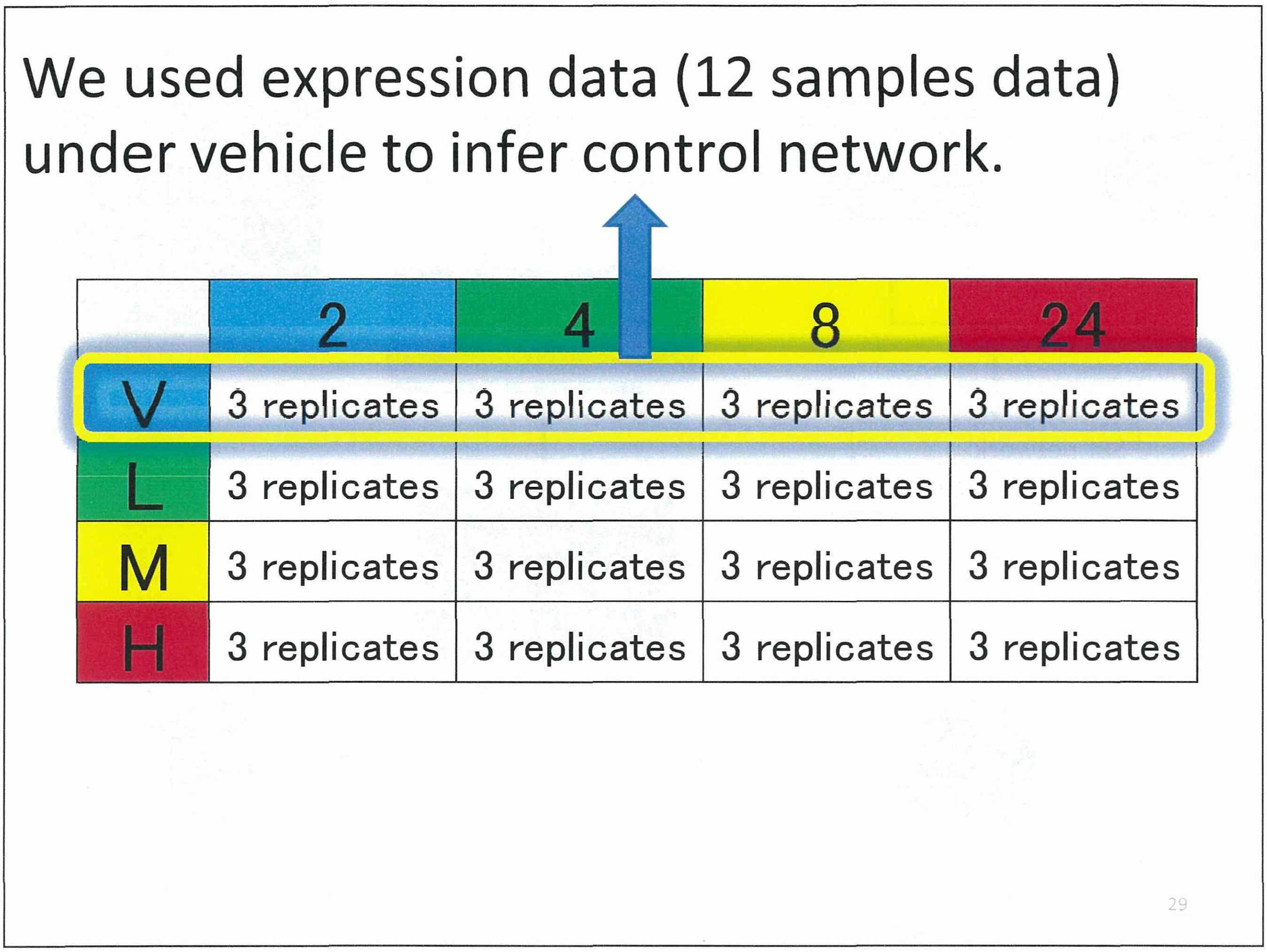
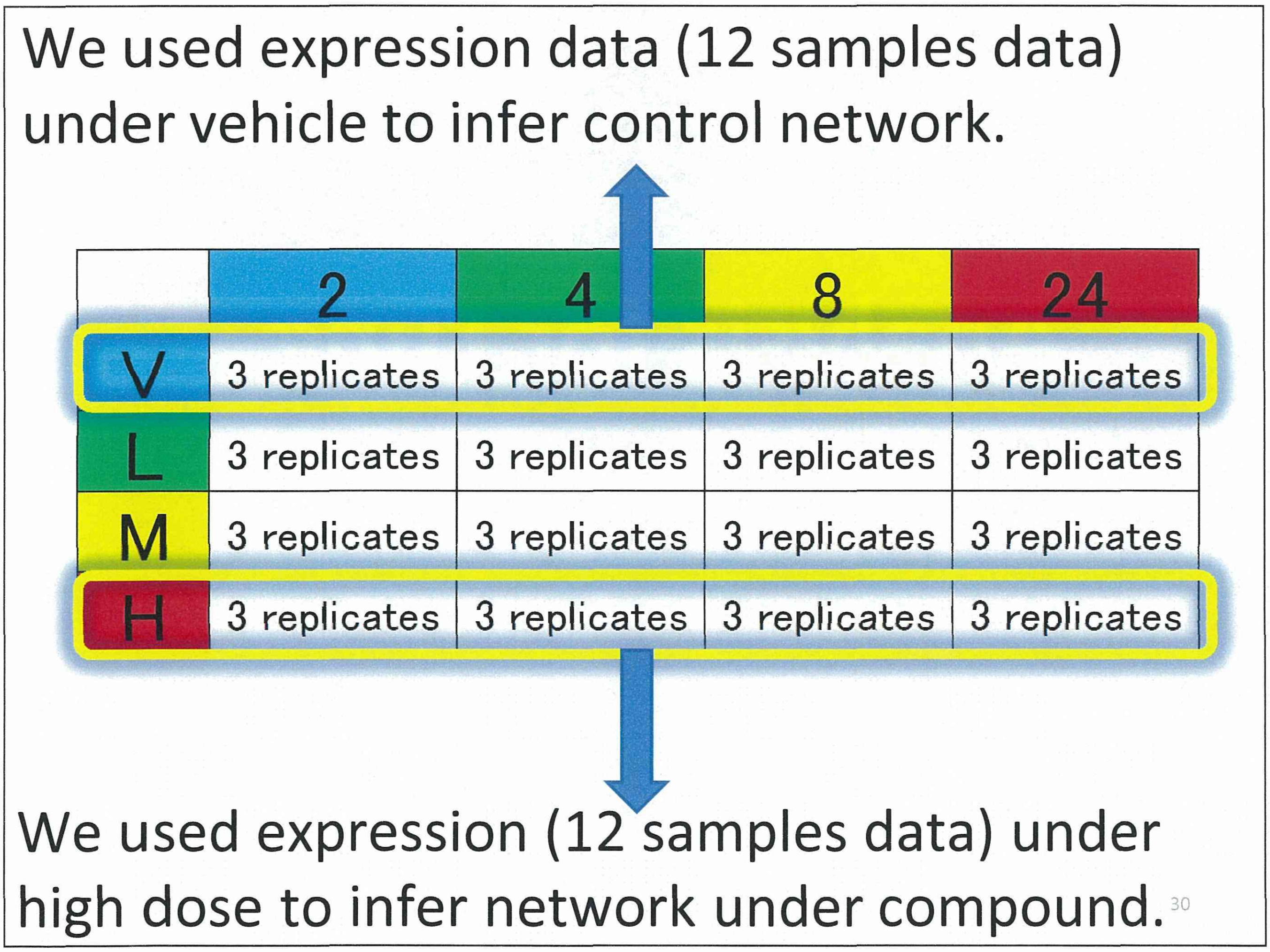


We used expression data (12 samples data) under vehicle to infer control network.

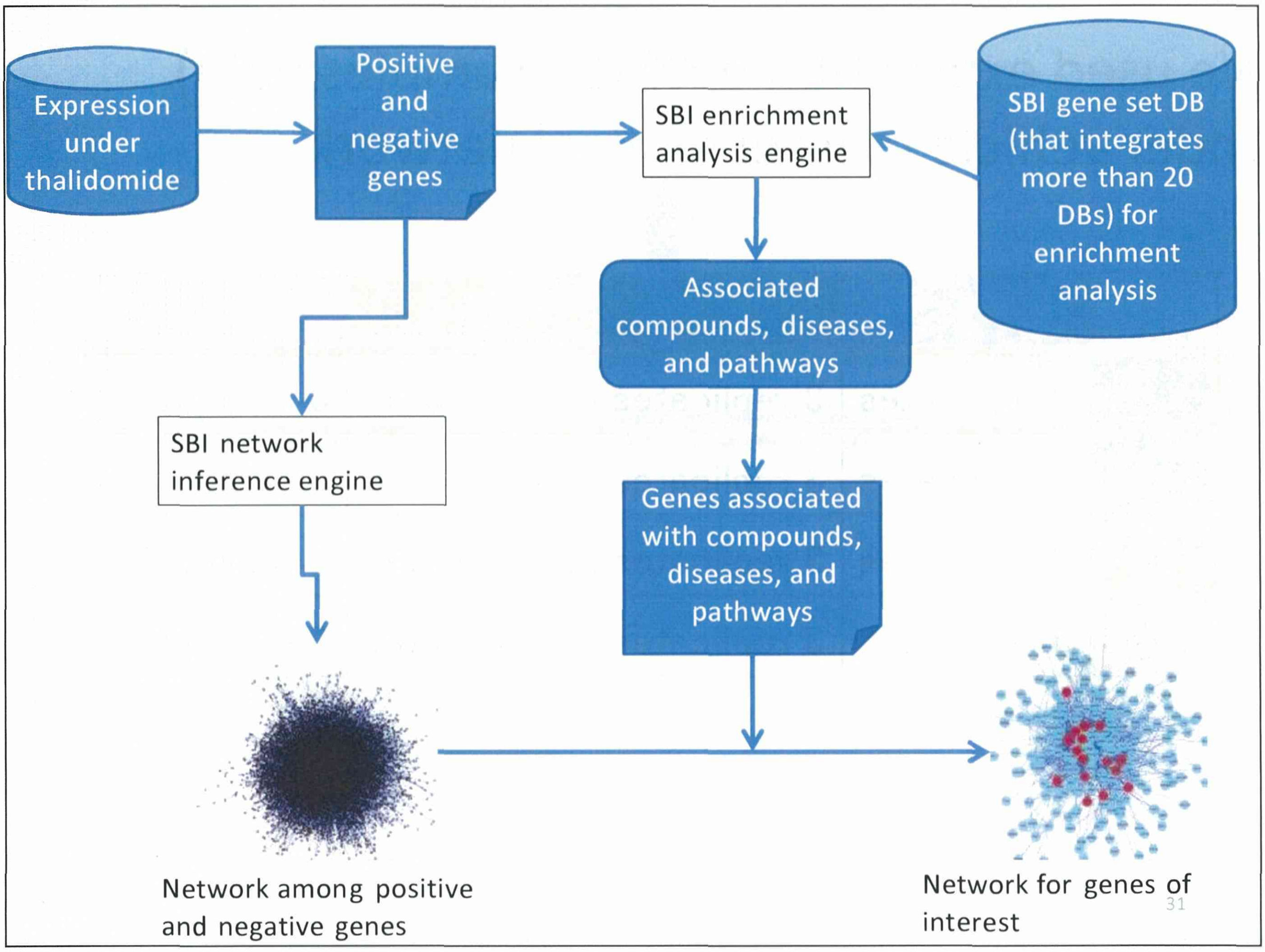
	2	4	8	24
V	3 replicates	3 replicates	3 replicates	3 replicates
L	3 replicates	3 replicates	3 replicates	3 replicates
M	3 replicates	3 replicates	3 replicates	3 replicates
H	3 replicates	3 replicates	3 replicates	3 replicates



We used expression data (12 samples data) under vehicle to infer control network.

	2	4	8	24
V	3 replicates	3 replicates	3 replicates	3 replicates
L	3 replicates	3 replicates	3 replicates	3 replicates
M	3 replicates	3 replicates	3 replicates	3 replicates
H	3 replicates	3 replicates	3 replicates	3 replicates

We used expression (12 samples data) under high dose to infer network under compound.


Expression under thalidomide

Positive and negative genes

SBI enrichment analysis engine

SBI gene set DB (that integrates more than 20 DBs) for enrichment analysis

Associated compounds, diseases, and pathways

SBI network inference engine

Genes associated with compounds, diseases, and pathways

Network among positive and negative genes

Network for genes of interest

Analysis for Lung (enrichment)

Enrichment analysis for compounds (positive)

- Positive genes are significantly associated with both of dexamethasone and glucocorticoide.
- 8 positive genes are associated with dexamethasone. EDN1, CDKN1A, FAS, FKBP5, BCL2L1, KLF15, ANGPTL4, and DDIT4
- 1 positive gene is associated with glucocorticoid. CDKN1A
- Top compoud is Z-ITED-FMK. Z-VAD-FMK is a apoptosis inhibitor in THP.1 cells which are derived from human AML cancer (acute monocytic leukemia)
- http://www.selleckchem.com/products/z-vad-fmk.html
- http://en.wikipedia.org/wiki/THP1_cell_line

Enrichment analysis for compounds (negative)

- Negative genes are significantly associated with dexamethasone.
- 1 negative genes are associated with dexamethasone. NCF1

Enrichment analysis for adverse effect (positive)

- Positive genes are significantly associated with pneumonia.
- 3 positive genes are associated with pneumonia. FAS, FOXO3, and BCL2L1

Enrichment analysis for phenotype (negative)

- Negative genes are significantly enriched with interstitial pneumonia, pneumonia, and abnormal circulating chemokine level.
- 1 negative gene is associated with interstitial pneumonia and abnormal circulating chemokine level. PTPN6
- 1 negative gene is associated with pneumonia. NCF1

List of genes of interest

- EDN1, CDKN1A, FAS, FKBP5, BCL2L1, KLF15, ANGPTL4, DDIT4, NCF1, FOXO3, and PTPN6

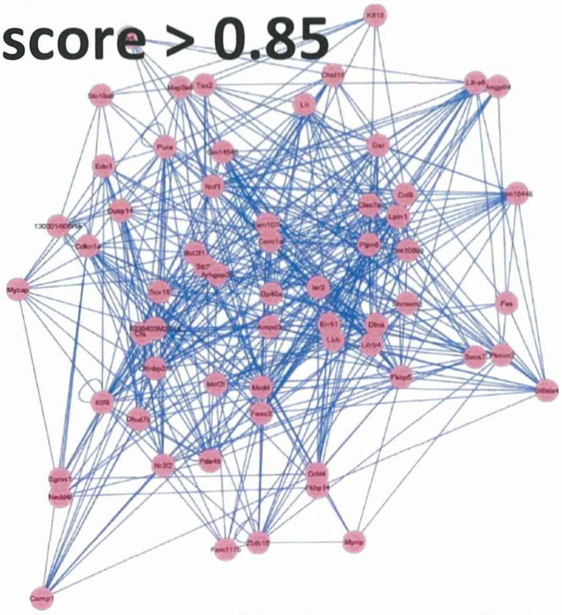
Analysis for Lung (network)

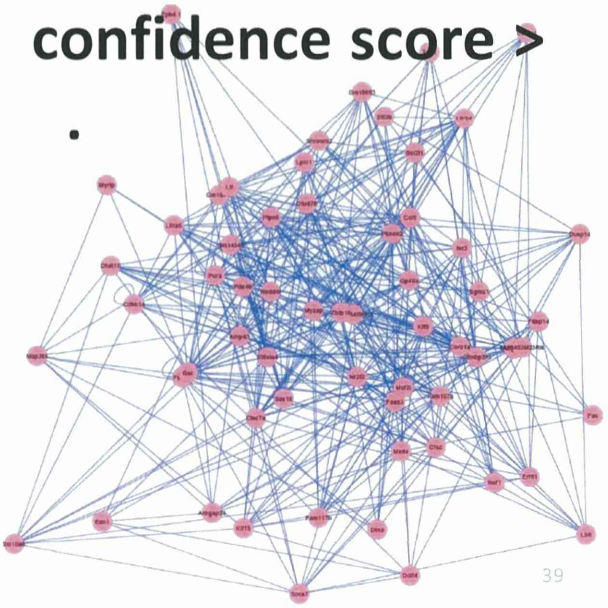
Network under control and that under compound

Control, confidence score > 0.85

Compound, confidence score >

•

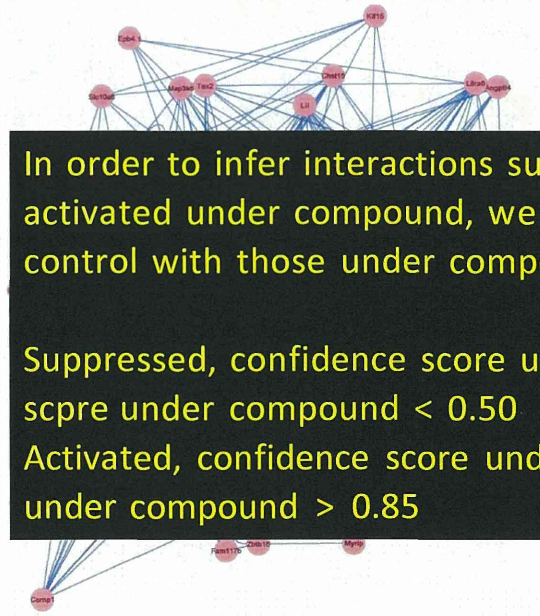


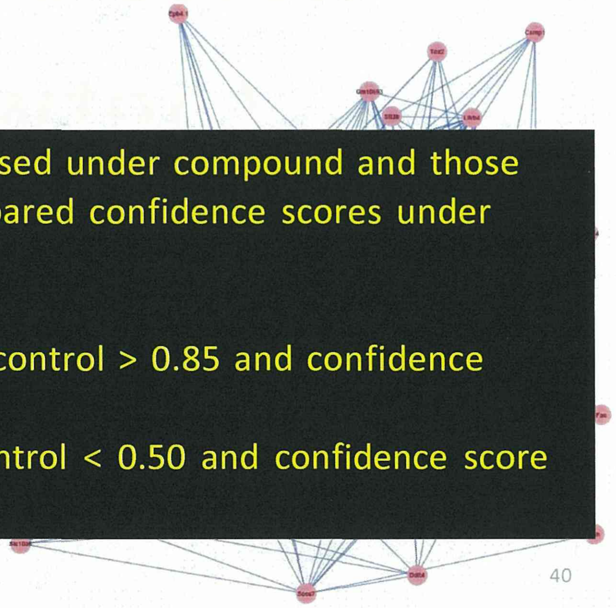


Network under control and that under compound

Control

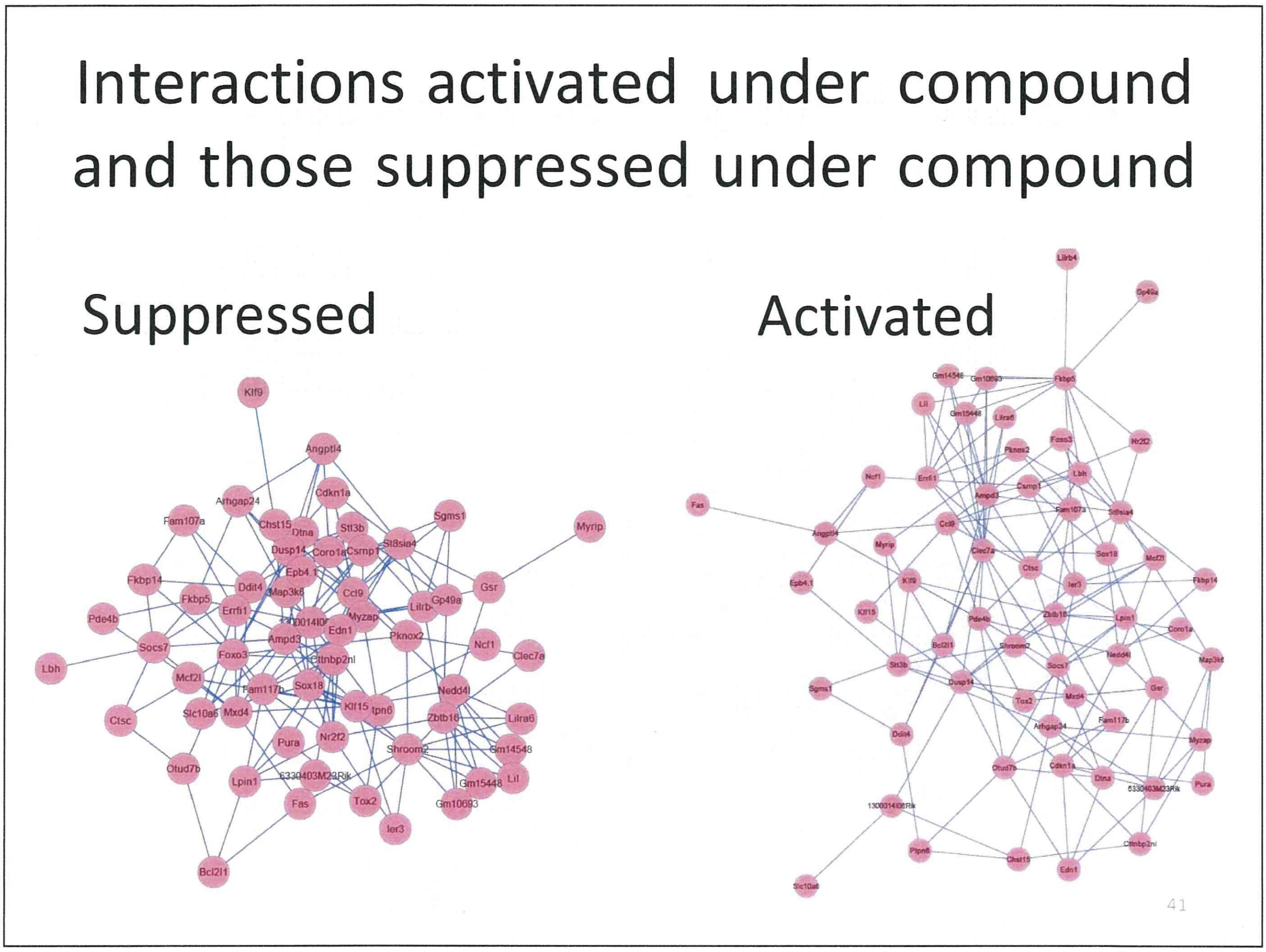
Compound





In order to infer interactions suppressed under compound and those activated under compound, we compared confidence scores under control with those under compound.

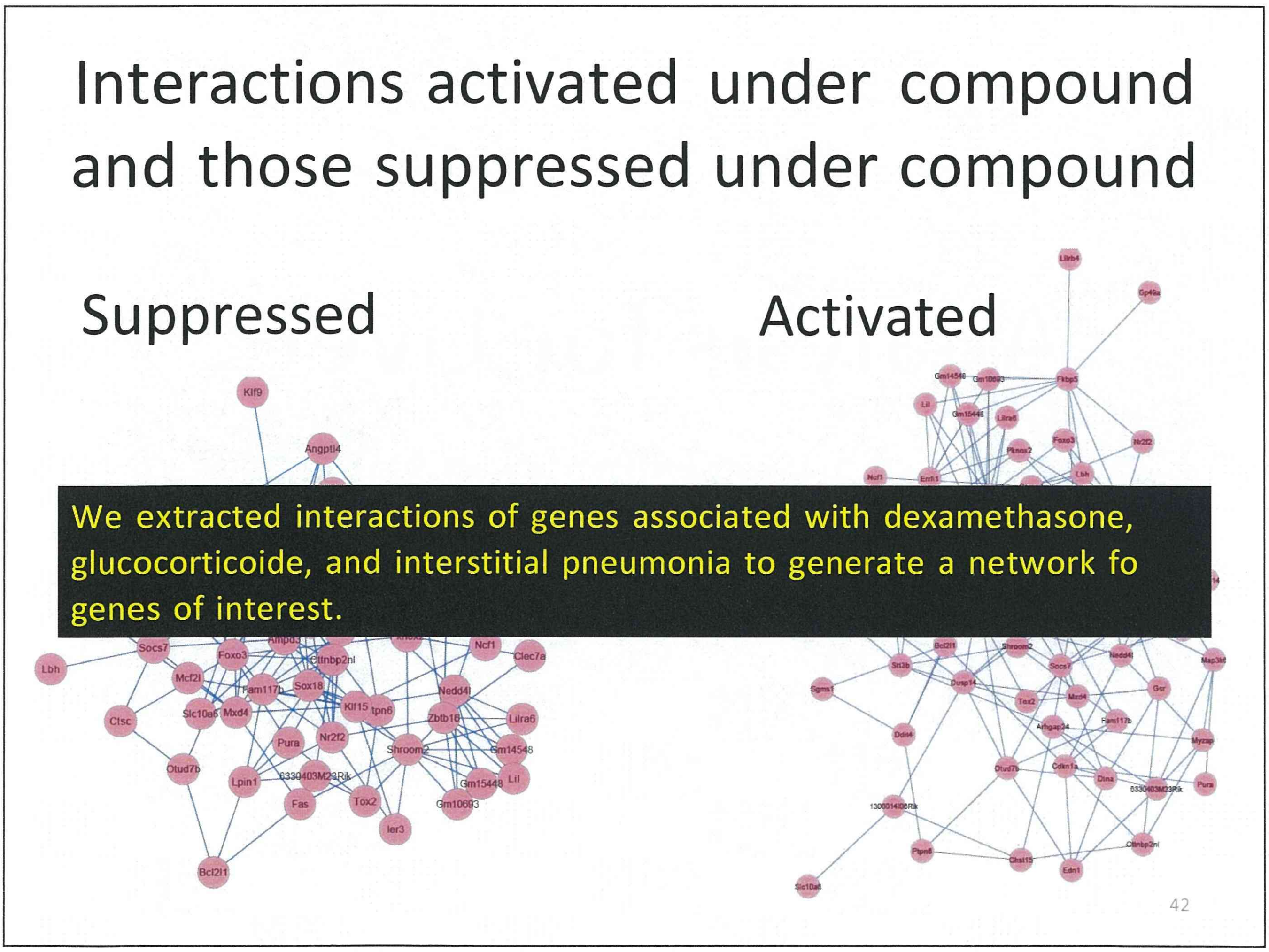
Suppressed, confidence score under control > 0.85 and confidence scpre under compound < 0.50
Activated, confidence score under control < 0.50 and confidence score under compound > 0.85



Interactions activated under compound and those suppressed under compound

Suppressed

Activated



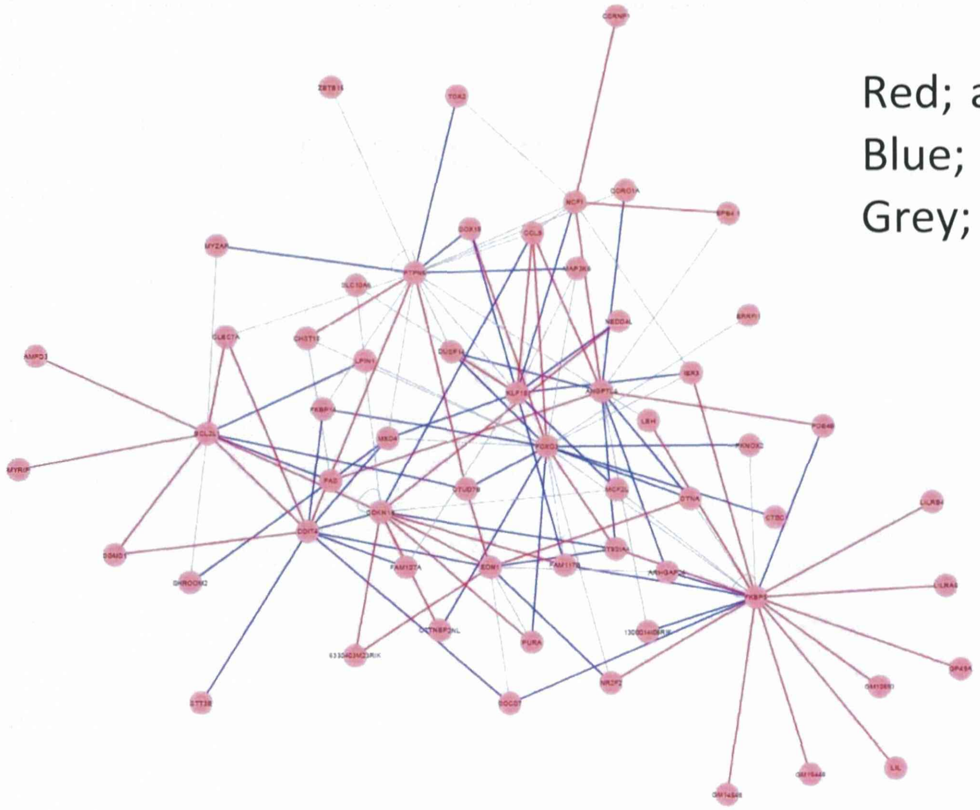
Interactions activated under compound and those suppressed under compound

Suppressed

Activated

We extracted interactions of genes associated with dexamethasone, glucocorticoide, and interstitial pneumonia to generate a network fo genes of interest.

Network for genes of interest



Red; activated
Blue; suppressed
Grey; common

Analysis for Liver (Enrichment)

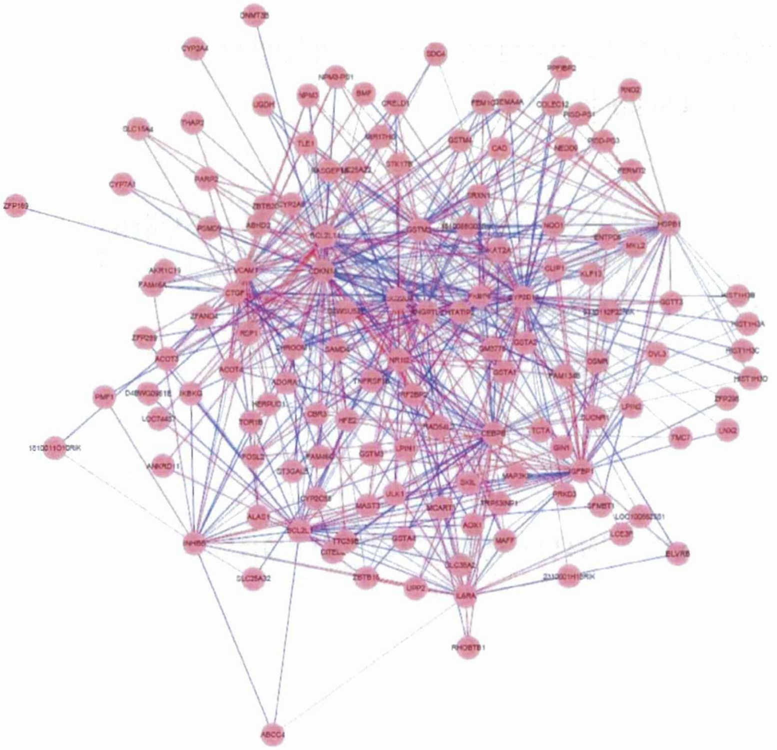
Enrichment analysis for compounds (positive)

- Positive genes are significantly associated with both of dexamethasone and glucocorticoide.
- 17 positive genes are associated with dexamethasone. HSPB1, ANGPTL4, IL6RA, FKBP5, IGFBP1, NR1I2, CEBPB, BCL2L1, TSC22D3, CYP2B10, INHBB, CTGF, VCAM1, GSTM2, CDKN1A, BCL2L11, TFRC
- 2 positive gene is associated with glucocorticoid. VCAM1 and CDKN1A

List of genes of interest

HSPB1, ANGPTL4, IL6RA, FKBP5, IGFBP1, NR1I2, CEBPB, BCL2L1, TSC22D3, CYP2B10, INHBB, CTGF, VCAM1, GSTM2, CDKN1A, BCL2L11, and TFRC

Network for genes of interest



Red; activated
Blue; suppressed
Grey; common

Network inference from percellome data in mouse fetus

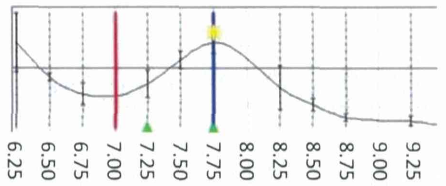
Dataset

- mouse fetus(dpc6.25-9.75) expression data
- Every 6 hour, expression level of each gene were measured.
- 3 replicates for each time point.

Purpose of study is to infer and visualize gene interactions in each stage of mouse fetus development as well as gene interaction across different stages of mouse fetus development by using **inference cloud**.

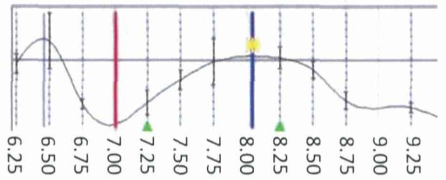
Groups of genes

Group1
421 genes


log MaxT1 36 42 ESPT1 18 24 Mokushi.TXT

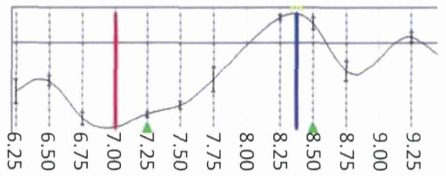
Expression Start Time = dpc7.00 - 7.25
Maximum Peak = dpc7.75 – .

Group2
42 genes


log MaxT1 43 48 ESPT1 18 24 Mokushi.TXT

Expression Start Time = dpc7.0 - .
Maximum Peak = dpc8.00 – .

Group3
125 genes


log MaxT1 49 54 ESPT1 18 24 Mokushi.TXT

Expression Start Time = dpc7.00 - 7.25
Maximum Peak = dpc8.25 – .

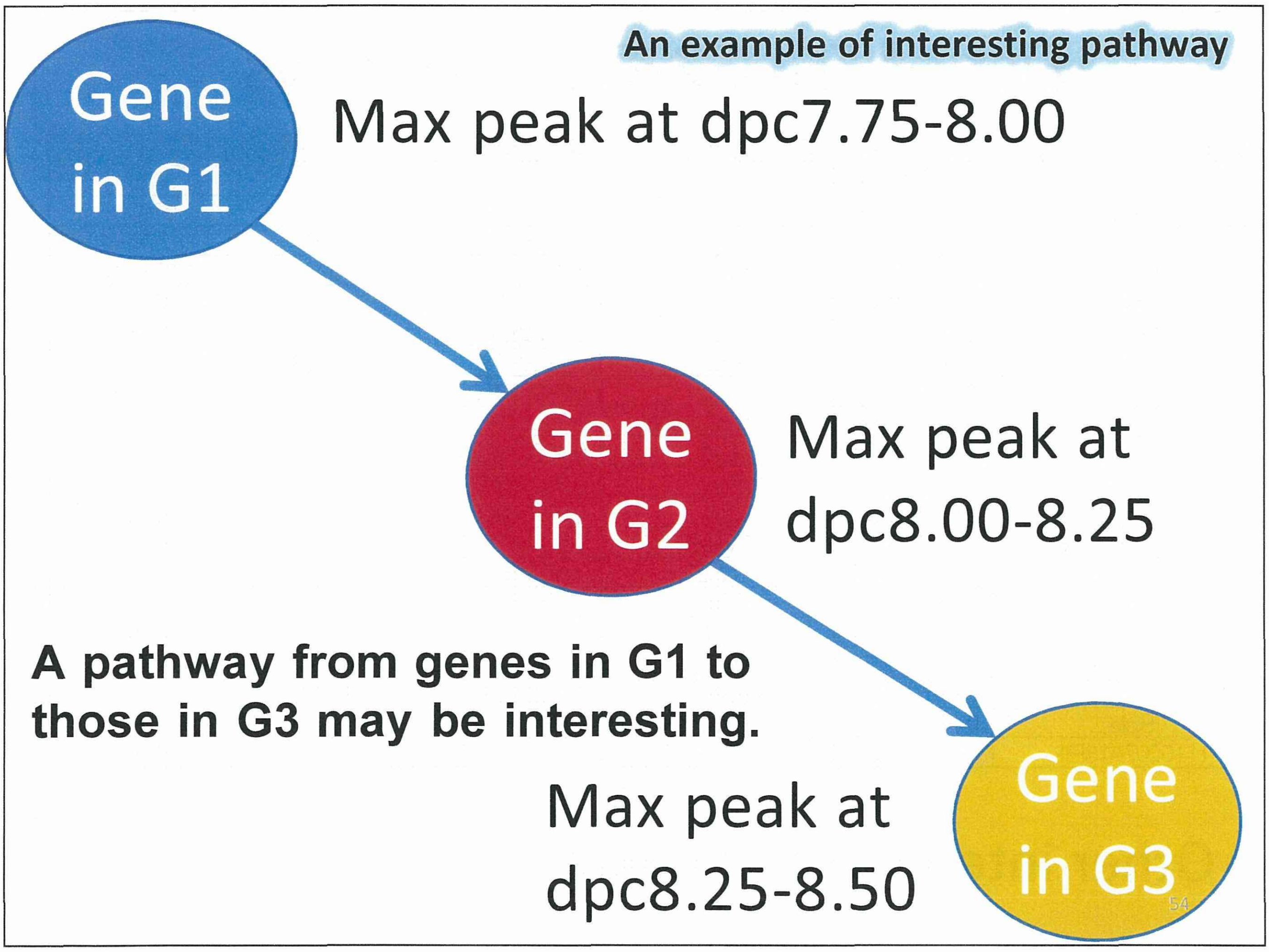
Groups of genes

- Group4 (3 genes); Expression Start Time = dpc6.50
- Group5 (7 genes); Expression Start Time = dpc6.75
- Group6 (239 genes); Expression Start Time = dpc7.25
- Group7 (837 genes); Expression Start Time = dpc7.50
- Group8 (209 genes); Expression Start Time = dpc7.75
- Group9 (28 genes); Expression Start Time = dpc8.25

Network inference

- We used expression data of 6.25 – 9.25 dpc（12 time points, 45 sample points）to infer the network among genes in the groups.
- Map group ID of the genes on the network to find interesting pathways
- We integrated results from these algorithms to calculate score for each regulatory link between two genes.

An example of interesting pathway



Max peak at dpc7.75-8.00

Max peak at dpc8.00-8.25

A pathway from genes in G1 to those in G3 may be interesting.

Max peak at dpc8.25-8.50

List of G1-G2-G3 pathways

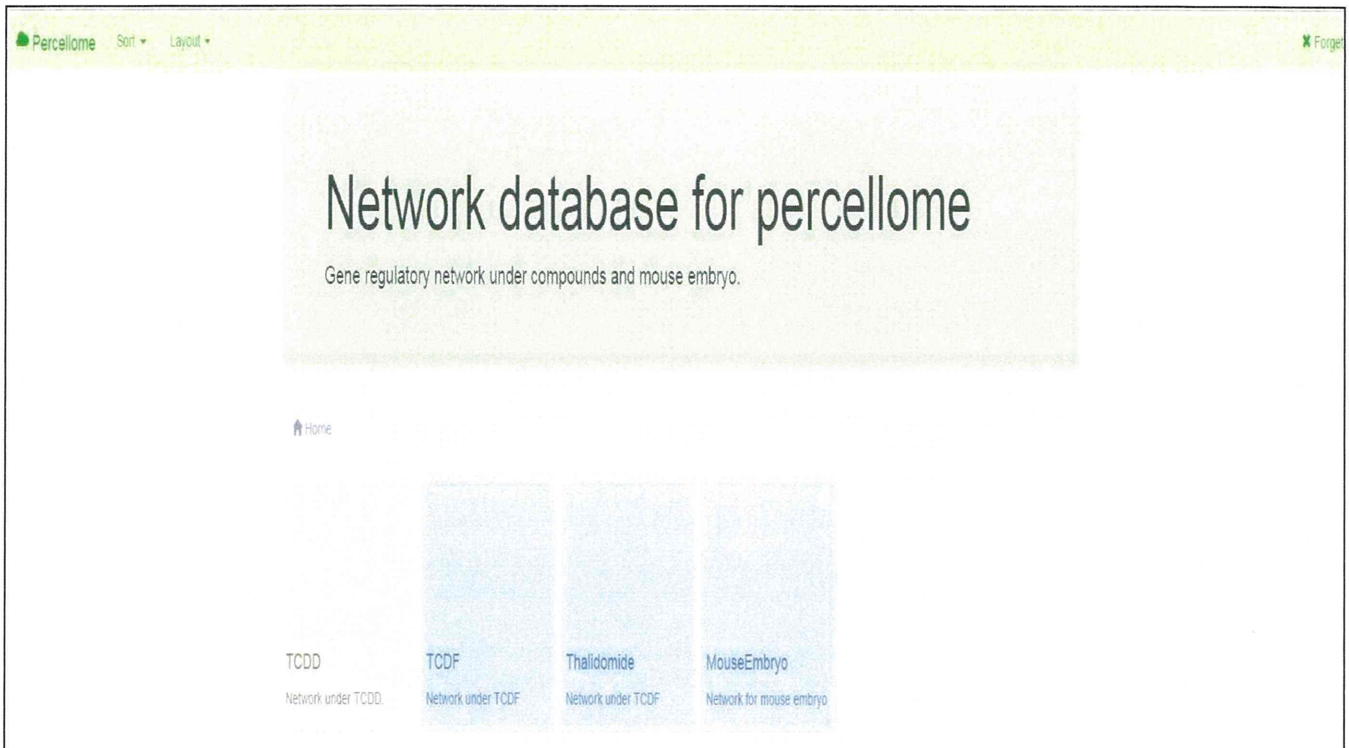
G1 (peak775-800)	edge 1	G2 (peak800-825)	edge2	G3 (peak825-850)	total score
Mbl2	0.986810155	2810022L02Rik	0.993874172	Cd248	1.980684327
Slit2	0.983554084	Isl1	0.992549669	Prrx1	1.976103753
Ppp1r1a	0.995309051	Lgi2	0.980629139	Vezf1	1.97593819
Gfra2	0.979525386	2810022L02Rik	0.993874172	Cd248	1.973399558
Ppp1r1a	0.995309051	Lgi2	0.97080574	Bche	1.966114791
Metrn	0.977373068	Sp6	0.972019868	Itih5	1.949392936
Aldh2	0.963245033	Ifitm2	0.983940397	Fxyd6	1.94718543
Smarcc1	0.964072848	Lgi2	0.980629139	Vezf1	1.944701987
Arid4b	0.949558499	2810022L02Rik	0.993874172	Cd248	1.943432671
Pla2g7	0.960375276	Lgi2	0.980629139	Vezf1	1.941004415
Ppp1r1a	0.954470199	Ifitm2	0.983940397	Fxyd6	1.938410596
Notch1	0.945695364	Isl1	0.992549669	Prrx1	1.938245033
5033421C21Rik	0.998509934	Twist2	0.938852097	Prrx1	1.937362031
Smarcc1	0.964072848	Lgi2	0.97080574	Bche	1.934878588
Pla2g7	0.960375276	Lgi2	0.97080574	Bche	1.931181016
Casq1	0.958940397	Sp6	0.972019868	Itih5	1.930960265
Als2cr4	0.936479029	2810022L02Rik	0.993874172	Cd248	1.930353201
Cbx5	0.987196468	Arhgap24	0.942825607	Kif26b	1.930022075
Sqle	0.934381898	2810022L02Rik	0.993874172	Cd248	1.92825607
1110007A13Rik	0.930022075	2810022L02Rik	0.993874172	Cd248	1.923896247

We used links with top 5 percent to make the list.

List of G1-G2-G3 pathways

G1 (peak775-800)	edge 1	G2 (peak800-825)	edge2	G3 (peak825-850)	total score
Mbl2	0.986810155	2810022L02Rik	0.993874172	Cd248	1.980684327
Slit2	0.983554084	Isl1	0.992549669	Prrx1	1.976103753
Ppp1r1a	0.995309051	Lgi2	0.980629139	Vezf1	1.97593819
Gfra2	0.979525386	2810022L02Rik	0.993874172	Cd248	1.973399558
Ppp1r1a	0.995309051	Lgi2	0.97080574	Bche	1.966114791
Metrn	0.977373068	Sp6	0.972019868	Itih5	1.949392936
Aldh2	0.963245033	Ifitm2	0.983940397	Fxyd6	1.94718543
Smarcc1	0.964072848	Lgi2	0.980629139	Vezf1	1.944701987
Arid4b	0.949558499	2810022L02Rik	0.993874172	Cd248	1.943432671
Pla2g7	0.960375276	Lgi2	0.980629139	Vezf1	1.941004415
Ppp1r1a	0.954470199	Ifitm2	0.983940397	Fxyd6	1.938410596
Notch1	0.945695364	Isl1	0.992549669	Prrx1	1.938245033
5033421C21Rik	0.998509934	Twist2	0.938852097	Prrx1	1.937362031
Smarcc1	0.964072848	Lgi2	0.97080574	Bche	1.934878588
Pla2g7	0.960375276	Lgi2	0.97080574	Bche	1.931181016
Casq1	0.958940397	Sp6	0.972019868	Itih5	1.930960265
Als2cr4	0.936479029	2810022L02Rik	0.993874172	Cd248	1.930353201
Cbx5	0.987196468	Arhgap24	0.942825607	Kif26b	1.930022075
Sqle	0.934381898	2810022L02Rik	0.993874172	Cd248	1.92825607
1110007A13Rik	0.930022075	2810022L02Rik	0.993874172	Cd248	1.923896247

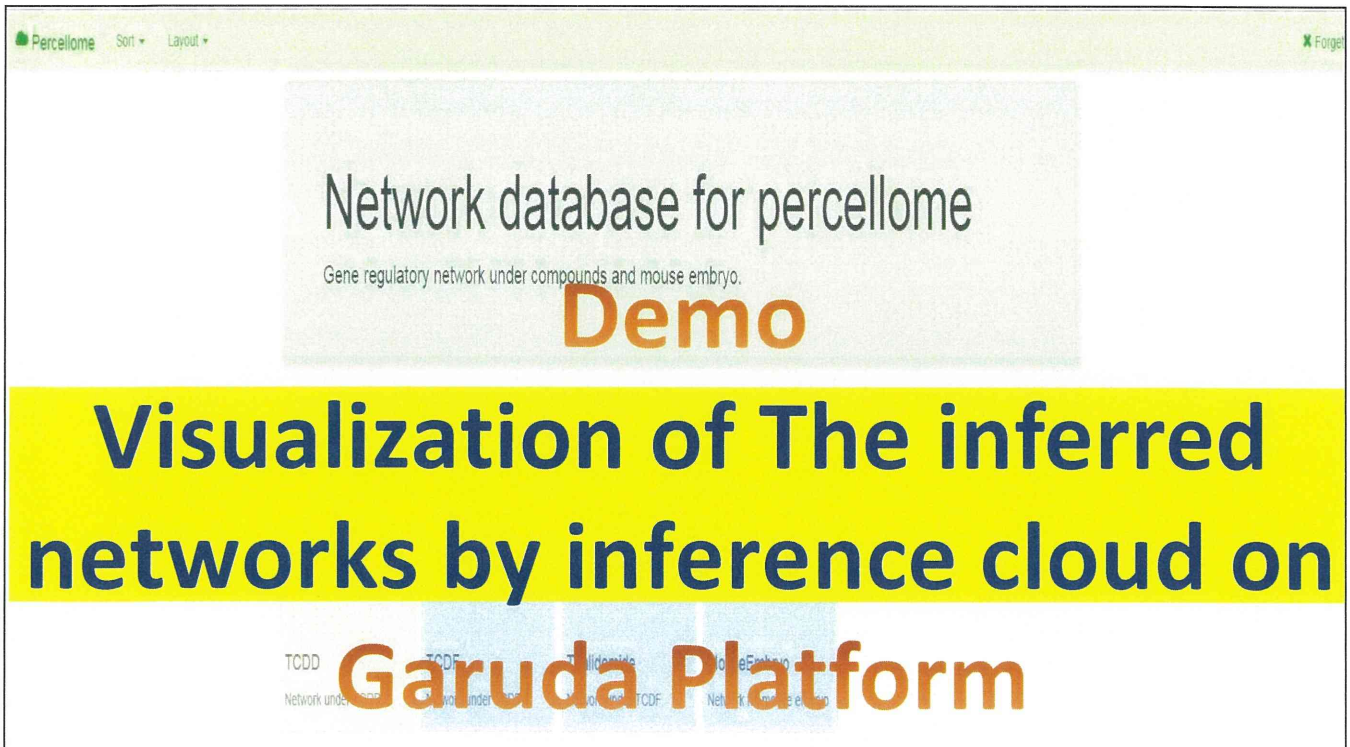
Other interesting pathways



Network database for percellome

Gene regulatory network under compounds and mouse embryo.

TCDD	TCDF	Thalidomide	MouseEmbryo
Network under TCDD.	Network under TCDF	Network under TCDF	Network for mouse embryo



Network database for percellome

Gene regulatory network under compounds and mouse embryo.

TCDD TCDF Thalidomide MouseEmbryo

Demo

Visualization of The inferred networks by inference cloud on Garuda Platform

別添 5

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
Janesick A, Nguyen TT, Aisaki K, Igarashi K, Kitajima S, Chandraratna RA, Kanno J, Blumberg B.	Active repression by RARγ signaling is required for vertebrate axial elongation.	Development	141 (11)	2260 - 2270	2014
Tanaka M, Aisaki K, Kitajima S, Igarashi K, Kanno J and Nakamura T	Gene expression response to EWS–FLI1 in mouse embryonic cartilage.	Genomics Data	2	296 - 298	2014
Tanaka M, Yamazaki Y, Kanno Y, Igarashi K, Aisaki K, Kanno J, Nakamura T.	Ewing's sarcoma precursors are highly enriched in embryonic osteochondrogenic progenitors.	J Clin Invest.	124 (7)	3061 - 3074	2014
Maria Marti-Solano, Ewan Birney, Antoine Bril, Oscar Della Pasqua, Hiroaki Kitano, Barend Mons, Ioannis Xenarios and Ferran Sanz	Integrative knowledge management to enhance pharmaceutical R&D.	Nature Reviews Drug Discovery	13 (4)	239 - 240	2014
Yoshiyuki ASAI; Takeshi ABE, Hideki OKA, Masao OKITA, Ken-ichi HAGIHARA, Samik GHOSH, Yukiko MATSUOKA, Yoshihisa KURACHI, Taishin NOMURA, Hiroaki KITANO	A Versatile Platform for Multilevel Modeling of Physiological Systems: SBML-PHML Hybrid Modeling and Simulation.	ABE Advanced Biomedical Engineering	3	50 - 58	2014
Tokiko Watanabe, Eiryo Kawakami, Jason E. Shoemaker, Tiago J.S. Lopes, Yukiko Matsuoka, Yuriko Tomita, Hiroko Kozuka-Hata, Takeo Gorai,	Influenza Virus-Host Interactome Screen as a Platform for Antiviral Drug Development	Cell Host & Microbe	16 (6)	795 - 805	2014

Tomoko Kuwahara, Eiji Takeda, Atsushi Nagata, Ryo Takano, Maki Kiso, Makoto Yamashita, Yuko Sakai-Tagawa, Hiroaki Katsura, Naoki Nonaka, Hiroko Fujii, Ken Fujii, Yukihiko Sugita, Takeshi Noda, Hideo Goto, Satoshi Fukuyama, Shinji Watanabe, Gabriele Neumann, Masaaki Oyama, Hiroaki Kitano, and Yoshihiro Kawaoka					
Jablonska Agnieszka and Natalia Polouliakh	In silico discovery of novel transcription factors regulated by mTOR pathway activities	Frontier in Cell and Developmental Biology ISSN: 2296-634X, DOI:10.3389 /fcell.	2 (23)	1 - 9	2014

別添 6

Ⅳ. 研究成果の刊行物・別刷