

*Interactive Toxicogenomics: Gene Set  
Discovery, Clustering and Analysis in Toxygates*

Nyström-Persson, J., Natsume-Kitatani, Y.,  
Igarashi, Y., Satoh, D., and Mizuguchi, K.

Supplementary Figures and Tables

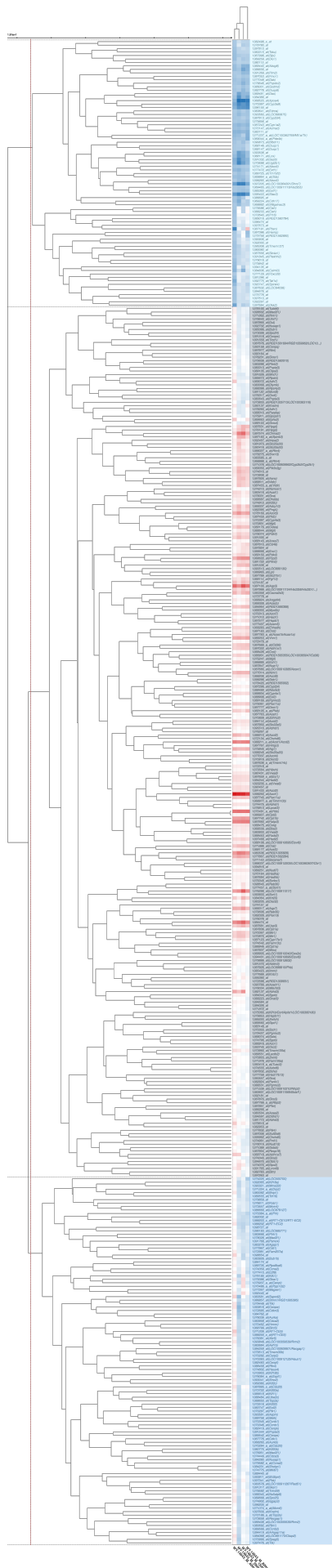
# Supplementary Figure S1

M dose/4 day (434 probes)

Steroid hormone biosynthesis  
[rno00140]  
77 probes

PPAR signaling pathway  
[rno03320]  
244 probes

Cell Cycle  
[R007]  
113 probes



## Supplementary Figure S1

Heatmap of gene expression profiles obtained by treatment of WY-14643 in genes whose expression intensities were affected in M dose/4 day

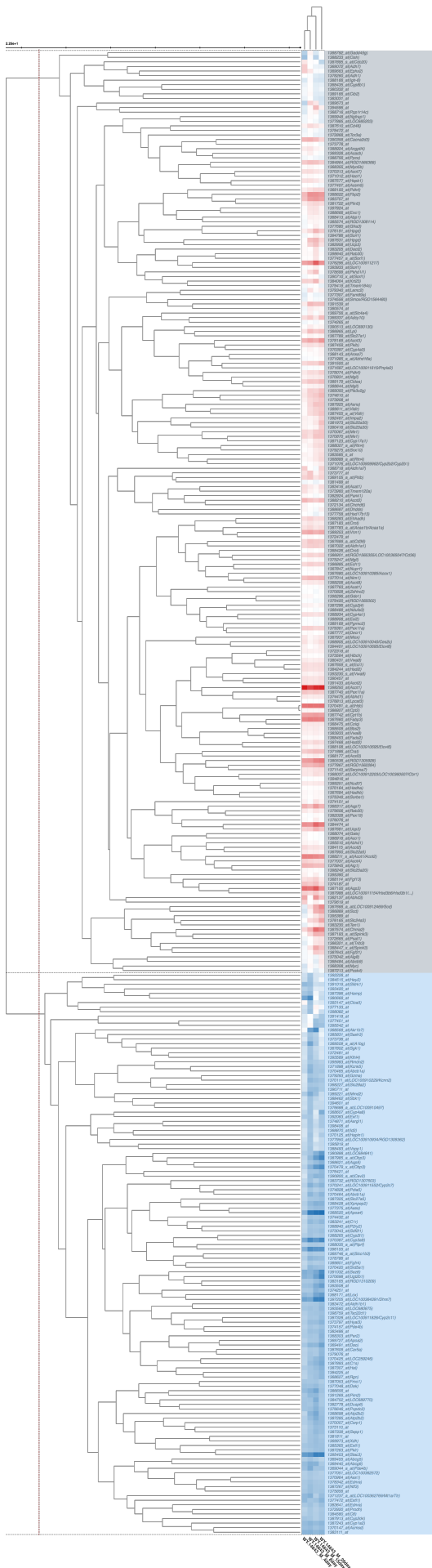
The x-axis represents experimental conditions (from left to right, 1) WY-14643 4day, 2) WY-14643 29day, 3) WY-14643 15day, 4) WY-14643 8day. The y-axis represents probes whose log<sub>2</sub> (fold change) value against the control group was 1.5 or more by 4day treatment of WY-14643.

# Supplementary Figure S2

M dose/8 day (325 probes)

PPAR signaling pathway  
[rno03320]  
202 probes

Steroid hormone biosynthesis  
[rno00140]  
123 probes

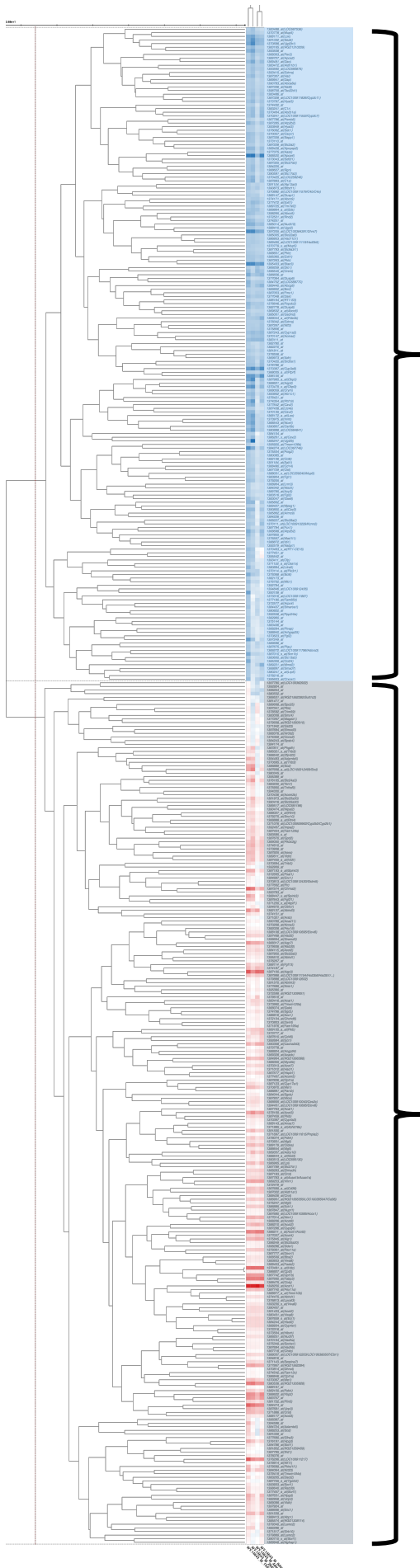


Supplementary Figure S2

Heatmap of gene expression profiles obtained by treatment of WY-14643 in genes whose expression intensities were affected in M dose/8 day

The x-axis represents experimental conditions (from left to right, 1) WY-14643 4day, 2) WY-14643 8day, 3) WY-14643 15day, 4) WY-14643 29day. The y-axis represents probes whose log<sub>2</sub> (fold change) value against the control group was 1.5 or more by 8day treatment of WY-14643.

## Supplementary Figure S3



M dose/15 day (420 probes)

Steroid hormone biosynthesis  
[rno00140]  
181 probes

PPAR signaling pathway  
[rno03320]  
239 probes

### Supplementary Figure S3

Heatmap of gene expression profiles obtained by treatment of WY-14643 in genes whose expression intensities were affected in M dose/15 day

The x-axis represents experimental conditions (from left to right, 1) WY-14643 15day, 2) WY-14643 29day, 3) WY-14643 4day, 4) WY-14643 8day. The y-axis represents probes whose  $\log_2$  (fold change) value against the control group was 1.5 or more by 15day treatment of WY-14643.

## Supplementary Figure S4

M dose/29 day (399 probes)

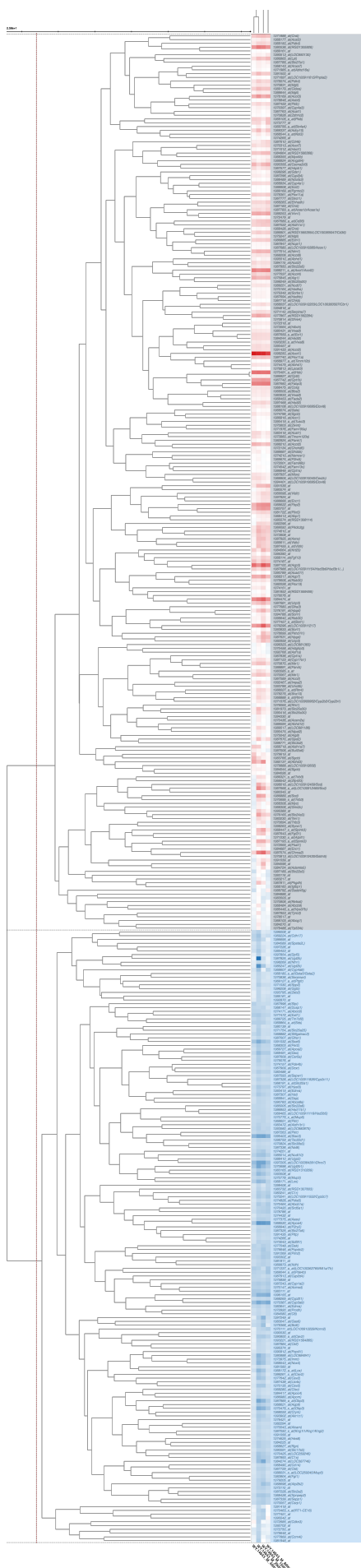
PPAR signaling pathway  
[rno03320]  
237 probes

Steroid hormone biosynthesis  
[rno00140]  
162 probes

### Supplementary Figure S4

Heatmap of gene expression profiles obtained by treatment of WY-14643 in genes whose expression intensities were affected in M dose/29 day

The x-axis represents experimental conditions (from left to right, 1) WY-14643 4day, 2) WY-14643 29day, 3) WY-14643 15day, 4) WY-14643 8day. The y-axis represents probes whose log-2 (fold change) value against the control group was 1.5 or more by 29day treatment of WY-14643.



Supplementary Table 1

L

	Grade	Degeneration, granular, eosinophilic	Necrosis	Single cell necrosis	Hypertrophy	Increased mitosis	Cell infiltration
		Hepatocyte	Hepatocyte	Hepatocyte	Bile duct, interlobular	Hepatocyte	Sinusoid
4 day	Minimal	0	0	0	0	3	0
	Slight	1	0	0	0	0	0
	Moderate	2	0	0	0	0	0
	Severe	0	0	0	0	0	0
8 day	Minimal	0	1	0	1	0	0
	Slight	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0
	Severe	3	0	0	0	0	0
15 day	Minimal	0	1	0	1	0	0
	Slight	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0
	Severe	3	0	0	0	0	0
29 day	Minimal	0	2	0	3	0	0
	Slight	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0
	Severe	3	0	0	0	0	0

M

	Grade	Degeneration, granular, eosinophilic	Necrosis	Single cell necrosis	Hypertrophy	Increased mitosis	Cell infiltration
		Hepatocyte	Hepatocyte	Hepatocyte	Bile duct, interlobular	Hepatocyte	Sinusoid
4 day	Minimal	0	0	0	0	1	0
	Slight	0	0	0	0	2	0
	Moderate	3	0	0	0	0	0
	Severe	0	0	0	0	0	0
8 day	Minimal	0	0	1	2	0	0
	Slight	0	0	0	1	0	0
	Moderate	0	0	0	0	0	0
	Severe	3	0	0	0	0	0
15 day	Minimal	0	1	0	2	0	0
	Slight	0	0	0	1	0	0
	Moderate	0	0	0	0	0	0
	Severe	3	0	0	0	0	0
29 day	Minimal	0	1	0	1	0	0
	Slight	0	1	0	2	0	0
	Moderate	0	0	0	0	0	0
	Severe	3	0	0	0	0	0

H

	Grade	Degeneration, granular, eosinophilic	Necrosis	Single cell necrosis	Hypertrophy	Increased mitosis	Cell infiltration	Granuloma
		Hepatocyte	Hepatocyte	Hepatocyte	Bile duct, interlobular	Hepatocyte	Sinusoid	(-)
4 day	Minimal	0	1	1	0	1	2	0
	Slight	0	0	0	0	1	0	0
	Moderate	3	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0
8 day	Minimal	0	0	0	2	3	0	1
	Slight	0	0	0	1	0	0	0
	Moderate	0	0	0	0	0	0	0
	Severe	3	0	0	0	0	0	0
15 day	Minimal	0	1	0	1	0	0	0
	Slight	0	0	0	2	0	0	0
	Moderate	0	0	0	0	0	0	0
	Severe	3	0	0	0	0	0	0
29 day	Minimal	0	1	0	3	0	0	1
	Slight	0	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0	0
	Severe	3	0	0	0	0	0	0

Supplementary Table 1 Pathology by repeated administration of WY-14643

WY-14643 was administered to rats (n=3) repeatedly for 4, 8, 15 or 29 days and the pathological observations were summarized. The numerical value in each cell of the table represents the number of rats that showed listed observation. L: 10 mg/kg BW, M: 30 mg/kg BW, H: 100 mg/kg BW. For the detailed information about the experimental conditions or the definitions of "Grade" of observations, refer to Open TG-GATEs (<http://toxico.nibiohn.go.jp/english/>).

Supplementary Table 2

M4 (434 probes)

cluster1 (244 probes)		
Pathways	p-value	matches
PPAR signaling pathway [rno03320]	3.97E-20	22
Fatty acid degradation [rno00071]	1.48E-19	18
Metabolism of lipids and lipoproteins [R-RNO-556833]	6.30E-17	39
Fatty acid metabolism [rno01212]	7.75E-14	15
Biosynthesis of unsaturated fatty acids [rno01040]	2.37E-13	12
<b>IPC</b>		
Metabolism of lipids and lipoproteins [R005]	1.16E-36	67
Glycerophospholipid metabolism Arachidonic acid metabolism [R010]	2.12E-09	20
Biological oxidations Chemical carcinogenesis [R006]	1.59E-04	17
Carbon metabolism [R009]	3.53E-03	11

cluster2 (113 probes)		
Pathways	p-value	matches
Cell Cycle [R-RNO-1640170]	6.93E-24	28
Cell Cycle, Mitotic [R-RNO-69278]	6.93E-24	27
M Phase [R-RNO-68886]	1.38E-15	17
Mitotic Prometaphase [6.17e-15]	6.17E-15	14
Cell Cycle [rno04110]	2.63E-14	15
<b>IPC</b>		
Cell Cycle [R007]	1.62E-25	34
Programmed Cell Death p53 signaling pathway [R018]	5.88E-06	10
Generic Transcription Pathway [R019]	0.03	8

cluster3 (77 probes)		
Pathways	p-value	matches
Steroid hormone biosynthesis [rno00140]	8.25E-03	5
<b>IPC</b>		
Biological oxidations Chemical carcinogenesis [R006]	3.38E-02	6
Glycerophospholipid metabolism Arachidonic acid metabolism [R010]	3.38E-02	5

M15 (420 probes)

cluster1 (239 probes)		
Pathways	p-value	matches
PPAR signaling pathway [rno03320]	2.20E-21	22
Metabolism of lipids and lipoproteins [R-RNO-556833]	5.05E-16	36
Fatty acid degradation [rno00071]	6.14E-14	14
Biosynthesis of unsaturated fatty acids [rno01040]	7.40E-14	12
Metabolism [R-RNO-1430728]	1.44E-13	53
<b>IPC</b>		
Metabolism of lipids and lipoproteins [R005]	3.78E-33	60
Glycerophospholipid metabolism Arachidonic acid metabolism [R010]	1.77E-09	19
Biological oxidations Chemical carcinogenesis [R006]	3.19E-08	21
Carbon metabolism [R009]	5.43E-03	10

cluster2 (181 probes)		
Pathways	p-value	matches
Steroid hormone biosynthesis [rno00140]	9.06E-05	9
Chemical carcinogenesis [rno05204]	0.0195	7
Metabolic pathways [rno01100]	0.0263	27
Bile secretion [rno04976]	0.0263	6
ABC transporters [rno02010]	0.0277	5
<b>IPC</b>		
Biological oxidations Chemical carcinogenesis [R006]	1.04E-04	15
ABC transporters [R062]	3.61E-03	5
Glycerophospholipid metabolism Arachidonic acid metabolism [R010]	1.08E-02	9
Complement and coagulation cascades [R031]	3.85E-02	5
Amino acid and derivative metabolism [R015]	4.20E-02	13

M8 (325 probes)

cluster1 (202 probes)		
Pathways	p-value	matches
PPAR signaling pathway [rno03320]	5.39E-22	22
Fatty acid degradation [rno00071]	1.62E-17	16
Metabolism of lipids and lipoproteins [R-RNO-556833]	3.03E-15	34
Biosynthesis of unsaturated fatty acids [rno01040]	3.53E-14	12
Metabolic pathways [rno01100]	1.91E-13	49
<b>IPC</b>		
Metabolism of lipids and lipoproteins [R005]	3.00E-36	61
Glycerophospholipid metabolism Arachidonic acid metabolism [R010]	5.29E-09	18
Biological oxidations Chemical carcinogenesis [R006]	2.23E-06	18
Carbon metabolism [R009]	6.67E-04	11
Pantothenate and CoA biosynthesis [R008]	1.89E-02	3

cluster2 (123 probes)		
Pathways	p-value	matches
Steroid hormone biosynthesis [rno00140]	3.65E-04	7
Bile secretion [rno04976]	0.000365	7
Metabolic pathways [rno01100]	0.00193	22
Metabolism [R-RNO-1430728]	4.29E-03	22
Retinol metabolism [rno00830]	4.29E-03	6
<b>IPC</b>		
Biological oxidations Chemical carcinogenesis [R006]	6.99E-06	13
Glycerophospholipid metabolism Arachidonic acid metabolism [R010]	6.99E-06	11
Metabolism of lipids and lipoproteins [R005]	0.00376	14
Transmembrane transport of small molecules [R015]	0.00376	12
Amino acid and derivative metabolism [R015]	0.01	8

M29 (399 probes)

cluster1 (237 probes)		
Pathways	p-value	matches
PPAR signaling pathway [rno03320]	9.83E-21	22
Fatty acid degradation [rno00071]	5.74E-15	15
Metabolism of lipids and lipoproteins [R-RNO-556833]	2.72E-14	35
Biosynthesis of unsaturated fatty acids [rno01040]	1.63E-13	12
Fatty acid metabolism [rno01212]	8.18E-13	14
<b>IPC</b>		
Metabolism of lipids and lipoproteins [R005]	4.21E-30	59
Glycerophospholipid metabolism Arachidonic acid metabolism [R010]	5.57E-09	19
Biological oxidations Chemical carcinogenesis [R006]	1.06E-07	21
Carbon metabolism [R009]	9.07E-03	10

cluster2 (162 probes)		
Pathways	p-value	matches
Steroid hormone biosynthesis [rno00140]	1.68E-06	10
Chemical carcinogenesis [rno05204]	5.03E-05	9
Metabolic pathways [rno01100]	6.84E-05	30
Metabolism [R-RNO-1430728]	1.00E-03	29
Retinol metabolism [rno00830]	0.00207	7
<b>IPC</b>		
Biological oxidations Chemical carcinogenesis [R006]	7.74E-08	18
Glycerophospholipid metabolism Arachidonic acid metabolism [R010]	1.28E-03	10
Complement and coagulation cascades [R031]	3.88E-03	6
Amino acid and derivative metabolism [R015]	2.98E-02	9
Metabolism of lipids and lipoproteins [R005]	3.57E-02	15

Test correction: Benjamini Hochberg  
cutoff for dendrogram: 4

Supplementary Table S2 Enriched pathways in genes whose expression intensities were affected by repeated administration of WY-14643

Probes whose log<sub>2</sub> (fold change) value against the control group was 1.5 or more were filtered, and were divided into clusters by interactive heatmap function on Toxygates (method: ward.D2, distance: pearson, cutoff for dendrogram: 4, test correction for enrichment analysis: Benjamini Hochberg, cutoff for enrichment analysis: p=0.05). Only the top 5 enriched pathways or integrative pathway clusters (IPCs) are listed. The expression profiles of these probes are shown in Supplementary Figure S1.

Supplementary Table S3

Gene list of "WY-downregulated genes"

Genes whose middle-dose expression value was half of or less than that of the corresponding control group at all the time points (4, 8, 15, and 29 days) were used for compound ranking to discover similar compounds to WY-14643 in terms of the downregulation of genes.

100362572	LOC100362572	Mpv17 transgene, kidney disease mutant-like (predicted)-like	Rattus norvegicus
100362769	Mt1f	metallothionein 1F	Rattus norvegicus
100364391	LOC100364391	dehydrogenase/reductase (SDR family) member 7-like	Rattus norvegicus
100911116	LOC100911116	3 beta-hydroxysteroid dehydrogenase type 5-like	Rattus norvegicus
114027	Dao	D-amino-acid oxidase	Rattus norvegicus
116663	Dusp6	dual specificity phosphatase 6	Rattus norvegicus
117522	Xpnpep2	X-prolyl aminopeptidase 2	Rattus norvegicus
155192	Abcg8	ATP binding cassette subfamily G member 8	Rattus norvegicus
171352	Cyp3a9	cytochrome P450, family 3, subfamily a, polypeptide 9	Rattus norvegicus
171380	Cyp2t1	cytochrome P450, family 2, subfamily t, polypeptide 1	Rattus norvegicus
171385	Acmsd	aminocarboxymuconate semialdehyde decarboxylase	Rattus norvegicus
171522	Cyp2d4	cytochrome P450, family 2, subfamily d, polypeptide 4	Rattus norvegicus
192247	Sez6	seizure related 6 homolog	Rattus norvegicus
24237	C6	complement C6	Rattus norvegicus
24297	Cyp1a2	cytochrome P450, family 1, subfamily a, polypeptide 2	Rattus norvegicus
24326	Ednra	endothelin receptor type A	Rattus norvegicus
24470	Hsd3b5	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 5	Rattus norvegicus
24567	Mt1	metallothionein 1	Rattus norvegicus
246142	Bmf	Bcl2 modifying factor	Rattus norvegicus
24626	Pde4b	phosphodiesterase 4B	Rattus norvegicus
24651	Pklr	pyruvate kinase, liver and RBC	Rattus norvegicus
24856	Ttr	transthyretin	Rattus norvegicus
24914	Lox	lysyl oxidase	Rattus norvegicus
25044	Sds	serine dehydratase	Rattus norvegicus
25080	Apoa4	apolipoprotein A4	Rattus norvegicus
25116	Hsd11b1	hydroxysteroid 11-beta dehydrogenase 1	Rattus norvegicus
25256	Fmo1	flavin containing monooxygenase 1	Rattus norvegicus
25559	Abcc8	ATP binding cassette subfamily C member 8	Rattus norvegicus
25560	Abcc9	ATP binding cassette subfamily C member 9	Rattus norvegicus
25698	Ass1	argininosuccinate synthase 1	Rattus norvegicus
286954	Ugt2b1	UDP glucuronosyltransferase 2 family, polypeptide	



B1 Rattus norvegicus  
 289827 Ugp2 UDP-glucose pyrophosphorylase 2 Rattus norvegicus  
 29276 Csrp1 cysteine and glycine-rich protein 1 Rattus  
 norvegicus  
 29277 Cyp2c11 cytochrome P450, subfamily 2, polypeptide 11  
 Rattus norvegicus  
 29301 Hal histidine ammonia lyase Rattus norvegicus  
 293688 Tm7sf2 transmembrane 7 superfamily member 2 Rattus  
 norvegicus  
 294228 RT1-S3 RT1 class Ib, locus S3 Rattus norvegicus  
 29758 St6galnac3 ST6 N-acetylgalactosaminide alpha-2,6-  
 sialyltransferase 3 Rattus norvegicus  
 298079 Aldh1b1 aldehyde dehydrogenase 1 family, member B1 Rattus  
 norvegicus  
 298107 Mup5 major urinary protein 5 Rattus norvegicus  
 299131 Dhrr7 dehydrogenase/reductase (SDR family) member 7  
 Rattus norvegicus  
 300993 Hyal3 hyaluronoglucosaminidase 3 Rattus norvegicus  
 303630 Wipi1 WD repeat domain, phosphoinositide interacting 1  
 Rattus norvegicus  
 303638 Abca8a ATP-binding cassette, subfamily A (ABC1), member 8a  
 Rattus norvegicus  
 313610 Extl1 exostosin-like glycosyltransferase 1 Rattus  
 norvegicus  
 314675 Btbd11 BTB domain containing 11 Rattus norvegicus  
 315084 Gsdmd gasdermin D Rattus norvegicus  
 360406 Ptpfr protein tyrosine phosphatase, receptor type, F  
 Rattus norvegicus  
 360718 Popdc2 popeye domain containing 2 Rattus norvegicus  
 361730 Tkfc triokinase and FMN cyclase Rattus norvegicus  
 362019 RGD1310209 similar to KIAA1324 protein Rattus  
 norvegicus  
 362895 Stac3 SH3 and cysteine rich domain 3 Rattus norvegicus  
 368066 Inmt indolethylamine N-methyltransferase Rattus  
 norvegicus  
 497811 Xdh xanthine dehydrogenase Rattus norvegicus  
 498545 Tsc22d1 TSC22 domain family, member 1 Rattus norvegicus  
 59114 Slc9a3r1 SLC9A3 regulator 1 Rattus norvegicus  
 63840 Per2 period circadian clock 2 Rattus norvegicus  
 64570 Nat8 N-acetyltransferase 8 Rattus norvegicus  
 680875 LOC680875 similar to dystonin isoform 1 Rattus  
 norvegicus  
 684841 LOC684841 similar to CG31613-PA Rattus norvegicus  
 83500 Slc22a8 solute carrier family 22 member 8 Rattus norvegicus  
 84386 Slpi secretory leukocyte peptidase inhibitor Rattus  
 norvegicus  
 85431 Nox4 NADPH oxidase 4 Rattus norvegicus  
 89787 Lrp3 LDL receptor related protein 3 Rattus norvegicus

Supplementary Table 4

M4 vs M8 (t-test, p-value&lt;0.01)

cluster1 (268 probes)		
Pathways	p-value	matches
Beta-catenin independent WNT signaling [R-RNO-3858494]	0.000955	9
PCP/CE pathway [R-RNO-4086400]	0.000955	8
Proteasome [mo03050]	0.00128	7
Cross-presentation of soluble exogenous antigens (endosomes) [R-RNO-1236978]	0.00261	6
Regulation of ornithine decarboxylase (ODC) [R-RNO-350562]	0.00261	6
AUF1 (hnRNP D0) binds and destabilizes mRNA [R-RNO-450408]	0.00261	6
Degradation of GLI1 by the proteasome [R-RNO-5610780]	0.00261	6
GLI3 is processed to GLI3R by the proteasome [R-RNO-5610785]	0.00261	6
Ribosome [rno03010]	0.00261	11
<b>IPC</b>	<b>p-value</b>	<b>matches</b>
Ribosome [R021]	0.00173	15
Organelle biogenesis and maintenance [R046]	0.0114	11
Amino acid and derivative metabolism [R008]	0.0264	12

cluster2 (188 probes)		
Pathways	p-value	matches
-	-	-
<b>IPC</b>	<b>p-value</b>	<b>matches</b>
Protein processing in endoplasmic reticulum [R028]	0.00193	9
Complement and coagulation cascades [R031]	0.00419	6

cluster3 (162 probes)		
Pathways	p-value	matches
Cam-PDE1 activation [R-RNO-111957]	0.000483	3
Ca <sup>2+</sup> pathway [R-RNO-4086398]	0.000483	5
Activation of CaMK IV [R-RNO-442745]	0.000483	3
Activation of Kainate Receptors upon glutamate binding [R-RNO-451326]	0.000483	4
Glycogen breakdown (glycogenolysis) [R-RNO-70221]	0.000483	4
<b>IPC</b>	<b>p-value</b>	<b>matches</b>
Carbohydrate metabolism [R029]	0.000372	10

Supplementary Table 4

Enriched pathways in genes whose expression intensities were significantly different between M4 and M8

Probes whose log<sub>2</sub> (fold change) value in M4 against that in M8 was significantly different by student's t-test (cutoff p-value: 0.01) were filtered, and were divided into clusters by interactive heatmap function on Toxygates (method: ward.D2, distance: pearson, cutoff for dendrogram: 6, test correction for enrichment analysis: Benjamini Hochberg, cutoff for enrichment analysis: p=0.05). Only the top 5 enriched pathways or integrative pathway clusters (IPCs) are listed. The expression profiles of these probes are shown in Figure 2.

Supplementary Table 5

Gene list of "M4vs8\_cluster1"

This cluster was obtained by hierarchical clustering (dendrogram cutoff: 6) of DEGs between WY-14643/M dose/4day and WY-14643/M dose/8day by student's t-test (cutoff: p-value=0.01).

The cluster that contained 268 probes was defined as "M4vs8\_cluster1".

100125373	Pnrc2	proline-rich nuclear receptor coactivator 2	Rattus norvegicus
100359945	Rslcan18	regulator of sex-limitation candidate 18	Rattus norvegicus
100360117	LOC100360117	ribosomal protein L8-like	Rattus norvegicus
100360522	LOC100360522	ribosomal protein P1-like	Rattus norvegicus
100360682	Snrpe	small nuclear ribonucleoprotein polypeptide E	Rattus norvegicus
100360846	LOC100360846	proteasome subunit beta type 6-like	Rattus norvegicus
100361269	Snrpa1	small nuclear ribonucleoprotein polypeptide A'	Rattus norvegicus
100362333	LOC100362333	DNA-directed DNA polymerase epsilon 3	Rattus norvegicus
100362980	LOC100362980	CG3918-like	Rattus norvegicus
100363012	Rps21-ps1	ribosomal protein S21, pseudogene 1	Rattus norvegicus
100363642	LOC100363642	coiled-coil domain-containing protein 41-like	Rattus norvegicus
100365711	LOC100365711	cytochrome c oxidase, subunit VIc-like	Rattus norvegicus
100910056	LOC100910056	UHRF1-binding protein 1-like	Rattus norvegicus
100910130	LOC100910130	protein FAM50A-like	Rattus norvegicus
100910370	LOC100910370	60S ribosomal protein L8-like	Rattus norvegicus
100911372	LOC100911372	40S ribosomal protein S6-like	Rattus norvegicus
100911847	LOC100911847	40S ribosomal protein S14-like	Rattus norvegicus
100912469	LOC100912469	acyl-CoA desaturase 2-like	Rattus norvegicus
100912578	LOC100912578	stress-70 protein, mitochondrial-like	Rattus norvegicus
114508	Fbp2	fructose-bisphosphatase 2	Rattus norvegicus
114517	Itga6	integrin subunit alpha 6	Rattus norvegicus
114764	Mapre1	microtubule-associated protein, RP/EB family, member 1	Rattus norvegicus
116561	Cltb	clathrin, light chain B	Rattus norvegicus
116656	Cdc123	cell division cycle 123	Rattus norvegicus

117557 Tpm3 tropomyosin 3 Rattus norvegicus  
140661 Rplp1 ribosomal protein, large, P1 Rattus norvegicus  
140922 Txnl1 thioredoxin-like 1 Rattus norvegicus  
140932 Bnip1 BCL2/adenovirus E1B interacting protein 1 Rattus  
norvegicus  
140937 Higd1a HIG1 hypoxia inducible domain family, member 1A  
Rattus norvegicus  
170900 Rbm14 RNA binding motif protein 14 Rattus norvegicus  
171085 Pcsk4 proprotein convertase subtilisin/kexin type 4  
Rattus norvegicus  
171142 Ehhadh enoyl-CoA hydratase and 3-hydroxyacyl CoA  
dehydrogenase Rattus norvegicus  
171178 Adh7 alcohol dehydrogenase 7 (class IV), mu or sigma  
polypeptide Rattus norvegicus  
171497 Sgk2 serum/glucocorticoid regulated kinase 2 Rattus  
norvegicus  
192362 Lamc2 laminin subunit gamma 2 Rattus norvegicus  
24157 Acaa1a acetyl-CoA acyltransferase 1 Rattus norvegicus  
24188 Aldh1a1 aldehyde dehydrogenase 1 family, member A1Rattus  
norvegicus  
24400 Gnb1 G protein subunit beta 1 Rattus norvegicus  
246282 Zfp91 zinc finger protein 91 Rattus norvegicus  
24644 Pgk1 phosphoglycerate kinase 1Rattus norvegicus  
24673 Ppp2cb protein phosphatase 2 catalytic subunit beta  
Rattus norvegicus  
24818 Tcp1 t-complex 1 Rattus norvegicus  
25098 Foxa1 forkhead box A1 Rattus norvegicus  
25151 Igf2r insulin-like growth factor 2 receptor Rattus  
norvegicus  
252855 Sfpq splicing factor proline and glutamine richRattus  
norvegicus  
252899 Miox myo-inositol oxygenase Rattus norvegicus  
25344 Phb prohibitin Rattus norvegicus  
25402 Casp3 caspase 3 Rattus norvegicus  
25403 Cast calpastatin Rattus norvegicus  
25405 Ccng1 cyclin G1 Rattus norvegicus  
25458 Gss glutathione synthetase Rattus norvegicus  
25579 Map3k12 mitogen activated protein kinase kinase kinase 12  
Rattus norvegicus  
25604 Pcmt1 protein-L-isoaspartate (D-aspartate) O-  
methyltransferase 1 Rattus norvegicus  
25612 Asns asparagine synthetase (glutamine-hydrolyzing)  
Rattus norvegicus  
260321 Fkbp4 FK506 binding protein 4 Rattus norvegicus  
266631 Rbm45 RNA binding motif protein 45 Rattus norvegicus  
26962 Rpl8 ribosomal protein L8 Rattus norvegicus  
282584 Mtmr9 myotubularin related protein 9 Rattus norvegicus  
286894 Parm1 prostate androgen-regulated mucin-like protein 1  
Rattus norvegicus  
287061 Rogdi rogdi homolog Rattus norvegicus  
287120 Tbl3 transducin (beta)-like 3 Rattus norvegicus  
287155 Stub1 STIP1 homology and U-box containing protein 1  
Rattus norvegicus  
287367 Cops3 COP9 signalosome subunit 3 Rattus norvegicus

287420 Pfas phosphoribosylformylglycinamide synthase Rattus  
norvegicus  
287444 Eif5a eukaryotic translation initiation factor 5A  
Rattus norvegicus  
287927 Ube2v2 ubiquitin conjugating enzyme E2 V2 Rattus  
norvegicus  
288065 Ccdc58 coiled-coil domain containing 58 Rattus norvegicus  
288471 Trrap transformation/transcription domain-associated  
protein Rattus norvegicus  
288599 Eif4h eukaryotic translation initiation factor 4H  
Rattus norvegicus  
289125 Acbd6 acyl-CoA binding domain containing 6 Rattus  
norvegicus  
289150 Cenpl centromere protein L Rattus norvegicus  
289990 Psmc6 proteasome 26S subunit, ATPase 6 Rattus norvegicus  
290027 Parp2 poly (ADP-ribose) polymerase 2 Rattus norvegicus  
290291 Cab39l calcium binding protein 39-like Rattus norvegicus  
290303 Spryd7 SPRY domain containing 7 Rattus norvegicus  
290401 Esd esterase D Rattus norvegicus  
290529 Fam213a family with sequence similarity 213, member A  
Rattus norvegicus  
291005 Gadd45g growth arrest and DNA-damage-inducible, gamma  
Rattus norvegicus  
291034 Mcur1 mitochondrial calcium uniporter regulator 1  
Rattus norvegicus  
291671 Hspa9 heat shock protein family A member 9 Rattus  
norvegicus  
292087 Urb2 URB2 ribosome biogenesis 2 homolog (S. cerevisiae)  
Rattus norvegicus  
292156 Sh3glb1 SH3 domain -containing GRB2-like endophilin B1  
Rattus norvegicus  
292306 Rnaset2 ribonuclease T2 Rattus norvegicus  
292485 Fuca2 fucosidase, alpha-L- 2, plasma Rattus norvegicus  
29261 Tyms thymidylate synthetase Rattus norvegicus  
292777 TbcB tubulin folding cofactor B Rattus norvegicus  
29284 Rps14 ribosomal protein S14 Rattus norvegicus  
292887 Akt1s1 AKT1 substrate 1 Rattus norvegicus  
29304 Rps6 ribosomal protein S6 Rattus norvegicus  
293113 Tmem126a transmembrane protein 126A Rattus norvegicus  
293149 Mrpl48 mitochondrial ribosomal protein L48 Rattus  
norvegicus  
29317 Csrp2 cysteine and glycine-rich protein 2 Rattus  
norvegicus  
293481 Tufm Tu translation elongation factor, mitochondrial  
Rattus norvegicus  
293613 RGD1309350 similar to transthyretin (4L369) Rattus  
norvegicus  
29384 H2afy H2A histone family, member Y Rattus norvegicus  
293862 Fam50a family with sequence similarity 50, member A  
Rattus norvegicus  
293888 Plgrkt plasminogen receptor with a C-terminal lysine  
Rattus norvegicus  
294009 Cuedc2 CUE domain containing 2 Rattus norvegicus  
294339 Mcm3ap minichromosome maintenance complex component 3

associated protein                      Rattus norvegicus  
 295088    Gmps        guanine monophosphate synthase        Rattus norvegicus  
 295171    Sh3d19    SH3 domain containing 19        Rattus norvegicus  
 295500    Metap1    methionyl aminopeptidase 1            Rattus norvegicus  
 295692    Nup35    nucleoporin 35        Rattus norvegicus  
 296570    Edf1        endothelial differentiation-related factor 1  
 Rattus norvegicus  
 296658    Ndufa8    NADH:ubiquinone oxidoreductase subunit A8 Rattus  
 norvegicus  
 29666    Psmb6    proteasome subunit beta 6 Rattus norvegicus  
 29674    Psma7    proteasome subunit alpha 7            Rattus norvegicus  
 296911    ST7        suppression of tumorigenicity 7        Rattus norvegicus  
 296913    Lsm8        LSM8 homolog, U6 small nuclear RNA associated  
 Rattus norvegicus  
 29728    Mcm4        minichromosome maintenance complex component 4  
 Rattus norvegicus  
 297372    Mrpl19    mitochondrial ribosomal protein L19            Rattus  
 norvegicus  
 297393    Nagk        N-acetylglucosamine kinase            Rattus norvegicus  
 297627    Rhno1    RAD9-HUS1-RAD1 interacting nuclear orphan 1  
 Rattus norvegicus  
 297694    Plbd1    phospholipase B domain containing 1            Rattus  
 norvegicus  
 297727    Mrps35    mitochondrial ribosomal protein S35            Rattus  
 norvegicus  
 298098    Pole3    polymerase (DNA directed), epsilon 3, accessory  
 subunit Rattus norvegicus  
 298441    Nasp        nuclear autoantigenic sperm protein            Rattus  
 norvegicus  
 298648    Tardbp    TAR DNA binding protein        Rattus norvegicus  
 298914    Itgb1bp1 integrin subunit beta 1 binding protein 1 Rattus  
 norvegicus  
 298917    Iah1        isoamyl acetate-hydrolyzing esterase 1 homolog  
 Rattus norvegicus  
 299041    RGD1565054        similar to 60S acidic ribosomal protein P1  
 Rattus norvegicus  
 300120    Fam118a    family with sequence similarity 118, member A  
 Rattus norvegicus  
 300447    Ecsit        ECSIT signalling integrator            Rattus norvegicus  
 300652    Sorl1    sortilin related receptor 1            Rattus norvegicus  
 300891    Morf4l1    mortality factor 4 like 1 Rattus norvegicus  
 301337    Plekhh2    pleckstrin homology domain containing B2        Rattus  
 norvegicus  
 301381    Tex30    testis expressed 30            Rattus norvegicus  
 301529    Dnpep    aspartyl aminopeptidase        Rattus norvegicus  
 301622    Dtymk    deoxythymidylate kinase        Rattus norvegicus  
 302864    Mmgt1    membrane magnesium transporter 1        Rattus norvegicus  
 304881    Tor1aip2 torsin 1A interacting protein 2        Rattus norvegicus  
 304919    Dars2    aspartyl-tRNA synthetase 2 (mitochondrial) Rattus  
 norvegicus  
 305910    Pspc1    paraspeckle component 1        Rattus norvegicus  
 306182    Ipo5        importin 5            Rattus norvegicus  
 306542    Brf2        BRF2, RNA polymerase III transcription initiation  
 factor 50 subunit            Rattus norvegicus

306628 Col4a2 collagen type IV alpha 2 chain Rattus norvegicus  
306994 Yae1d1 Yae1 domain containing 1 Rattus norvegicus  
307091 Akr1e2 aldo-keto reductase family 1, member E2 Rattus  
norvegicus  
307947 Set SET nuclear proto-oncogene Rattus norvegicus  
308113 Cnksr3 Cnksr family member 3 Rattus norvegicus  
308607 E2f8 E2F transcription factor 8 Rattus norvegicus  
308652 Smox spermine oxidase Rattus norvegicus  
308820 Ccdc90b coiled-coil domain containing 90B Rattus norvegicus  
308871 Rnf121 ring finger protein 121 Rattus norvegicus  
309098 Tubgcp2 tubulin, gamma complex associated protein 2  
Rattus norvegicus  
309176 Mrpl49 mitochondrial ribosomal protein L49 Rattus  
norvegicus  
309570 Slc18b1 solute carrier family 18 member B1 Rattus  
norvegicus  
310811 Palmd palmdelphin Rattus norvegicus  
311078 Psm14 proteasome 26S subunit, non-ATPase 14 Rattus  
norvegicus  
311130 Prkra protein activator of interferon induced protein  
kinase EIF2AK2 Rattus norvegicus  
311191 Ckap5 cytoskeleton associated protein 5 Rattus norvegicus  
311821 Agpat2 1-acylglycerol-3-phosphate 0-acyltransferase 2  
Rattus norvegicus  
311855 RGD1305178 similar to Hypothetical protein MGC11690  
Rattus norvegicus  
311903 Mrrf mitochondrial ribosome recycling factor Rattus  
norvegicus  
312299 Ezh2 enhancer of zeste 2 polycomb repressive complex 2  
subunit Rattus norvegicus  
312824 Recql RecQ like helicase Rattus norvegicus  
313108 Mms22l MMS22-like, DNA repair protein Rattus norvegicus  
313647 Hp1bp3 heterochromatin protein 1, binding protein 3  
Rattus norvegicus  
313929 Ncoa1 nuclear receptor coactivator 1 Rattus norvegicus  
314652 RGD1564744 similar to 60S acidic ribosomal protein P1  
Rattus norvegicus  
315150 Adsl adenylosuccinate lyase Rattus norvegicus  
315649 Sik2 salt-inducible kinase 2 Rattus norvegicus  
316348 Pdcl3 phosducin-like 3 Rattus norvegicus  
316611 Agap1 ArfGAP with GTPase domain, ankyrin repeat and PH  
domain 1 Rattus norvegicus  
317259 Nono non-POU domain containing, octamer-binding Rattus  
norvegicus  
317464 Msl3 male-specific lethal 3 homolog (Drosophila)  
Rattus norvegicus  
360664 Ten1 TEN1 CST complex subunit Rattus norvegicus  
360915 Cops4 COP9 signalosome subunit 4 Rattus norvegicus  
360950 Wdr1 WD repeat domain 1 Rattus norvegicus  
361005 Chchd1 coiled-coil-helix-coiled-coil-helix domain  
containing 1 Rattus norvegicus  
361191 Nsun2 NOP2/Sun RNA methyltransferase family, member 2  
Rattus norvegicus  
361301 Tpgs2 tubulin polyglutamylase complex subunit 2 Rattus

norvegicus  
 361452 Ltv1 LTV1 ribosome biogenesis factor Rattus norvegicus  
 361510 Sult2a2 sulfotransferase family 2A, dehydroepiandrosterone  
 (DHEA)-preferring, member 2 Rattus norvegicus  
 361624 Akip1 A-kinase interacting protein 1 Rattus norvegicus  
 361666 Bccip BRCA2 and CDKN1A interacting protein Rattus  
 norvegicus  
 361821 Col6a2 collagen type VI alpha 2 chain Rattus norvegicus  
 361888 Srek1ip1 SREK1-interacting protein 1 Rattus norvegicus  
 361956 Rsrc1 arginine and serine rich coiled-coil 1 Rattus  
 norvegicus  
 362129 Gtdc1 glycosyltransferase-like domain containing 1  
 Rattus norvegicus  
 362152 Hnrnpa3 heterogeneous nuclear ribonucleoprotein A3 Rattus  
 norvegicus  
 362156 Zdhhc5 zinc finger, DHHC-type containing 5 Rattus  
 norvegicus  
 362228 Naa20 N(alpha)-acetyltransferase 20, NatB catalytic  
 subunit Rattus norvegicus  
 362419 Tamm41 TAM41 mitochondrial translocator assembly and  
 maintenance homolog Rattus norvegicus  
 362557 Ndc1 NDC1 transmembrane nucleoporin Rattus norvegicus  
 362626 Rsrp1 arginine and serine rich protein 1 Rattus  
 norvegicus  
 362905 Emc2 ER membrane protein complex subunit 2 Rattus  
 norvegicus  
 362943 Adck5 aarF domain containing kinase 5 Rattus norvegicus  
 362972 Pnpla3 patatin-like phospholipase domain containing 3  
 Rattus norvegicus  
 363009 Uhrf1bp1l UHRF1 binding protein 1-like Rattus  
 norvegicus  
 363061 Sdhd succinate dehydrogenase complex subunit D Rattus  
 norvegicus  
 363068 Commd4 COMM domain containing 4 Rattus norvegicus  
 363334 Stap2 signal transducing adaptor family member 2 Rattus  
 norvegicus  
 364227 Asb3 ankyrin repeat and SOCS box-containing 3 Rattus  
 norvegicus  
 366474 Col16a1 collagen type XVI alpha 1 chain Rattus norvegicus  
 366595 Sypl1 synaptophysin-like 1 Rattus norvegicus  
 366872 Cep83 centrosomal protein 83 Rattus norvegicus  
 406195 Tcf19 transcription factor 19 Rattus norvegicus  
 494445 Srsf2 serine and arginine rich splicing factor 2 Rattus  
 norvegicus  
 499374 RGD1561333 similar to 60S ribosomal protein L8  
 Rattus norvegicus  
 500006 Pex1 peroxisomal biogenesis factor 1 Rattus norvegicus  
 500028 LOC500028 hypothetical protein LOC500028 Rattus  
 norvegicus  
 500616 Socs5 suppressor of cytokine signaling 5 Rattus  
 norvegicus  
 501072 Acaa1b acetyl-Coenzyme A acyltransferase 1B Rattus  
 norvegicus  
 501620 RGD1564480 similar to polyamine oxidase isoform 2



Rattus norvegicus

50556 Exoc6 exocyst complex component 6 Rattus norvegicus

50559 Acot1 acyl-CoA thioesterase 1 Rattus norvegicus

54322 Cox6c cytochrome c oxidase subunit 6C Rattus norvegicus

56785 Ralgapa1 Ral GTPase activating protein catalytic alpha subunit 1 Rattus norvegicus

58823 Nckap1 NCK-associated protein 1 Rattus norvegicus

58940 H2afz H2A histone family, member Z Rattus norvegicus

59317 Epb41l1 erythrocyte membrane protein band 4.1-like 1 Rattus norvegicus

619440 Aarsd1 alanyl-tRNA synthetase domain containing 1 Rattus norvegicus

64044 Casp8 caspase 8 Rattus norvegicus

64372 Timm8b translocase of inner mitochondrial membrane 8 homolog B Rattus norvegicus

64526 Ech1 enoyl-CoA hydratase 1 Rattus norvegicus

64539 Ndufv3 NADH:ubiquinone oxidoreductase subunit V3 Rattus norvegicus

64667 Sgta small glutamine rich tetratricopeptide repeat containing alpha Rattus norvegicus

65169 Scamp3 secretory carrier membrane protein 3 Rattus norvegicus

654495 Zdhhc16 zinc finger, DHHC-type containing 16 Rattus norvegicus

680039 LOC680039 hypothetical protein LOC680039 Rattus norvegicus

680747 Mrpl20 mitochondrial ribosomal protein L20 Rattus norvegicus

680835 LOC680835 similar to cullin 7 Rattus norvegicus

681062 Slbp stem-loop binding protein Rattus norvegicus

683687 Snx9 sorting nexin 9 Rattus norvegicus

684270 LOC684270 similar to isochorismatase domain containing 2 Rattus norvegicus

684830 Ttc32 tetratricopeptide repeat domain 32 Rattus norvegicus

685059 Msrb1 methionine sulfoxide reductase B1 Rattus norvegicus

686032 Smlr1 small leucine-rich protein 1 Rattus norvegicus

687118 Dedd2 death effector domain containing 2 Rattus norvegicus

687575 U2af1 U2 small nuclear RNA auxiliary factor 1 Rattus norvegicus

688815 LOC688815 similar to prohibitin Rattus norvegicus

689176 Tmem64 transmembrane protein 64 Rattus norvegicus

690085 Bcl7a BCL tumor suppressor 7A Rattus norvegicus

690349 Lbhd1 LBH domain containing 1 Rattus norvegicus

690441 Atp5j2 ATP synthase, H<sup>+</sup> transporting, mitochondrial Fo complex, subunit F2 Rattus norvegicus

691501 Snapc5 small nuclear RNA activating complex, polypeptide 5 Rattus norvegicus

79227 Thoc6 THO complex 6 Rattus norvegicus

79242 Hpgd hydroxyprostaglandin dehydrogenase 15 (NAD) Rattus norvegicus

79243 Hsd17b2 hydroxysteroid (17-beta) dehydrogenase 2 Rattus norvegicus

81530	Pdk2	pyruvate dehydrogenase kinase 2	Rattus norvegicus
81684	Mipep	mitochondrial intermediate peptidase	Rattus norvegicus
81775	Rps21	ribosomal protein S21	Rattus norvegicus
81827	Psmc5	proteasome 26S subunit, ATPase 5	Rattus norvegicus
83422	Pias2	protein inhibitor of activated STAT, 2	Rattus norvegicus
83614	Pias3	protein inhibitor of activated STAT, 3	Rattus norvegicus
83792	Scd2	stearoyl-Coenzyme A desaturase 2	Rattus norvegicus
83800	Clta	clathrin, light chain A	Rattus norvegicus
84389	Ccnh	cyclin H	Rattus norvegicus
84575	Fads1	fatty acid desaturase 1	Rattus norvegicus
84581	Hdac6	histone deacetylase 6	Rattus norvegicus
85492	Psmb7	proteasome subunit beta 7	Rattus norvegicus

Supplementary Table 6

Gene list of "M4vs8\_cluster2"

This cluster was obtained by hierarchical clustering (dendrogram cutoff: 6) of DEGs between

WY-14643/M dose/4day and WY-14643/M dose/8day by student's t-test (cutoff: p-value=0.01).

The cluster that contained 188 probes was defined as "M4vs8\_cluster2".

100360218	LOC100360218	interleukin 13 receptor, alpha 1-like	Rattus norvegicus
100362495	Haus5	HAUS augmin-like complex, subunit 5	Rattus norvegicus
100363266	Igip	IgA-inducing protein	Rattus norvegicus
100363500	LOC100363500	hypothetical LOC100363500	Rattus norvegicus
100911986	LOC100911986	zinc finger protein GLI4-like	Rattus norvegicus
100912615	LOC100912615	transmembrane protein 19-like	Rattus norvegicus
113961	Gorasp2	golgi reassembly stacking protein 2	Rattus norvegicus
114002	Ndst2	N-deacetylase and N-sulfotransferase 2	Rattus norvegicus
116782	Pcdhgc3	protocadherin gamma subfamily C, 3	Rattus norvegicus
117517	C7	complement C7	Rattus norvegicus
117556	Sv2b	synaptic vesicle glycoprotein 2b	Rattus norvegicus
154985	Cyp26a1	cytochrome P450, family 26, subfamily a, polypeptide 1	Rattus norvegicus
170699	Atp2c1	ATPase secretory pathway Ca <sup>2+</sup> transporting 1	Rattus norvegicus
171070	Ptpn21	protein tyrosine phosphatase, non-receptor type 21	Rattus norvegicus
171563	Nav2	neuron navigator 2	Rattus norvegicus
192242	Akr1d1	aldo-keto reductase family 1, member D1	Rattus norvegicus
192262	C1s	complement C1s	Rattus norvegicus
24184	Ak2	adenylate kinase 2	Rattus norvegicus
24236	C4bbp	complement component 4 binding protein, beta	Rattus norvegicus
24312	Dhfr	dihydrofolate reductase	Rattus norvegicus
24413	Nr3c1	nuclear receptor subfamily 3, group C, member 1	Rattus norvegicus
24421	Gsta1	glutathione S-transferase alpha 1	Rattus norvegicus
246284	Atrx	ATRX, chromatin remodeler	Rattus norvegicus
24718	Reln	reelin	Rattus norvegicus
24852	Tpm4	tropomyosin 4	Rattus norvegicus
24904	Slc22a1	solute carrier family 22 member 1	Rattus norvegicus
24908	Dnajb9	DnaJ heat shock protein family (Hsp40) member B9	Rattus norvegicus
25043	Eln	elastin	Rattus norvegicus

25087	Kng2	kininogen 2	Rattus norvegicus	
25114	Fgfr4	fibroblast growth factor receptor 4	Rattus norvegicus	
252895	Pcdhga9	protocadherin gamma subfamily A, 9	Rattus norvegicus	
252897	Pcdhga11	protocadherin gamma subfamily A, 11	Rattus norvegicus	
252963	Il13ra1	interleukin 13 receptor subunit alpha 1	Rattus norvegicus	
25308	Cstb	cystatin B	Rattus norvegicus	
25374	Alad	aminolevulinate dehydratase	Rattus norvegicus	
25423	Ctsc	cathepsin C	Rattus norvegicus	
25506	P4hb	prolyl 4-hydroxylase subunit beta	Rattus norvegicus	
25587	Id2	inhibitor of DNA binding 2, HLH protein	Rattus norvegicus	
25596	Rpn1	ribophorin I	Rattus norvegicus	
25603	Marcks	myristoylated alanine rich protein kinase C substrate	Rattus norvegicus	
25617	Hspa5	heat shock protein family A member 5	Rattus norvegicus	
25636	Prkaca	protein kinase cAMP-activated catalytic subunit alpha	Rattus norvegicus	
25642	Cyp3a23/3a1	cytochrome P450, family 3, subfamily a, polypeptide 23/polypeptide 1	Rattus norvegicus	
266689	Cyp4f6	cytochrome P450, family 4, subfamily f, polypeptide 6	Rattus norvegicus	
287441	Zbtb4	zinc finger and BTB domain containing 4	Rattus norvegicus	
287479	Shpk	sedoheptulokinase	Rattus norvegicus	
287607	Mtmr4	myotubularin related protein 4	Rattus norvegicus	
287731	Lsm12	LSM12 homolog	Rattus norvegicus	
288124	Nectin3	nectin cell adhesion molecule 3	Rattus norvegicus	
288692	Wsb2	WD repeat and SOCS box-containing 2	Rattus norvegicus	
288783	Ormdl2	ORMDL sphingolipid biosynthesis regulator 2	Rattus norvegicus	
289372	Smyd2	SET and MYND domain containing 2	Rattus norvegicus	
290363	Rcctb2	RCC1 and BTB domain containing protein 2	Rattus norvegicus	
290642	Ccdc124	coiled-coil domain containing 124	Rattus norvegicus	
291403	Zadh2	zinc binding alcohol dehydrogenase, domain containing 2	Rattus norvegicus	
291440	Cxxc1	CXXC finger protein 1	Rattus norvegicus	
291635	Pcdhga7	protocadherin gamma subfamily A, 7	Rattus norvegicus	
291637	Pcdhga5	protocadherin gamma subfamily A, 5	Rattus norvegicus	
293067	Zfand6	zinc finger AN1-type containing 6	Rattus norvegicus	
29339	Apcs	amyloid P component, serum	Rattus norvegicus	
293774	Dtx4	deltex E3 ubiquitin ligase 4	Rattus norvegicus	
29439	Jtb	jumping translocation breakpoint	Rattus norvegicus	
294410	Man1a1	mannosidase, alpha, class 1A, member 1	Rattus norvegicus	
29468	Pdia3	protein disulfide isomerase family A, member 3		

Rattus norvegicus  
295231 Glmp glycosylated lysosomal membrane protein Rattus norvegicus  
295674 Plekha3 pleckstrin homology domain containing A3 Rattus norvegicus  
296554 Tubb4b tubulin, beta 4B class IVb Rattus norvegicus  
298104 Tmem268 transmembrane protein 268 Rattus norvegicus  
298370 Txndc12 thioredoxin domain containing 12 Rattus norvegicus  
298757 Atl2 atlastin GTPase 2 Rattus norvegicus  
298861 Ptrhd1 peptidyl-tRNA hydrolase domain containing 1 Rattus norvegicus  
299732 Lta4h leukotriene A4 hydrolase Rattus norvegicus  
299800 Tmem19 transmembrane protein 19 Rattus norvegicus  
300115 Arhgap8 Rho GTPase activating protein 8 Rattus norvegicus  
300674 Arcn1 archain 1 Rattus norvegicus  
300955 Nck1 NCK adaptor protein 1 Rattus norvegicus  
300981 Acyl1 aminoacylase 1 Rattus norvegicus  
301579 Armc9 armadillo repeat containing 9 Rattus norvegicus  
301861 LOC301861 similar to ARP2 actin-related protein 2 homolog (yeast) Rattus norvegicus  
302898 Rsl1d1 ribosomal L1 domain containing 1 Rattus norvegicus  
303563 Nags N-acetylglutamate synthase Rattus norvegicus  
304577 Ung uracil-DNA glycosylase Rattus norvegicus  
304929 F5 coagulation factor V Rattus norvegicus  
305156 Arhgap24 Rho GTPase activating protein 24 Rattus norvegicus  
306630 Abhd13 abhydrolase domain containing 13 Rattus norvegicus  
306647 Champ1 chromosome alignment maintaining phosphoprotein 1 Rattus norvegicus  
308265 Lats1 large tumor suppressor kinase 1 Rattus norvegicus  
310773 Cept1 choline/ethanolamine phosphotransferase 1 Rattus norvegicus  
311021 Nmi N-myc (and STAT) interactor Rattus norvegicus  
311332 Dll4 delta like canonical Notch ligand 4 Rattus norvegicus  
311483 Rrbp1 ribosome binding protein 1 Rattus norvegicus  
311637 Slc35c2 solute carrier family 35 member C2 Rattus norvegicus  
312670 Adipor2 adiponectin receptor 2 Rattus norvegicus  
312828 Etnk1 ethanolamine kinase 1 Rattus norvegicus  
313961 Smc6 structural maintenance of chromosomes 6 Rattus norvegicus  
314157 Fbxo33 F-box protein 33 Rattus norvegicus  
315047 Laptm4b lysosomal protein transmembrane 4 beta Rattus norvegicus  
315500 Eepd1 endonuclease/exonuclease/phosphatase family domain containing 1 Rattus norvegicus  
315989 Manf mesencephalic astrocyte-derived neurotrophic factor Rattus norvegicus  
316916 Clptm1l CLPTM1-like Rattus norvegicus  
317599 Atp11c ATPase phospholipid transporting 11C Rattus norvegicus  
361043 Tm9sf1 transmembrane 9 superfamily member 1 Rattus norvegicus  
361050 Rcctb1 RCC1 and BTB domain containing protein 1 Rattus norvegicus

norvegicus

361213 Sptlc1 serine palmitoyltransferase, long chain base  
subunit 1 Rattus norvegicus

361261 Ccny cyclin Y Rattus norvegicus

361289 Colec12 collectin sub-family member 12 Rattus norvegicus

361749 Il33 interleukin 33 Rattus norvegicus

361991 S100a16 S100 calcium binding protein A16 Rattus norvegicus

362359 Mpp6 membrane palmitoylated protein 6 Rattus norvegicus

362472 Cspp1 centrosome and spindle pole associated protein 1  
Rattus norvegicus

362861 Slc41a2 solute carrier family 41 member 2 Rattus norvegicus

362862 Hsp90b1 heat shock protein 90 beta family member 1 Rattus  
norvegicus

363159 Gpd1l glycerol-3-phosphate dehydrogenase 1-like Rattus  
norvegicus

363425 Cav2 caveolin 2 Rattus norvegicus

363989 Phlda3 pleckstrin homology-like domain, family A, member 3  
Rattus norvegicus

364843 Pcdhga8 protocadherin gamma subfamily A, 8 Rattus  
norvegicus

364844 Pcdhgb7 protocadherin gamma subfamily B, 7 Rattus  
norvegicus

364845 Pcdhgb8 protocadherin gamma subfamily B, 8 Rattus  
norvegicus

365466 Cpn1 carboxypeptidase N subunit 1 Rattus norvegicus

366169 Rtf1 Rtf1, Paf1/RNA polymerase II complex component,  
homolog (S. cerevisiae) Rattus norvegicus

366381 Cdc26 cell division cycle 26 Rattus norvegicus

474143 Clec4a C-type lectin domain family 4, member A Rattus  
norvegicus

498241 RGD1564614 similar to complement factor H-related  
protein Rattus norvegicus

498846 Pcdhga2 protocadherin gamma subfamily A, 2 Rattus  
norvegicus

498847 Pcdhga3 protocadherin gamma subfamily A, 3 Rattus  
norvegicus

498849 Pcdhga10 protocadherin gamma subfamily A, 10 Rattus  
norvegicus

498850 Pcdhga12 protocadherin gamma subfamily A, 12 Rattus  
norvegicus

500039 RGD1562178 similar to Adenylate kinase 2 Rattus  
norvegicus

500893 Gli4 GLI family zinc finger 4 Rattus norvegicus

501083 Pdcd6ip programmed cell death 6 interacting protein  
Rattus norvegicus

501569 Tmem47 transmembrane protein 47 Rattus norvegicus

553129 Pcdhga1 protocadherin gamma subfamily A, 1 Rattus  
norvegicus

56759 Rnase4 ribonuclease A family member 4 Rattus norvegicus

56766 Leprot leptin receptor overlapping transcript Rattus  
norvegicus

58838 Sh2b3 SH2B adaptor protein 3 Rattus norvegicus

60423 Slc28a2 solute carrier family 28 member 2 Rattus norvegicus

64014 Dusp12 dual specificity phosphatase 12 Rattus norvegicus

64185	Cap1	adenylate cyclase associated protein 1	Rattus norvegicus
64202	Calr	calreticulin	Rattus norvegicus
64367	Ppib	peptidylprolyl isomerase B	Rattus norvegicus
64552	Mpeg1	macrophage expressed 1	Rattus norvegicus
64619	Zfp238	zinc finger protein 238	Rattus norvegicus
64681	Mvp	major vault protein	Rattus norvegicus
65144	Pdzk1	PDZ domain containing 1	Rattus norvegicus
65165	Tmed2	transmembrane p24 trafficking protein 2	Rattus norvegicus
66028	Arl6ip5	ADP-ribosylation factor like GTPase 6 interacting protein 5	Rattus norvegicus
678772	Casd1	CAS1 domain containing 1	Rattus norvegicus
679692	Lpgat1	lysophosphatidylglycerol acyltransferase 1	Rattus norvegicus
680782	Spcs3	signal peptidase complex subunit 3	Rattus norvegicus
686179	Ttc39c	tetratricopeptide repeat domain 39C	Rattus norvegicus
688405	Cdk2ap2	cyclin-dependent kinase 2 associated protein 2	Rattus norvegicus
688478	Commd2	COMM domain containing 2	Rattus norvegicus
79438	Igfals	insulin-like growth factor binding protein, acid labile subunit	Rattus norvegicus
81646	Creb1	cAMP responsive element binding protein 1	Rattus norvegicus
81748	Pls3	plastin 3	Rattus norvegicus
83501	Cdh2	cadherin 2	Rattus norvegicus
83534	Tpp1	tripeptidyl peptidase 1	Rattus norvegicus
83576	Sort1	sortilin 1	Rattus norvegicus
83586	Usf1	upstream transcription factor 1	Rattus norvegicus
84027	Gsk3b	glycogen synthase kinase 3 beta	Rattus norvegicus
84475	Cxcr3	C-X-C motif chemokine receptor 3	Rattus norvegicus
85332	Prkcdbp	protein kinase C, delta binding protein	Rattus norvegicus
94168	Spp2	secreted phosphoprotein 2	Rattus norvegicus
94269	Fez2	fasciculation and elongation protein zeta 2	Rattus norvegicus

Supplementary Table 7

Gene list of "M4vs8\_cluster3"

This cluster was obtained by hierarchical clustering (dendrogram cutoff: 6) of DEGs between

WY-14643/M dose/4day and WY-14643/M dose/8day by student's t-test (cutoff: p-value=0.01).

The cluster that contained 162 probes was defined as "M4vs8\_cluster3".

100125372	Ces1f	carboxylesterase 1F	Rattus norvegicus
100360302	Sec16a	SEC16 homolog A, endoplasmic reticulum export factor	Rattus norvegicus
100911750	LOC100911750	N-acetyllactosaminide beta-1,3-N-acetylglucosaminyltransferase-like	Rattus norvegicus
114517	Itga6	integrin subunit alpha 6	Rattus norvegicus
114558	Becn1	beclin 1	Rattus norvegicus
116504	Mprp	myosin phosphatase Rho interacting protein	Rattus norvegicus
116641	Lgals8	galectin 8	Rattus norvegicus
116655	Hnrnpm	heterogeneous nuclear ribonucleoprotein M	Rattus norvegicus
116686	Gsr	glutathione-disulfide reductase	Rattus norvegicus
140934	Ikbkap	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein	Rattus norvegicus
171337	Rap1b	RAP1B, member of RAS oncogene family	Rattus norvegicus
24242	Calm1	calmodulin 1	Rattus norvegicus
24244	Calm3	calmodulin 3	Rattus norvegicus
24385	Gck	glucokinase	Rattus norvegicus
24400	Gnb1	G protein subunit beta 1	Rattus norvegicus
246282	Zfp91	zinc finger protein 91	Rattus norvegicus
24645	Pgm1	phosphoglucomutase 1	Rattus norvegicus
24851	Tpm1	tropomyosin 1, alpha	Rattus norvegicus
25094	Mitf	melanogenesis associated transcription factor	Rattus norvegicus
25283	Gclc	glutamate-cysteine ligase, catalytic subunit	Rattus norvegicus
25578	Ywhaz	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta	Rattus norvegicus
266764	Tbkbp1	TBK1 binding protein 1	Rattus norvegicus
282587	Cttnbp2	cortactin binding protein 2	Rattus norvegicus
282635	Mbnl1	muscleblind-like splicing regulator 1	Rattus norvegicus
287170	Snrnp25	small nuclear ribonucleoprotein U11/U12 subunit 25	Rattus norvegicus
287719	Ifi35	interferon-induced protein 35	Rattus norvegicus
287986	Eif4g1	eukaryotic translation initiation factor 4 gamma, 1	Rattus norvegicus
288692	Wsb2	WD repeat and SOCS box-containing 2	Rattus norvegicus
288921	Fbxw9	F-box and WD repeat domain containing 9	Rattus norvegicus



289424 Xpr1 xenotropic and polytropic retrovirus receptor 1  
Rattus norvegicus  
289820 Actr2 ARP2 actin related protein 2 homolog Rattus  
norvegicus  
290577 Wapl WAPL cohesin release factor Rattus norvegicus  
291320 Fam188a family with sequence similarity 188, member A  
Rattus norvegicus  
292022 Ddx19a DEAD-box helicase 19A Rattus norvegicus  
292155 Hs2st1 heparan sulfate 2-O-sulfotransferase 1 Rattus  
norvegicus  
293186 Lyve1 lymphatic vessel endothelial hyaluronan receptor 1  
Rattus norvegicus  
293489 Slx1b SLX1 structure-specific endonuclease subunit  
homolog B (*S. cerevisiae*) Rattus norvegicus  
29355 Pkn1 protein kinase N1 Rattus norvegicus  
293667 B4gat1 beta-1,4-glucuronyltransferase 1 Rattus norvegicus  
293939 Erlin1 ER lipid raft associated 1 Rattus norvegicus  
293967 Smc5 structural maintenance of chromosomes 5 Rattus  
norvegicus  
294004 Dpcd deleted in primary ciliary dyskinesia Rattus  
norvegicus  
29534 Pex2 peroxisomal biogenesis factor 2 Rattus norvegicus  
295457 Cisd2 CDGSH iron sulfur domain 2 Rattus norvegicus  
29562 Prps1 phosphoribosyl pyrophosphate synthetase 1 Rattus  
norvegicus  
29606 Pcsk7 proprotein convertase subtilisin/kexin type 7  
Rattus norvegicus  
296634 Nup214 nucleoporin 214 Rattus norvegicus  
297387 Mob1a MOB kinase activator 1A Rattus norvegicus  
298084 Zbtb5 zinc finger and BTB domain containing 5 Rattus  
norvegicus  
298712 Gpalpp1 GPALPP motifs containing 1 Rattus norvegicus  
299811 Cpsf6 cleavage and polyadenylation specific factor 6  
Rattus norvegicus  
300284 Alg13 ALG13, UDP-N-acetylglucosaminyltransferase subunit  
Rattus norvegicus  
300837 Leo1 LE01 homolog, Paf1/RNA polymerase II complex  
component Rattus norvegicus  
302863 Slc9a6 solute carrier family 9 member A6 Rattus norvegicus  
302969 Srrm2 serine/arginine repetitive matrix 2 Rattus  
norvegicus  
304294 Rnf216 ring finger protein 216 Rattus norvegicus  
304786 Elk4 ELK4, ETS transcription factor Rattus norvegicus  
305264 Ugt2b10 UDP glucuronosyltransferase 2 family, polypeptide  
B10 Rattus norvegicus  
305889 Thtpa thiamine triphosphatase Rattus norvegicus  
306254 Pbrm1 polybromo 1 Rattus norvegicus  
306487 Mtus1 microtubule associated tumor suppressor 1 Rattus  
norvegicus  
306871 Dsp desmoplakin Rattus norvegicus  
307595 RGD1562794 similar to establishment of cohesion 1  
homolog 1 Rattus norvegicus  
309262 Nsdhl NAD(P) dependent steroid dehydrogenase-like  
Rattus norvegicus

309639 Anks1a ankyrin repeat and sterile alpha motif domain  
containing 1A Rattus norvegicus  
310538 Fnip2 folliculin interacting protein 2 Rattus norvegicus  
311118 Tlk1 tousled-like kinase 1 Rattus norvegicus  
311483 Rrbp1 ribosome binding protein 1 Rattus norvegicus  
311743 Zak sterile alpha motif and leucine zipper containing  
kinase AZK Rattus norvegicus  
311911 Rabgap1 RAB GTPase activating protein 1 Rattus norvegicus  
313139 Slc35a1 solute carrier family 35 member A1 Rattus  
norvegicus  
314273 Dcaf5 DDB1 and CUL4 associated factor 5 Rattus norvegicus  
316313 Dst dystonin Rattus norvegicus  
316531 Tuba4a tubulin, alpha 4A Rattus norvegicus  
360531 Sap30l SAP30-like Rattus norvegicus  
360563 Ncbp3 nuclear cap binding subunit 3 Rattus norvegicus  
361842 Sar1a secretion associated, Ras related GTPase 1A  
Rattus norvegicus  
362029 Agl amylo-alpha-1, 6-glucosidase, 4-alpha-  
glucanotransferase Rattus norvegicus  
362359 Mpp6 membrane palmitoylated protein 6 Rattus norvegicus  
362461 C2cd5 C2 calcium-dependent domain containing 5 Rattus  
norvegicus  
362514 Tstd2 thiosulfate sulfurtransferase like domain  
containing 2 Rattus norvegicus  
362883 Slc35e3 solute carrier family 35, member E3 Rattus  
norvegicus  
363022 Zfp846 zinc finger protein 846 Rattus norvegicus  
363029 Swsap1 SWIM-type zinc finger 7 associated protein 1  
Rattus norvegicus  
363077 Dis3l DIS3-like exosome 3'-5' exoribonuclease Rattus  
norvegicus  
363118 Nmnat3 nicotinamide nucleotide adenylyltransferase 3  
Rattus norvegicus  
363445 Usp9x ubiquitin specific peptidase 9, X-linked Rattus  
norvegicus  
365410 Osbp oxysterol binding protein Rattus norvegicus  
366311 Clvs1 clavesin 1 Rattus norvegicus  
497961 Nlk nemo like kinase Rattus norvegicus  
498411 Hus1 HUS1 checkpoint clamp component Rattus norvegicus  
499443 Lims1 LIM zinc finger domain containing 1 Rattus  
norvegicus  
501232 Cesl1 carboxylesterase-like 1 Rattus norvegicus  
50663 Calm2 calmodulin 2 Rattus norvegicus  
58840 Mapk6 mitogen-activated protein kinase 6 Rattus  
norvegicus  
58954 Klf6 Kruppel-like factor 6 Rattus norvegicus  
59076 Grk6 G protein-coupled receptor kinase 6 Rattus  
norvegicus  
64314 Casp2 caspase 2 Rattus norvegicus  
64391 Dapk3 death-associated protein kinase 3 Rattus norvegicus  
65134 Stx5 syntaxin 5 Rattus norvegicus  
679127 Rrp12 ribosomal RNA processing 12 homolog Rattus  
norvegicus  
680014 Esco1 establishment of sister chromatid cohesion N-

acetyltransferase 1 Rattus norvegicus  
 680562 LOC680562 similar to Mob4B protein Rattus norvegicus  
 681740 Jarid2 jumonji and AT-rich interaction domain containing 2  
 Rattus norvegicus  
 685029 Anapc13 anaphase promoting complex subunit 13 Rattus  
 norvegicus  
 686295 Wdr82 WD repeat domain 82 Rattus norvegicus  
 689116 Ncbp2 nuclear cap binding protein subunit 2 Rattus  
 norvegicus  
 689134 Sec61g Sec61 translocon gamma subunit Rattus norvegicus  
 689755 Ccdc167 coiled-coil domain containing 167 Rattus norvegicus  
 689997 Fam91a1 family with sequence similarity 91, member A1  
 Rattus norvegicus  
 690693 Ddx19b DEAD-box helicase 19B Rattus norvegicus  
 690779 LOC690779 similar to Mob4B protein Rattus norvegicus  
 81727 Mvk mevalonate kinase Rattus norvegicus  
 83469 Lrp4 LDL receptor related protein 4 Rattus norvegicus  
 83536 Mkln1 muskelin 1 Rattus norvegicus  
 83584 Casp6 caspase 6 Rattus norvegicus  
 83720 Fat1 FAT atypical cadherin 1 Rattus norvegicus  
 84599 Tmed10 transmembrane p24 trafficking protein 10 Rattus  
 norvegicus  
 89842 Mbtps1 membrane-bound transcription factor peptidase, site  
 1 Rattus norvegicus