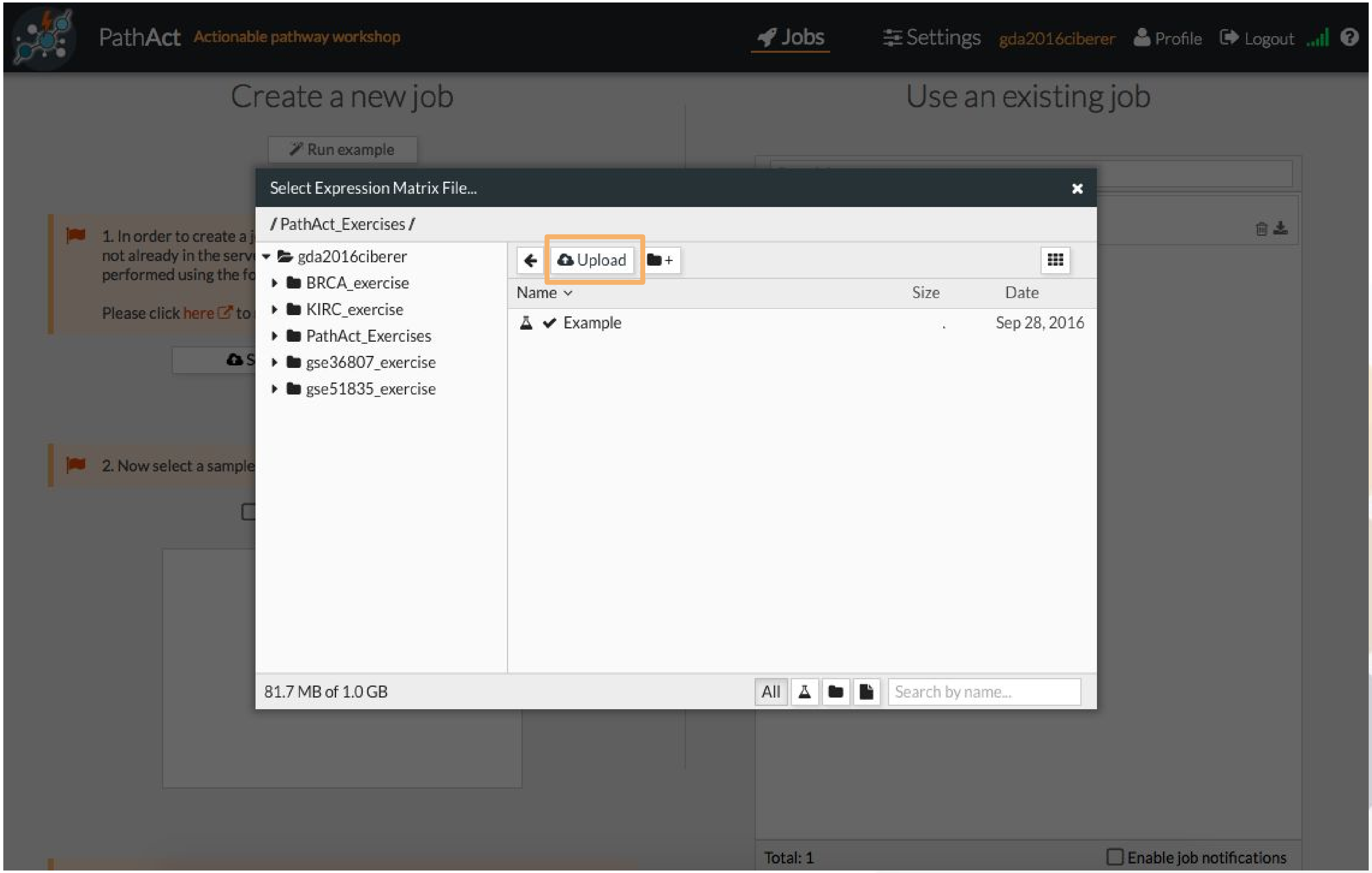
✓ HCC4006_mutant_dmso-hcc4006_mutant_dmso.txt
Pathact-Init Done 28/9/2016 12:11:39

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

Total: 3

☐ Enable job notifications

Select data



Create a new job

Use an existing job

1. In order to create a j
not already in the serv
performed using the fo

Please click here to

2. Now select a sample

Select Expression Matrix File...

/ PathAct_Exercises /

- gda2016ciberer
  - BRCA_exercise
  - KIRC_exercise
  - PathAct_Exercises
  - gse36807_exercise
  - gse51835_exercise

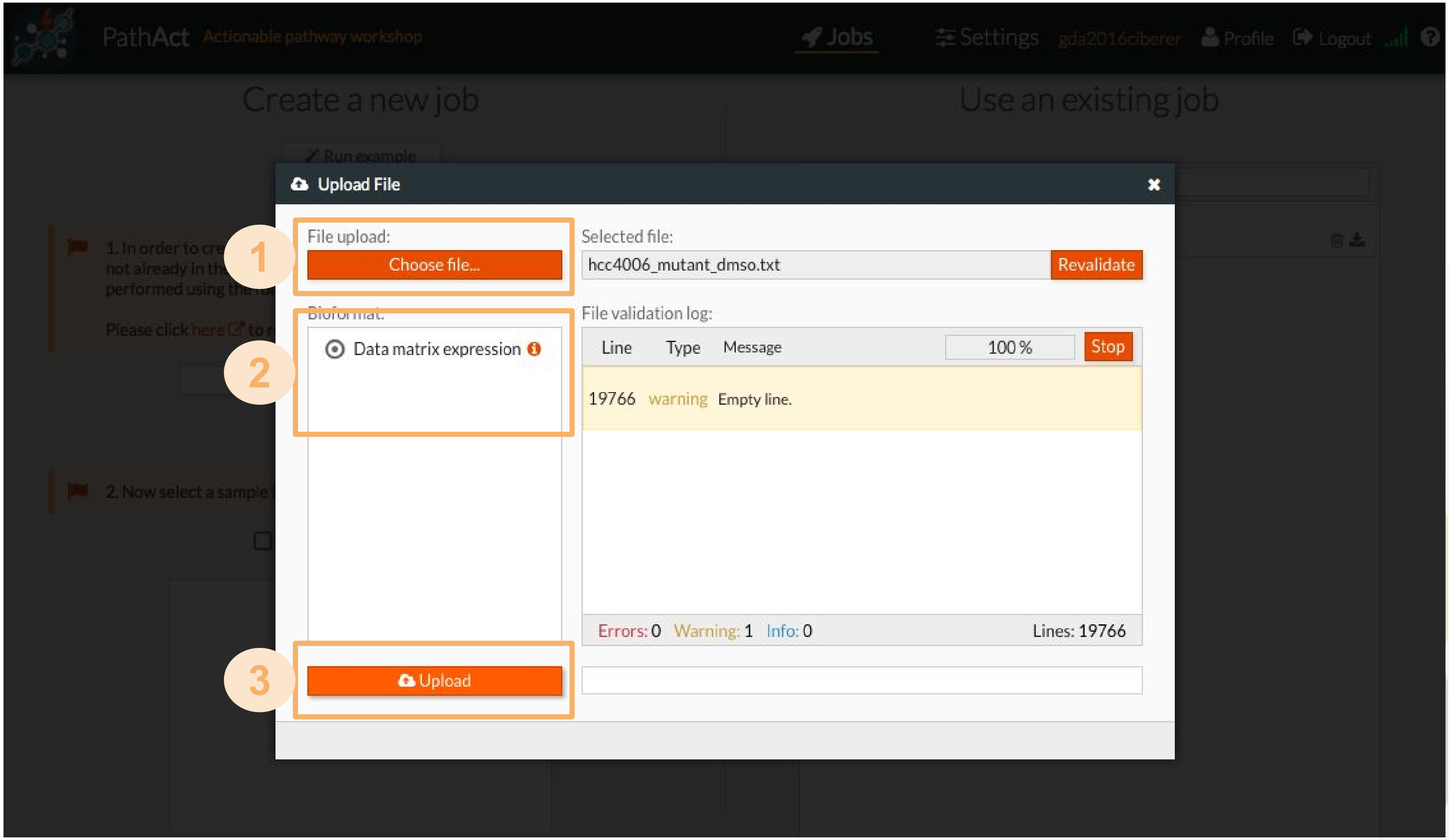
Name	Size	Date
✓ Example	.	Sep 28, 2016

81.7 MB of 1.0 GB

Total: 1

☐ Enable job notifications

Select data



File upload:

Selected file: hcc4006_mutant_dmso.txt

Bioformat:

◉ Data matrix expression

File validation log:

Line	Type	Message
19766	warning	Empty line.

100 %

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

Select data

gene expression data

http://bioinfo.cipf.es/gda16ciberer

File format

Columns: GeneIDs + Sample

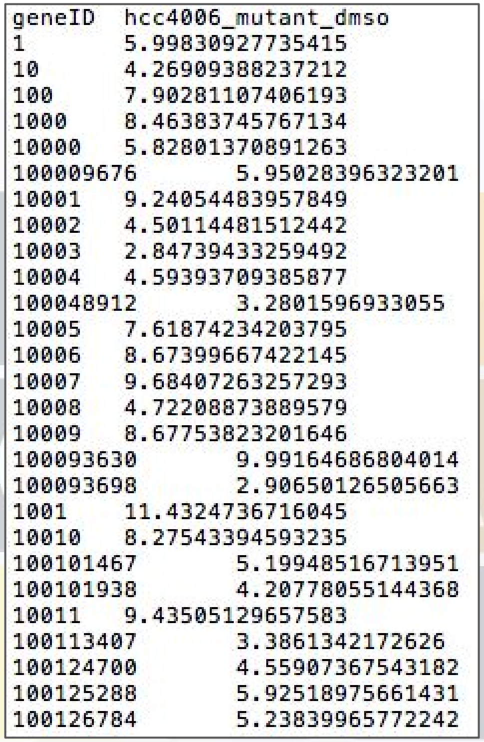
Rows: EntrezGene (id)

Example

Non-small cell lung cancer (NSCLC)

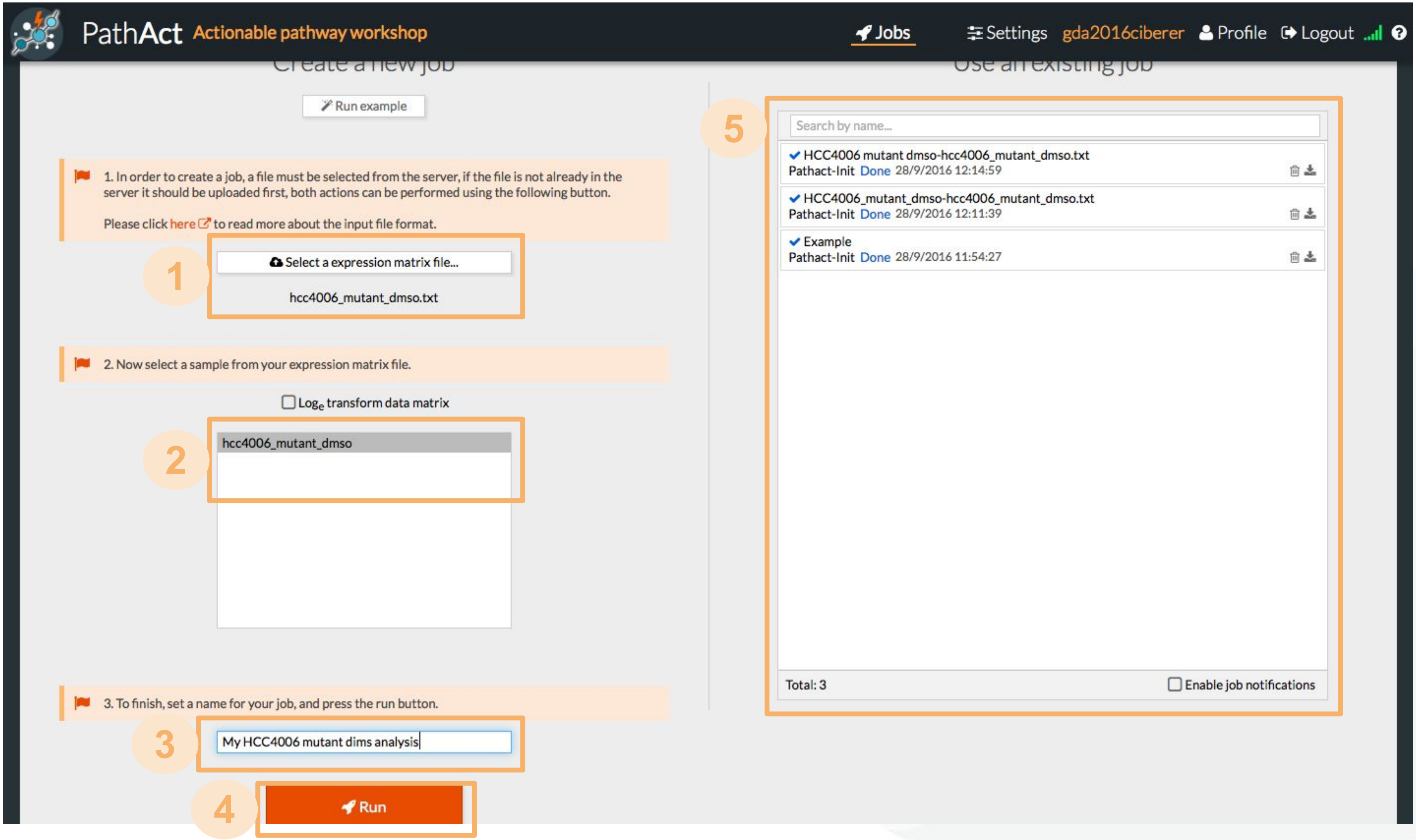
EGFR mutant

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



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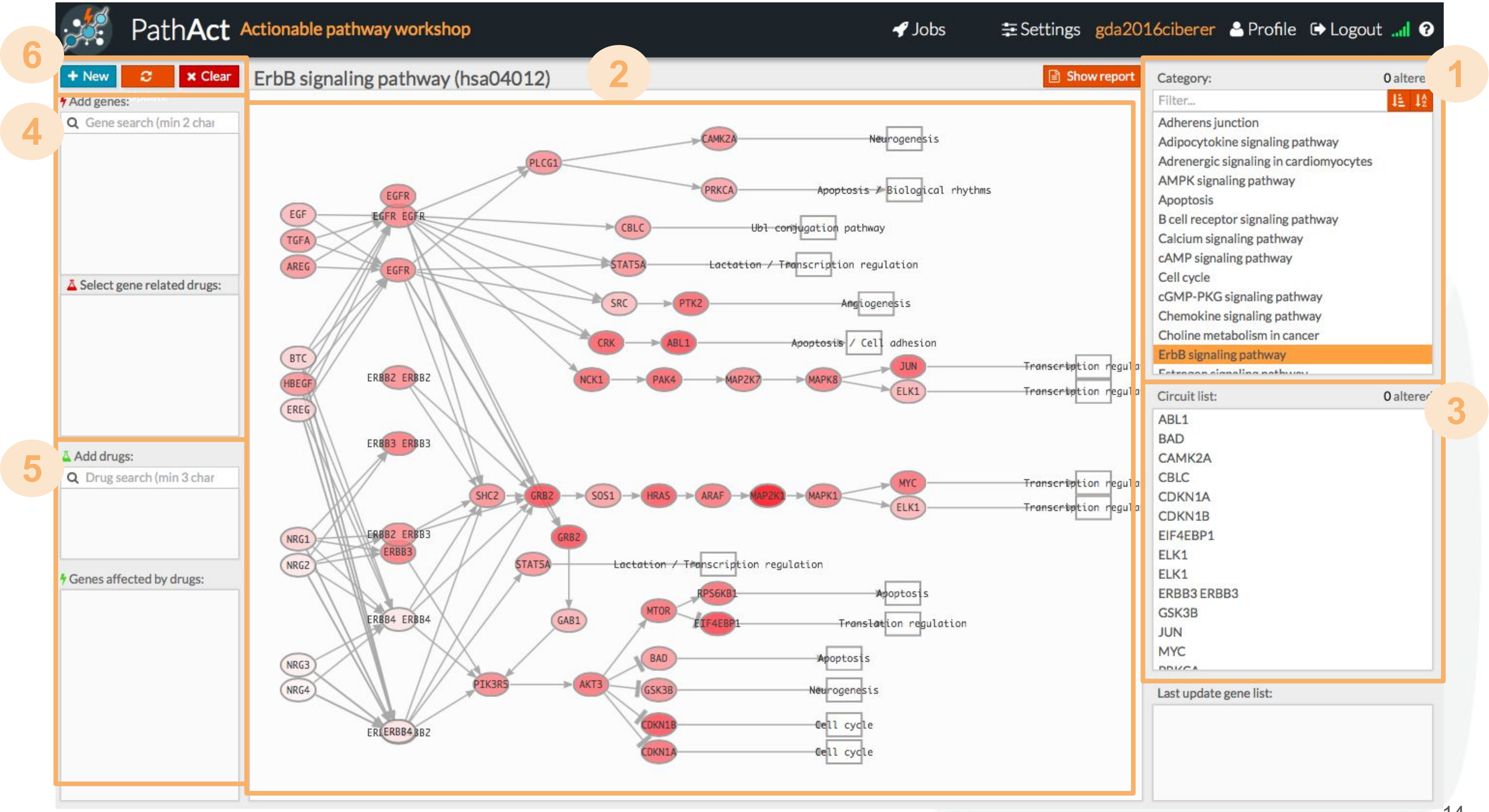
Total: 3

☐ Enable job notifications

PathAct overview



Category: 0 altere

Filter...

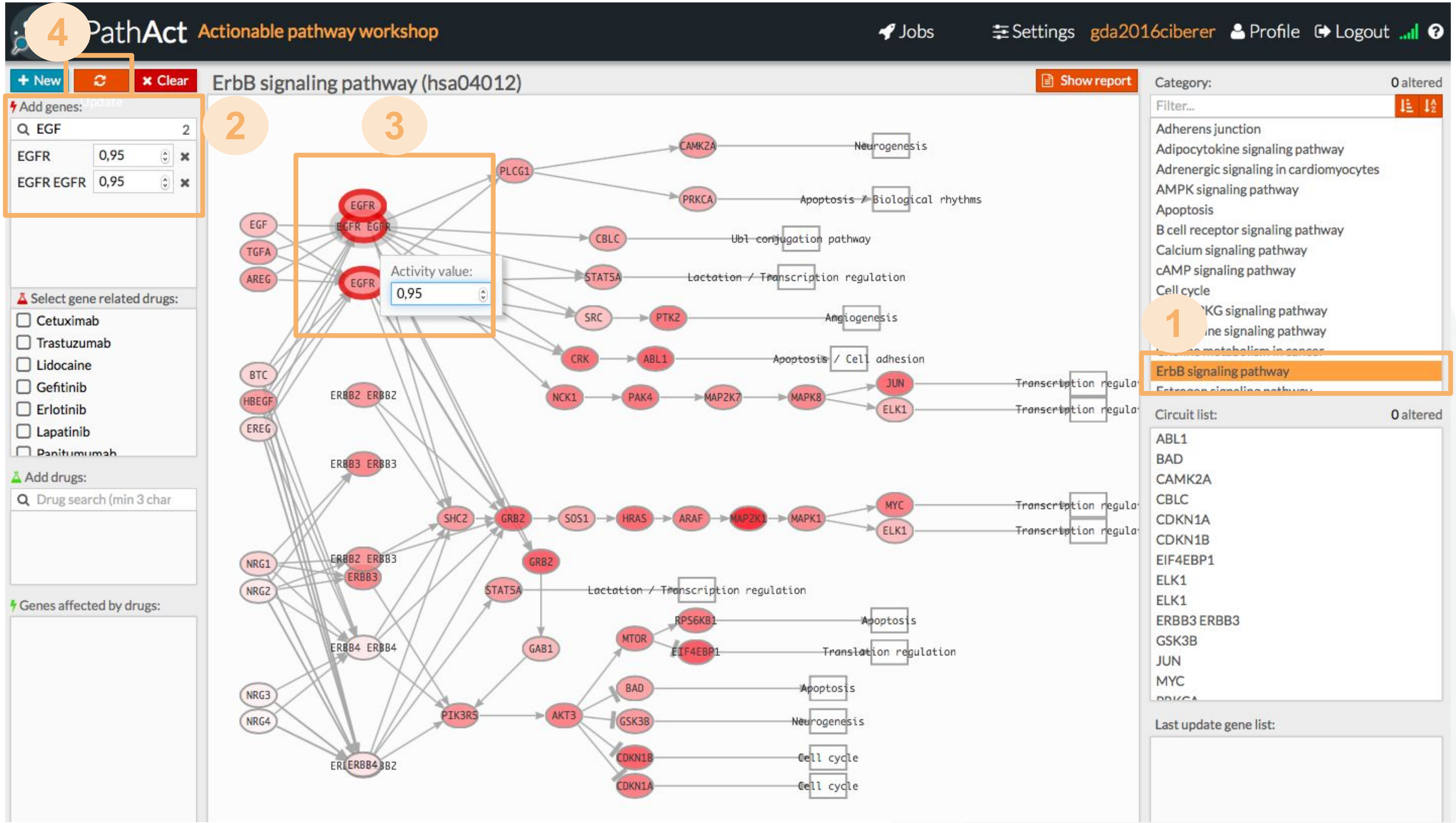
- Adherens junction
- Adipocytokine signaling pathway
- Adrenergic signaling in cardiomyocytes
- AMPK signaling pathway
- Apoptosis
- B cell receptor signaling pathway
- Calcium signaling pathway
- cAMP signaling pathway
- Cell cycle
- cGMP-PKG signaling pathway
- Chemokine signaling pathway
- Choline metabolism in cancer
- ErbB signaling pathway

Circuit list: 0 altered

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

Last update gene list:

Overexpression



ErbB signaling pathway (hsa04012)

Add genes:

EGF	2
EGFR	0,95
EGFR EGFR	0,95

Activity value: 0,95

Select gene related drugs:

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

Add drugs:

Drug search (min 3 char

Genes affected by drugs:

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
- …KG signaling pathway
- …ine signaling pathway
- …e metabolism in cancer
- ErbB signaling pathway
- Estrogen signaling pathway

Circuit list: 0 altered

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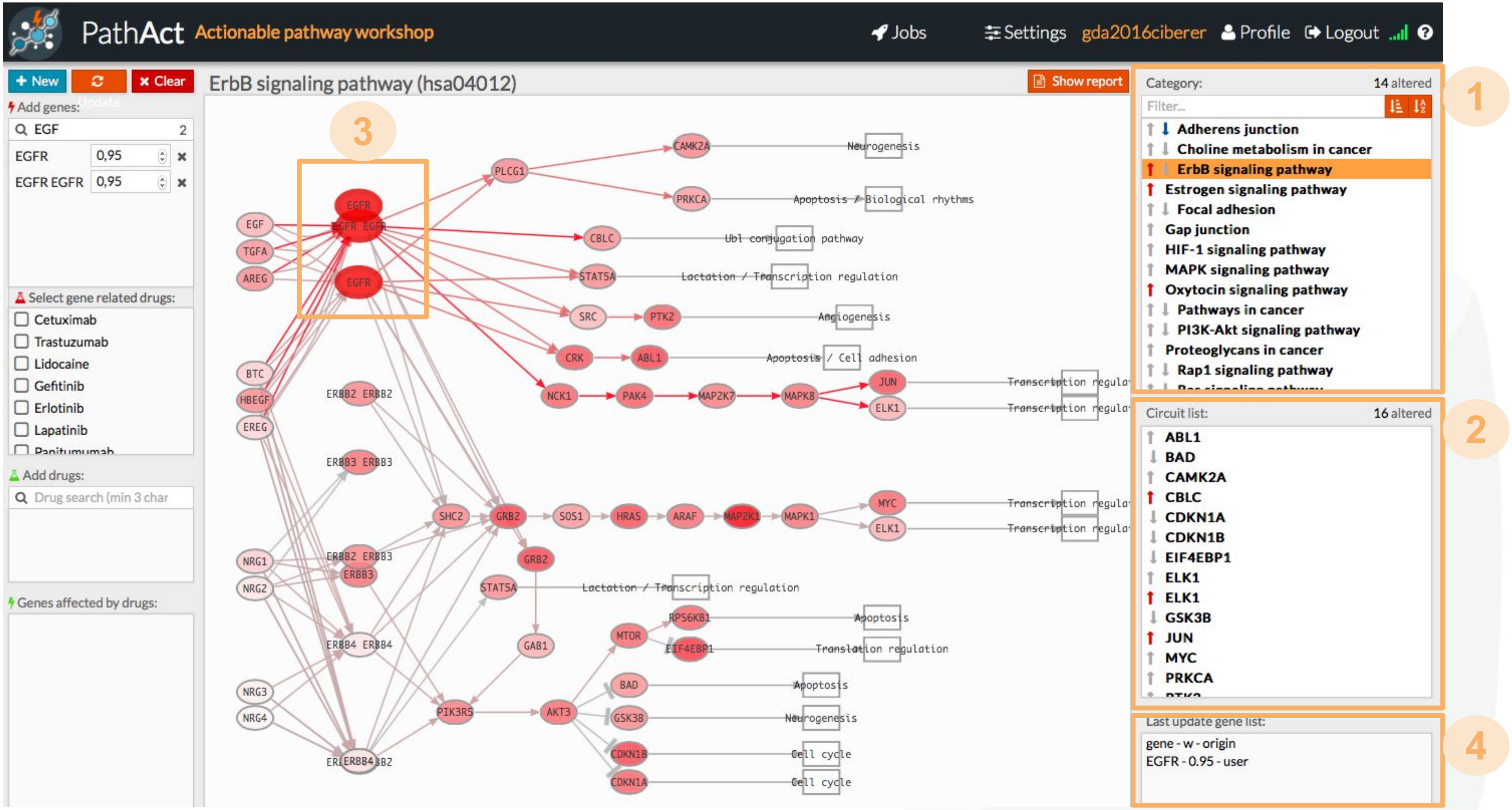
- CBLC
- CDKN1A
- CDKN1B
- EIF4EBP1
- ELK1
- ELK1
- ERBB3 ERBB3
- GSK3B
- JUN
- MYC
- PRKCA

Last update gene list:

Overexpression



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- ☐ Lidocaine
- ☐ Gefitinib
- ☐ Erlotinib
- ☐ Lapatinib
- ☐ Panitumumab

Add drugs:

Drug search (min 3 char

Genes affected by drugs:

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

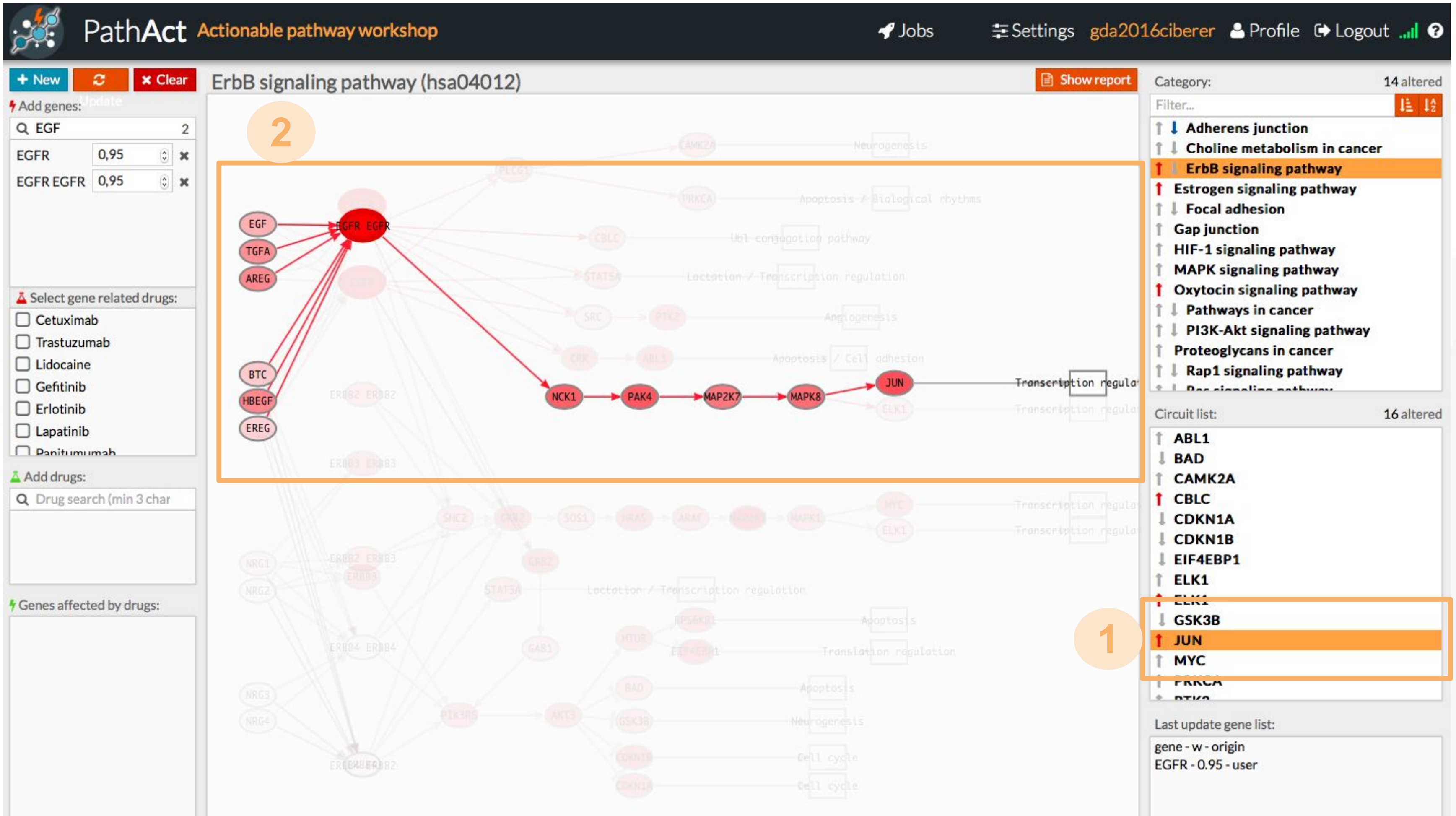
Circuit list: 16 altered

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

Last update gene list:

gene - w - origin
EGFR - 0.95 - user

Overexpression



ErbB signaling pathway (hsa04012)

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:

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

- ↑ ABL1
- ↓ BAD
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- ↑ ELK1
- ↑ ELK1
- ↓ GSK3B
- ↑ JUN
- ↑ MYC
- ↑ PRKCA

Last update gene list:

gene - w - origin
EGFR - 0.95 - user

Results interpretation

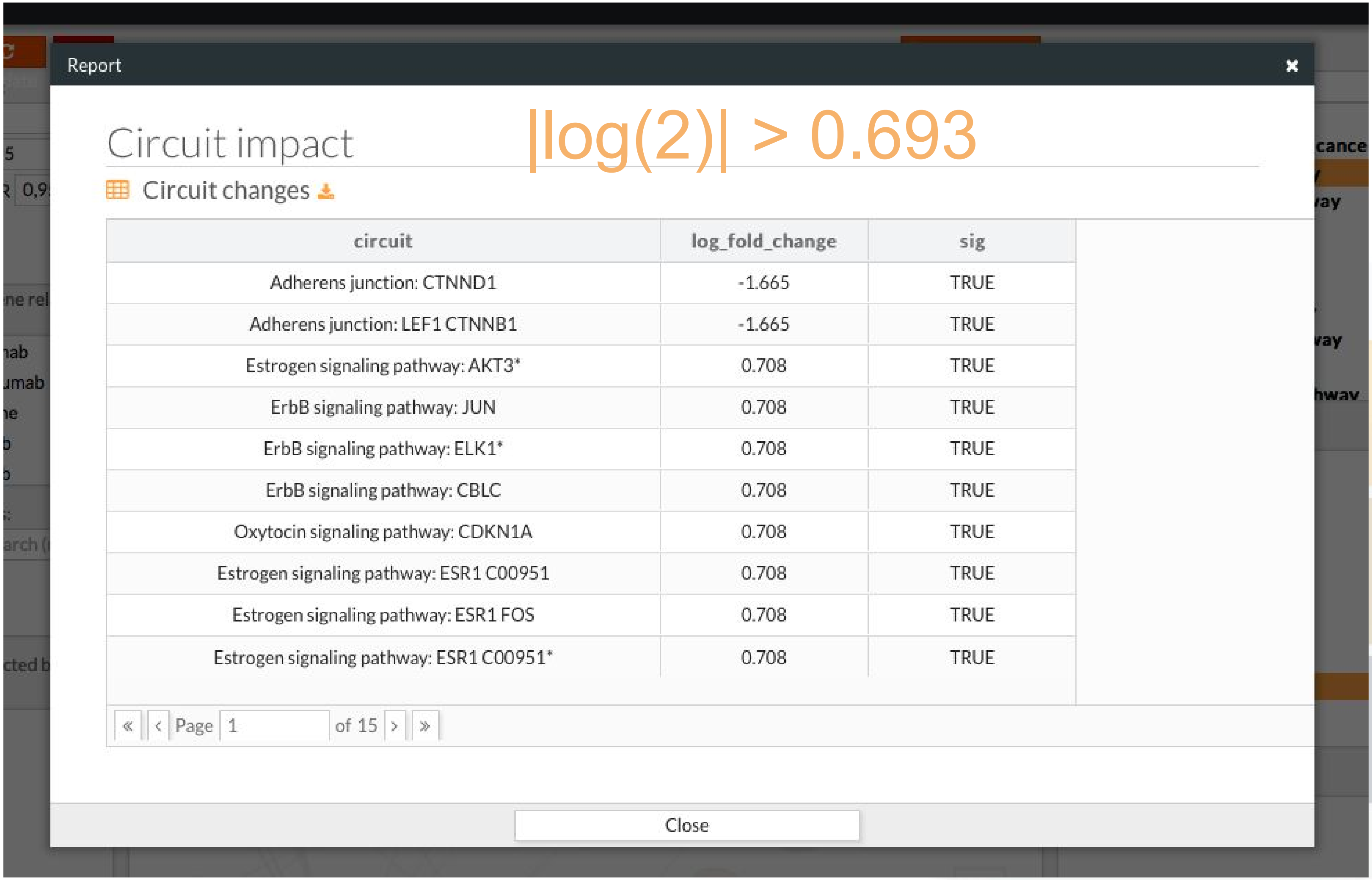
Configure fold change: 2

$|\log(2)| > 0.693$

Configure drug action weight:

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

Report



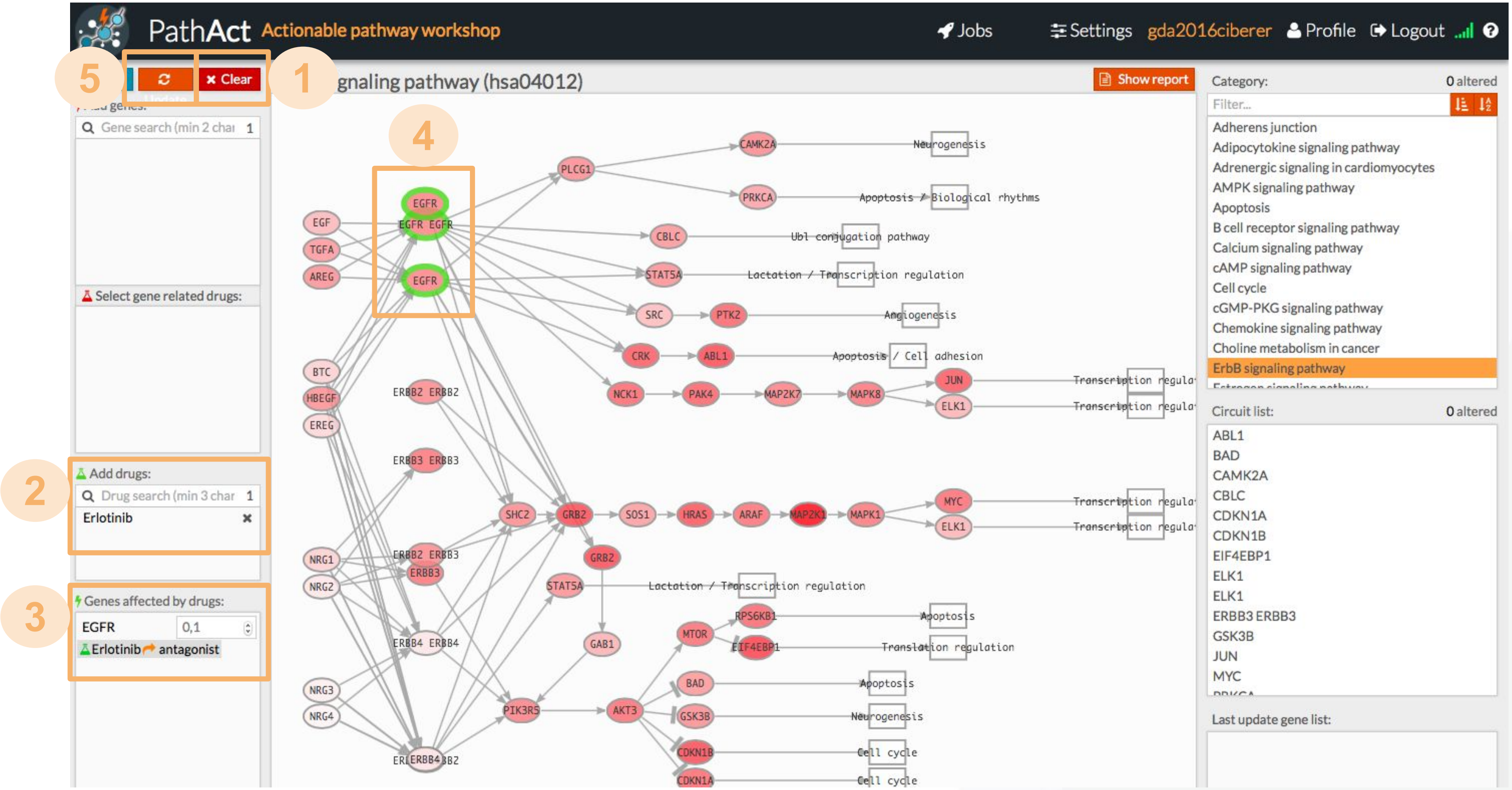
Circuit impact

|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

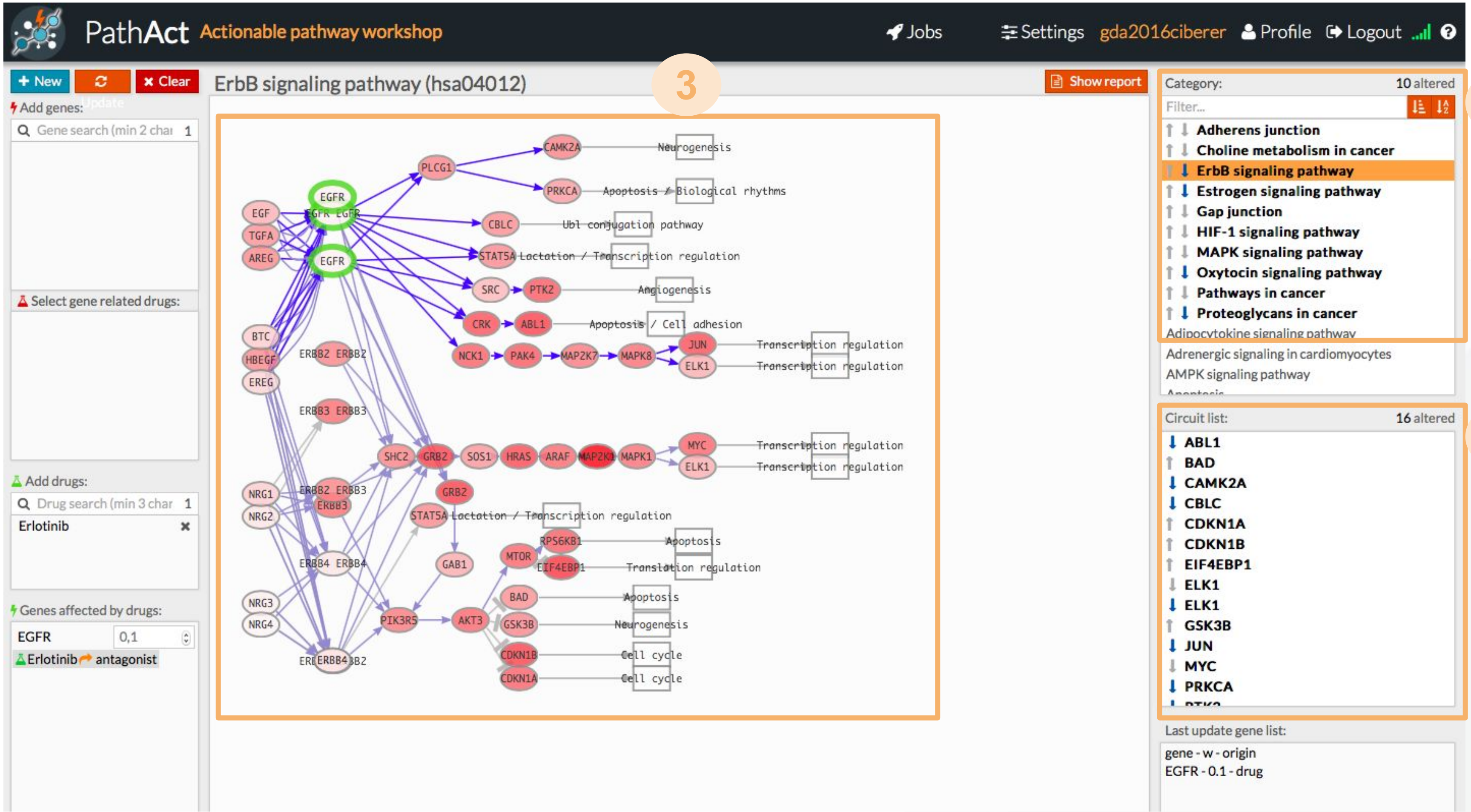
Drug action



Add drugs:
Drug search (min 3 char 1
Erlotinib

Genes affected by drugs:
EGFR 0,1
Erlotinib antagonist

Drug action



ErbB signaling pathway (hsa04012)

Add genes:

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

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

Circuit list: 16 altered

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

Last update gene list:

gene - w - origin
EGFR - 0.1 - drug

Thanks for your attention

Any questions?