

MMP: matrix metalloproteinase
 TIMP: tissue inhibitor of metalloproteinase
 TIMP-3
 Int-63: integrin beta-3
 PAK: serine/threonine protein kinase PAK
 PGDH: prostaglandin 15-hydroxydehydrogenase
 PGES: prostaglandin-E synthase
 PKA: cAMP-dependent protein kinase
 RGS: Regulator of G-protein signaling

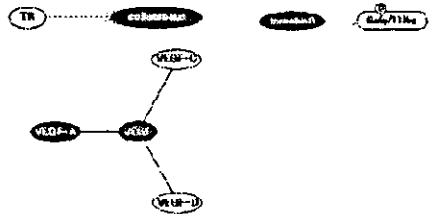


図9 四塩化炭素, イソニアジドで共通に発現増加した分子ネットワーク

Threshold 2.0 Down-regulation

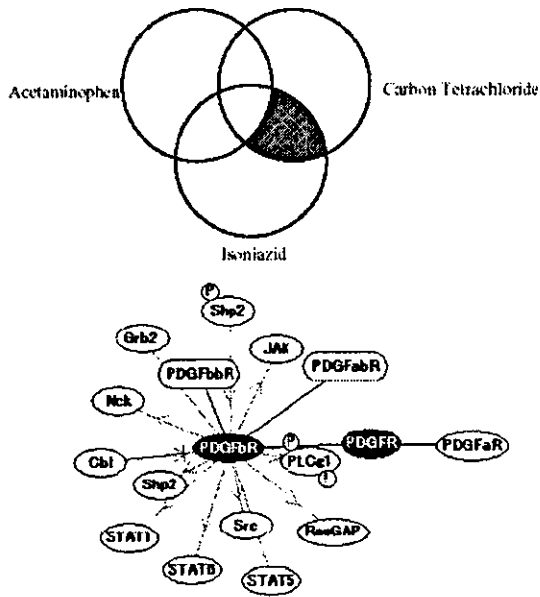


図10 四塩化炭素, イソニアジドで共通に発現減少した分子ネットワーク

PDGFR: platelet derived growth factor receptor
 PDGFβR: platelet derived growth factor beta receptor

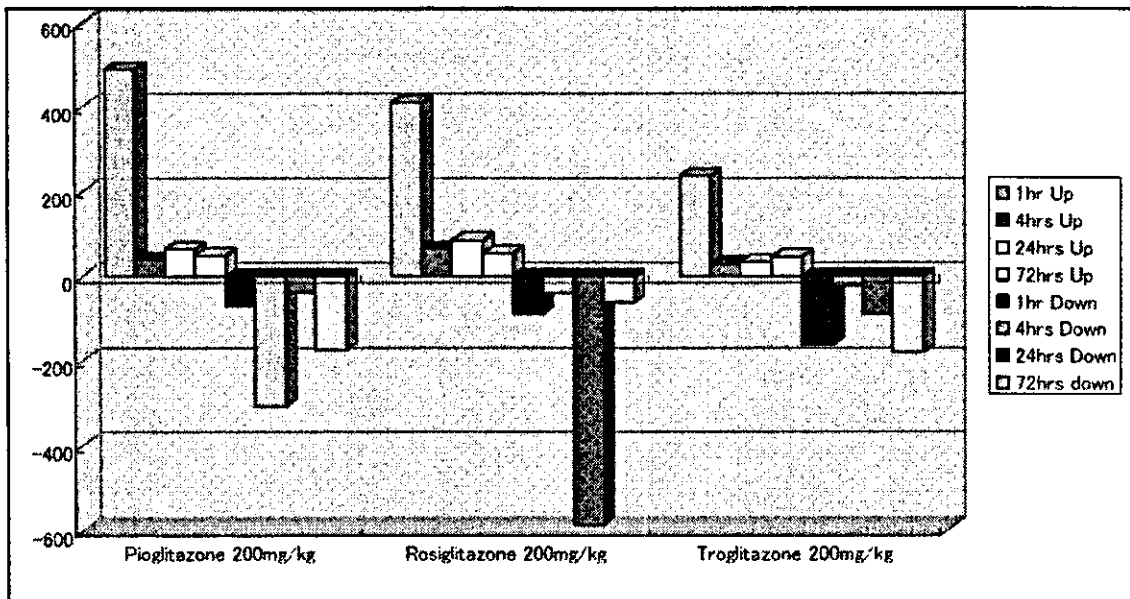
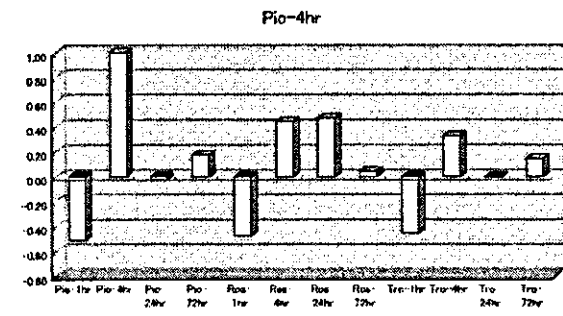
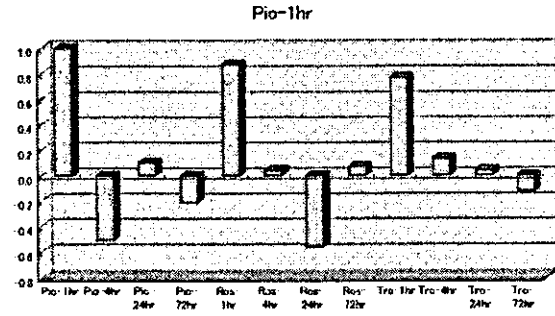
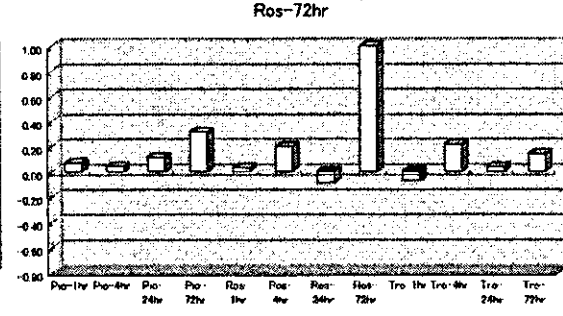
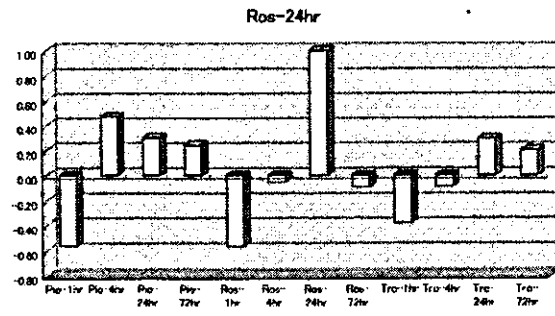
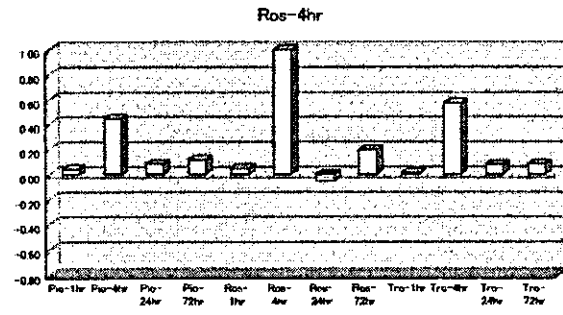
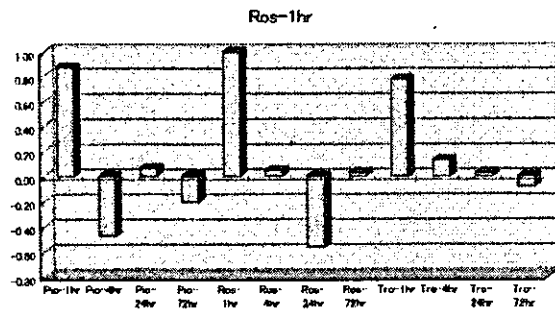
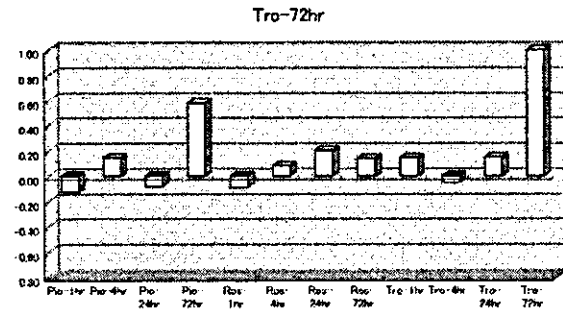
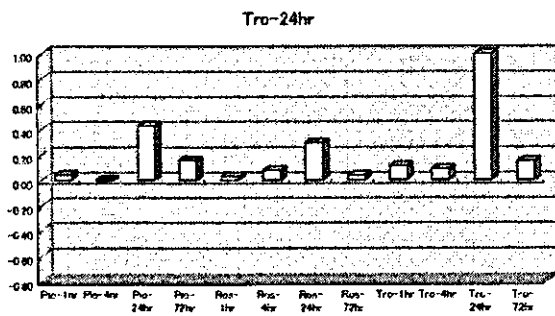
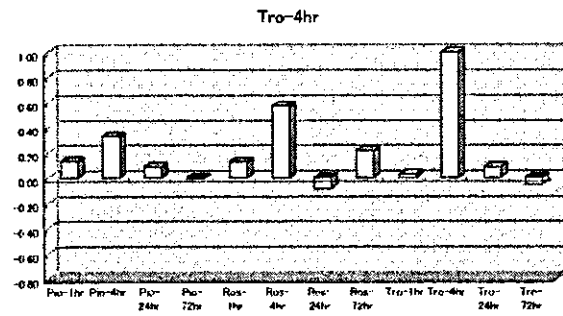
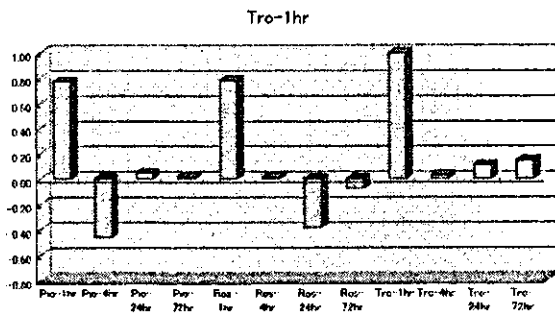


図11 PPAR γ 作用薬暴露時の経時的発現変動遺伝子数 (Threshold 2.0)



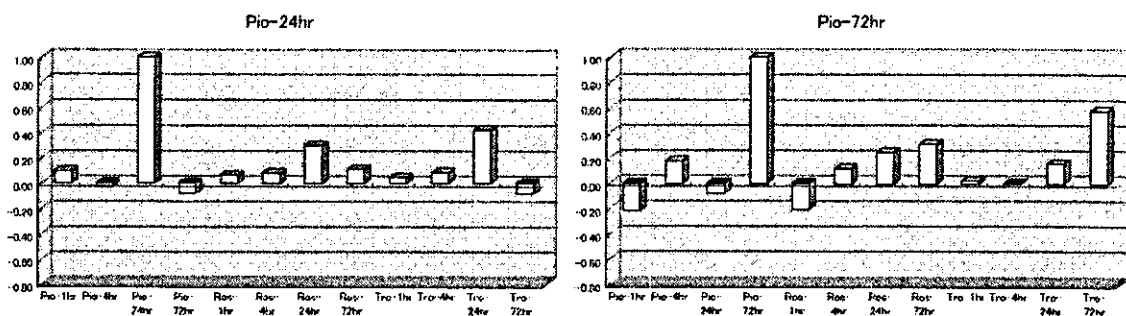


図12 遺伝子発現パターンの経時的相関 (すべてのデータを使用)

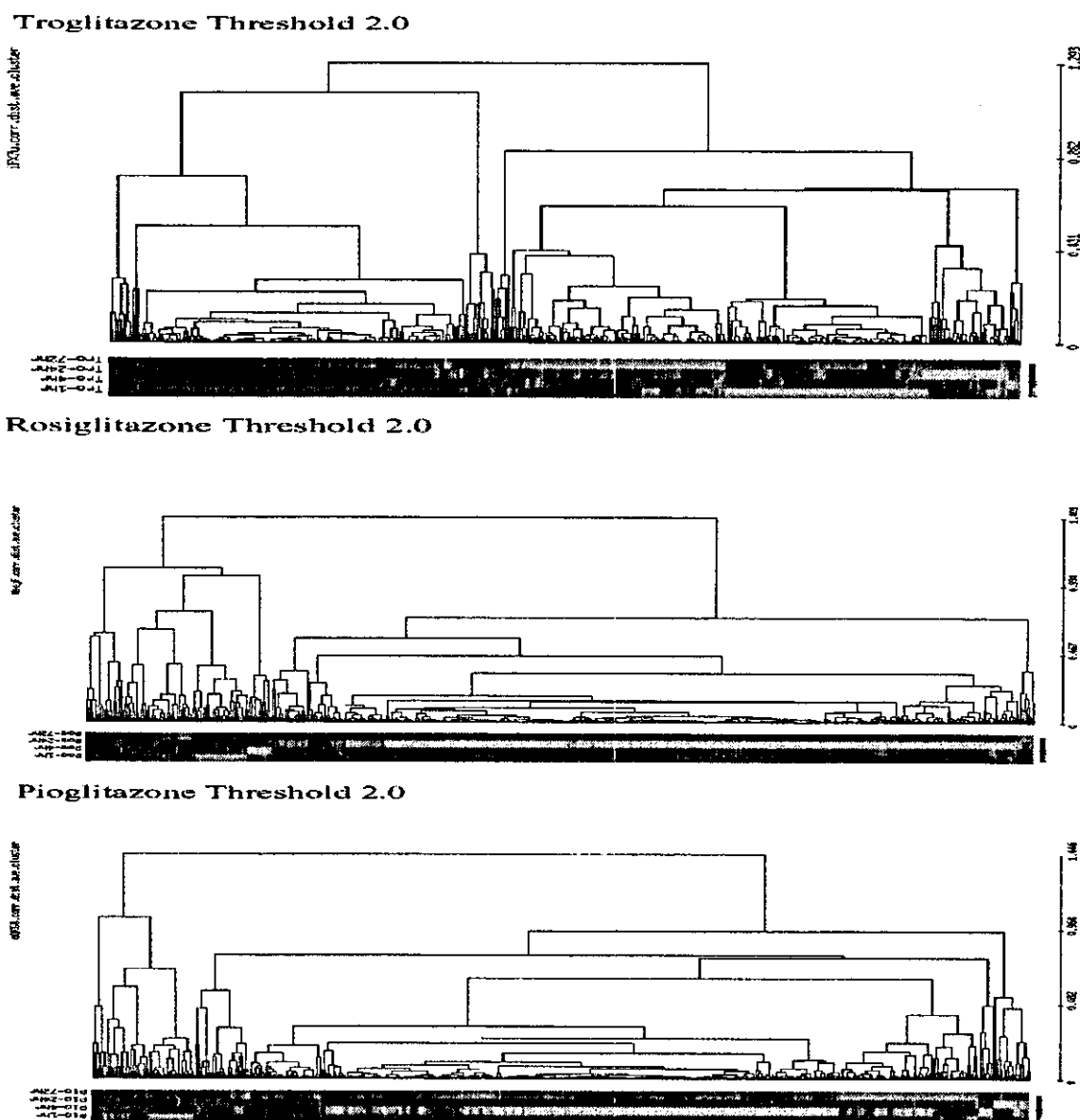
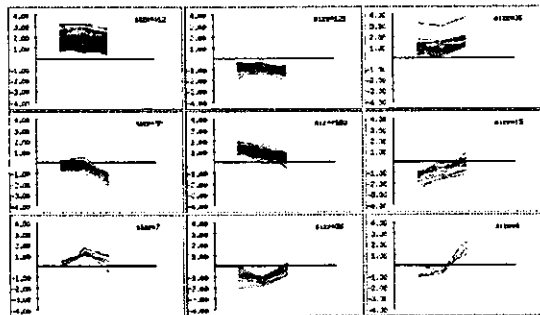


図13 薬剤別階層的クラスタリング (Threshold 2.0)

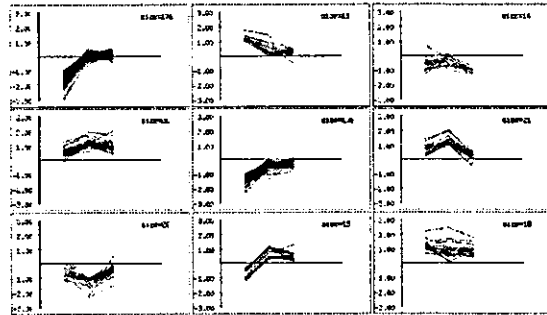
Time Course : 1hr

k-means clustering



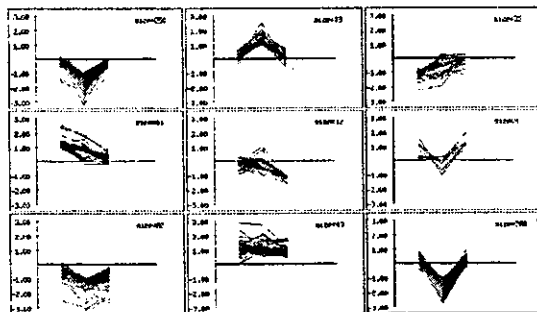
Time Course : 4hr

k-means clustering



Time Course : 24hr

k-means clustering



Time Course : 72hr

k-means clustering

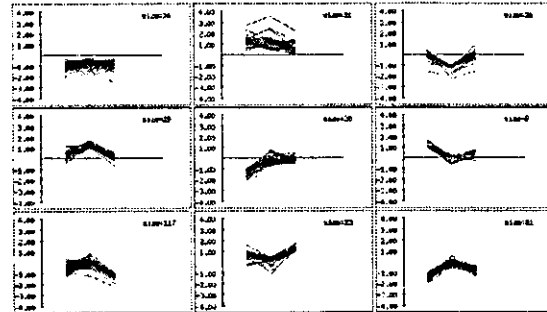


図 1 4 3 薬剤の経時的な K-means クラスタリング (K=9)

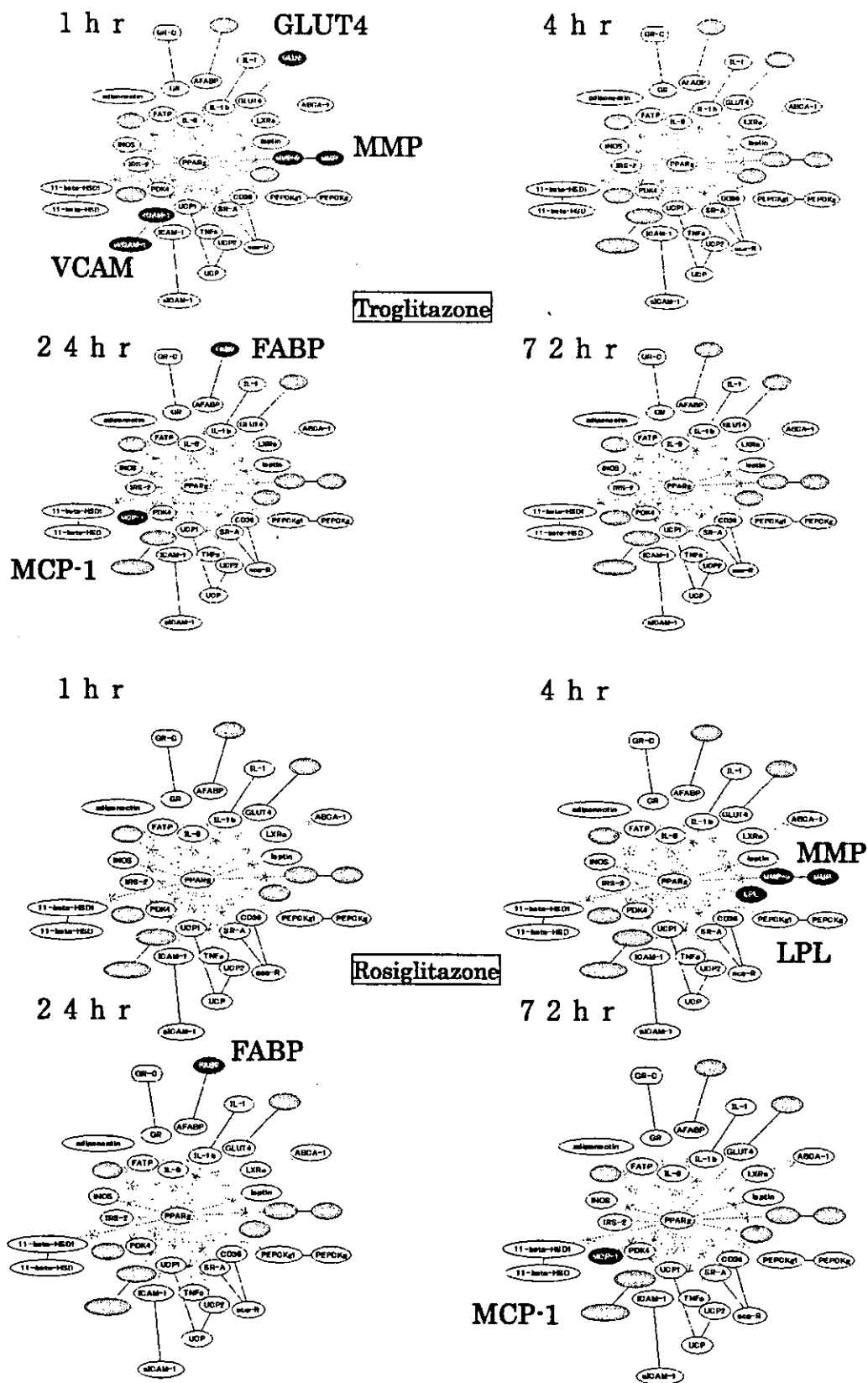


図15 PPAR γ に関連するネットワーク上での遺伝子発現変化

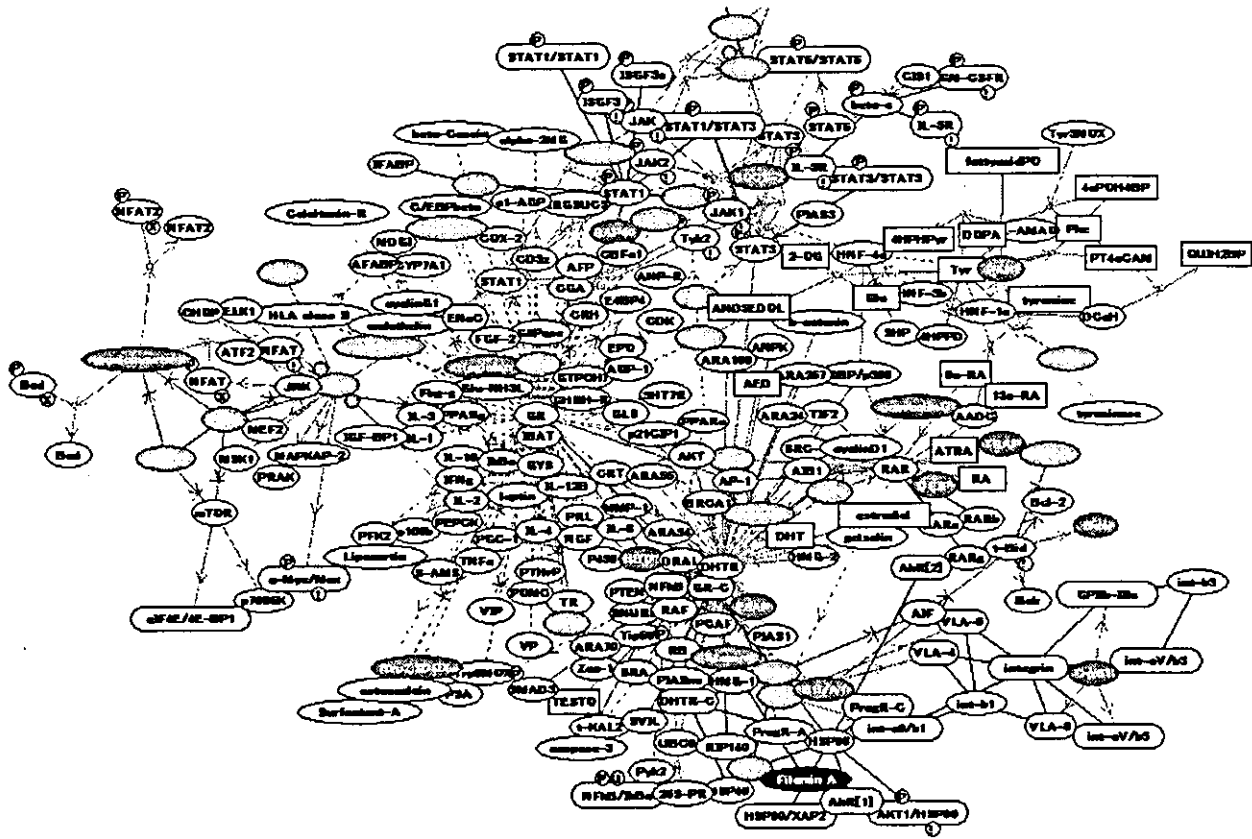
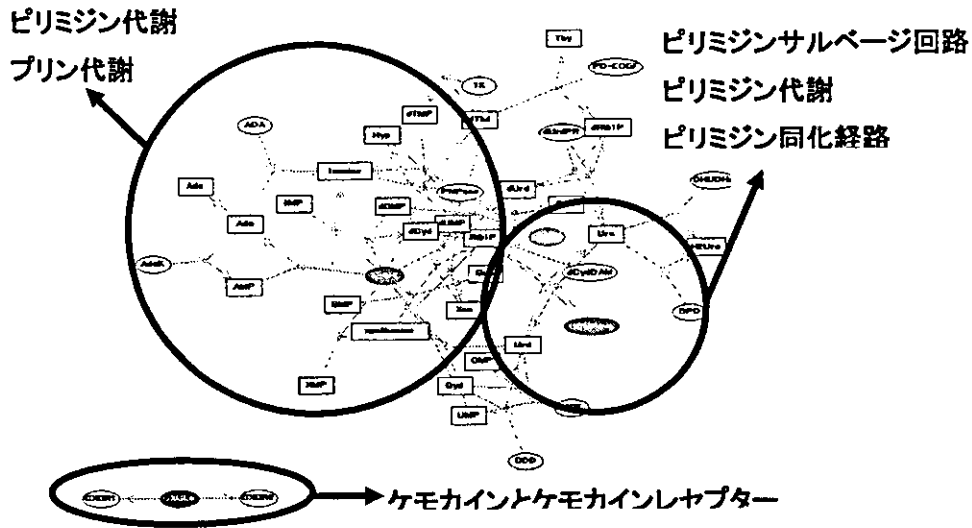


図16 共通して遺伝子発現減少した遺伝子クラスターの分子ネットワーク

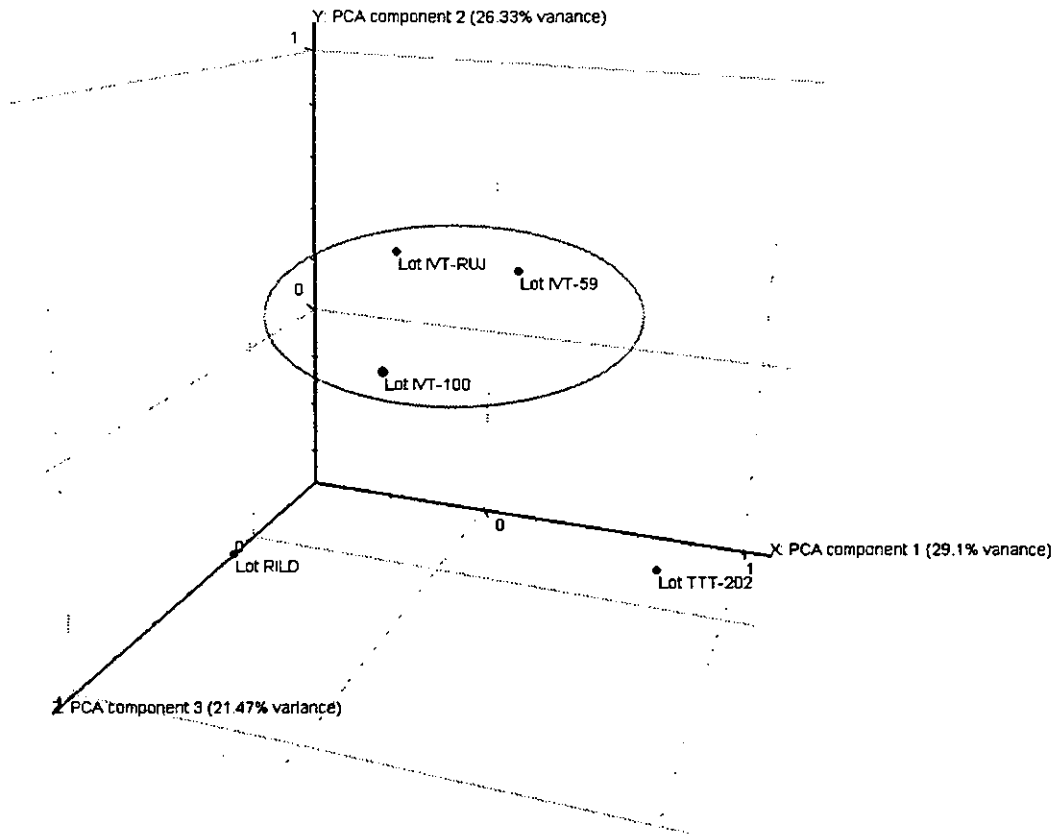


図 1. 主成分分析による各ロットの遺伝子発現プロファイルの比較

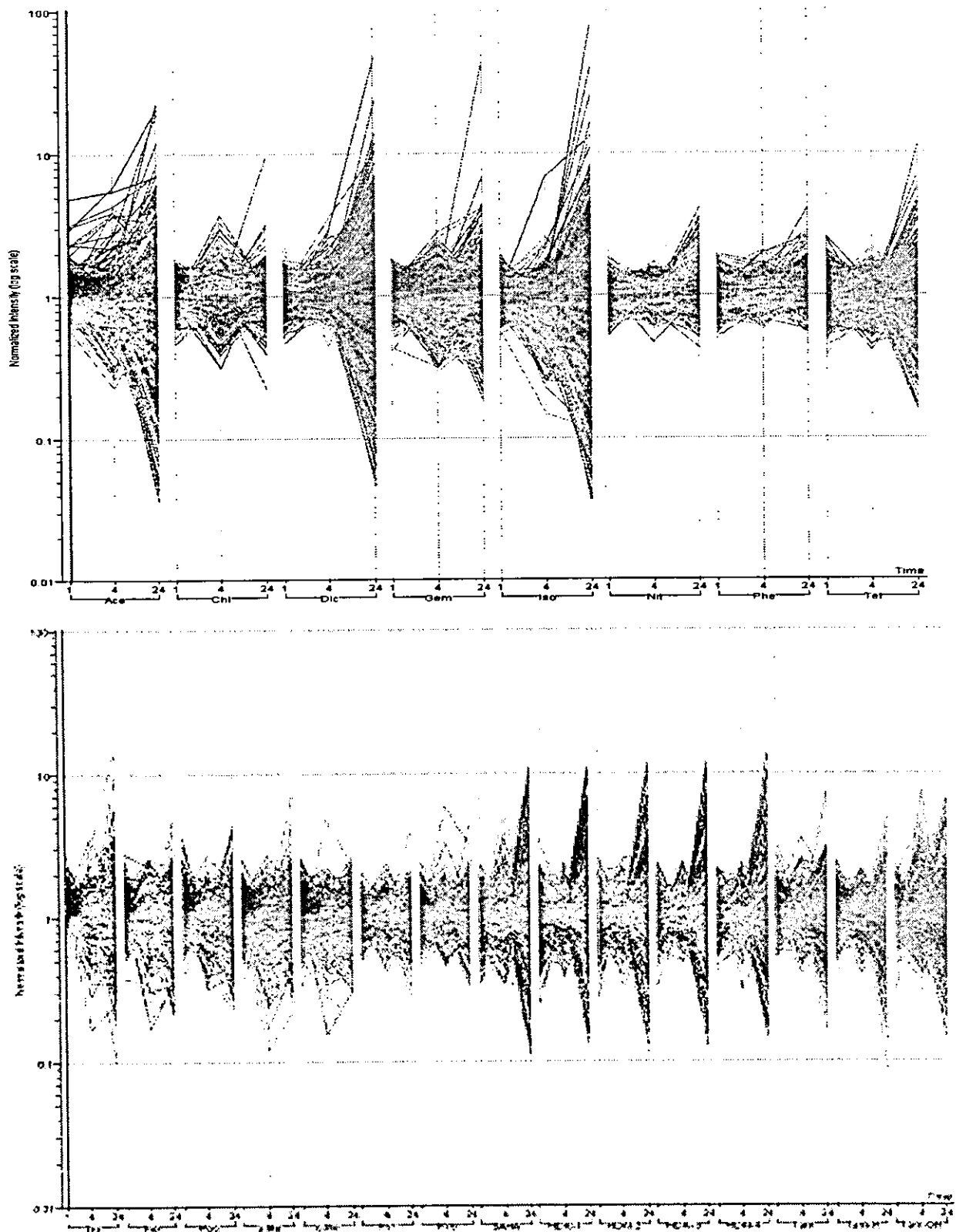


図 2. 薬剤曝露による遺伝子発現の経時的変化

上図：肝毒性薬剤 8 剤 下図：データベース検証用化合物 (15 化合物)

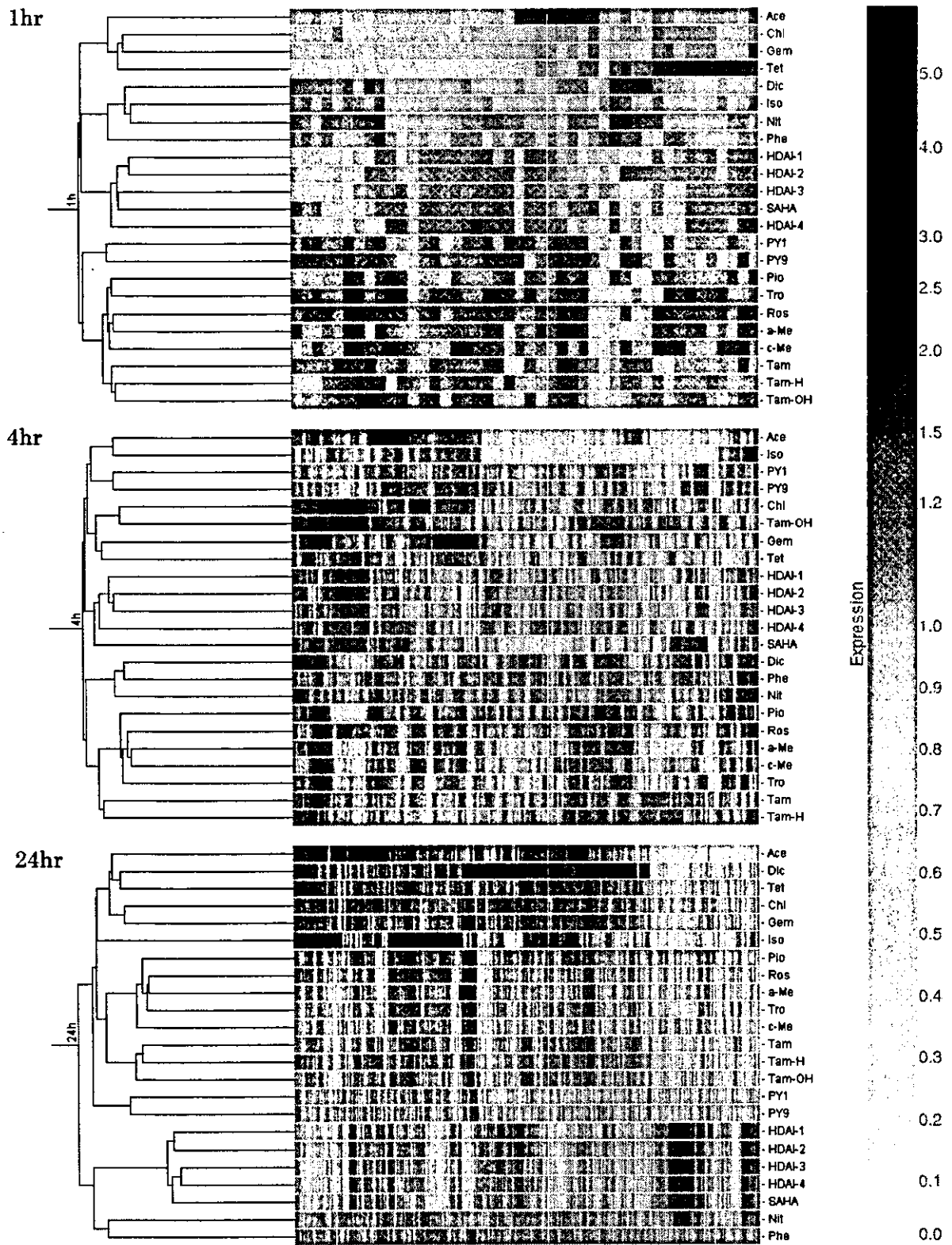
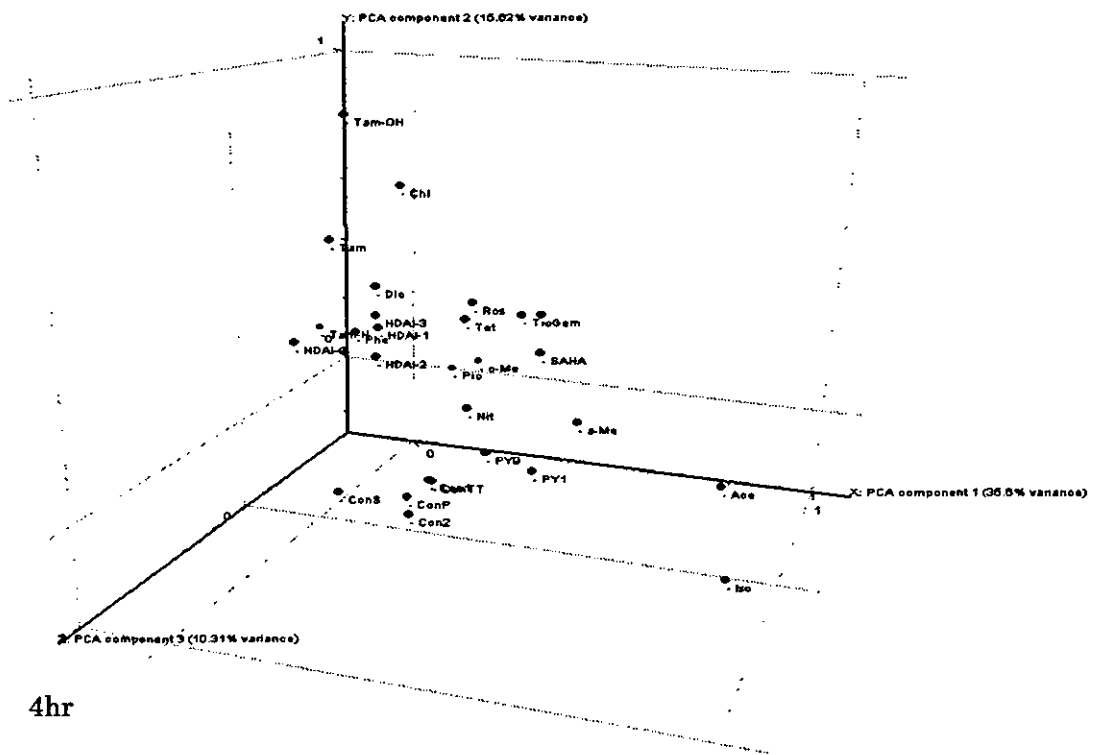
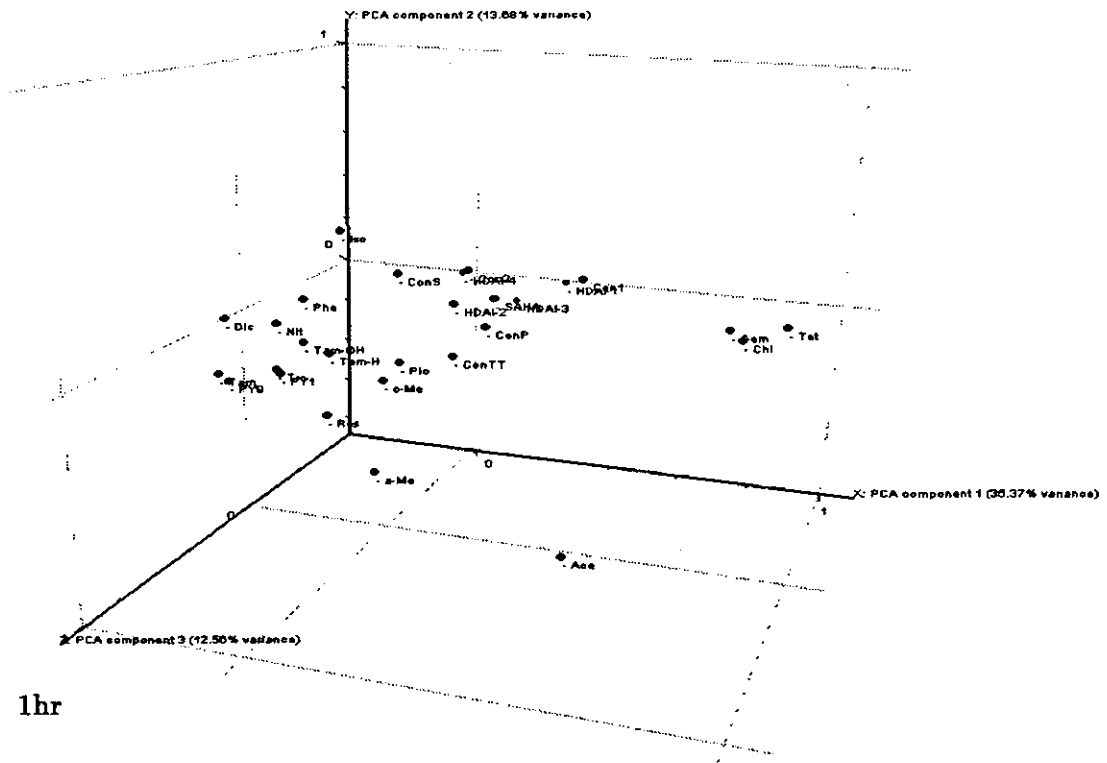


図3. クラスター解析による遺伝子発現のパターン分類の結果



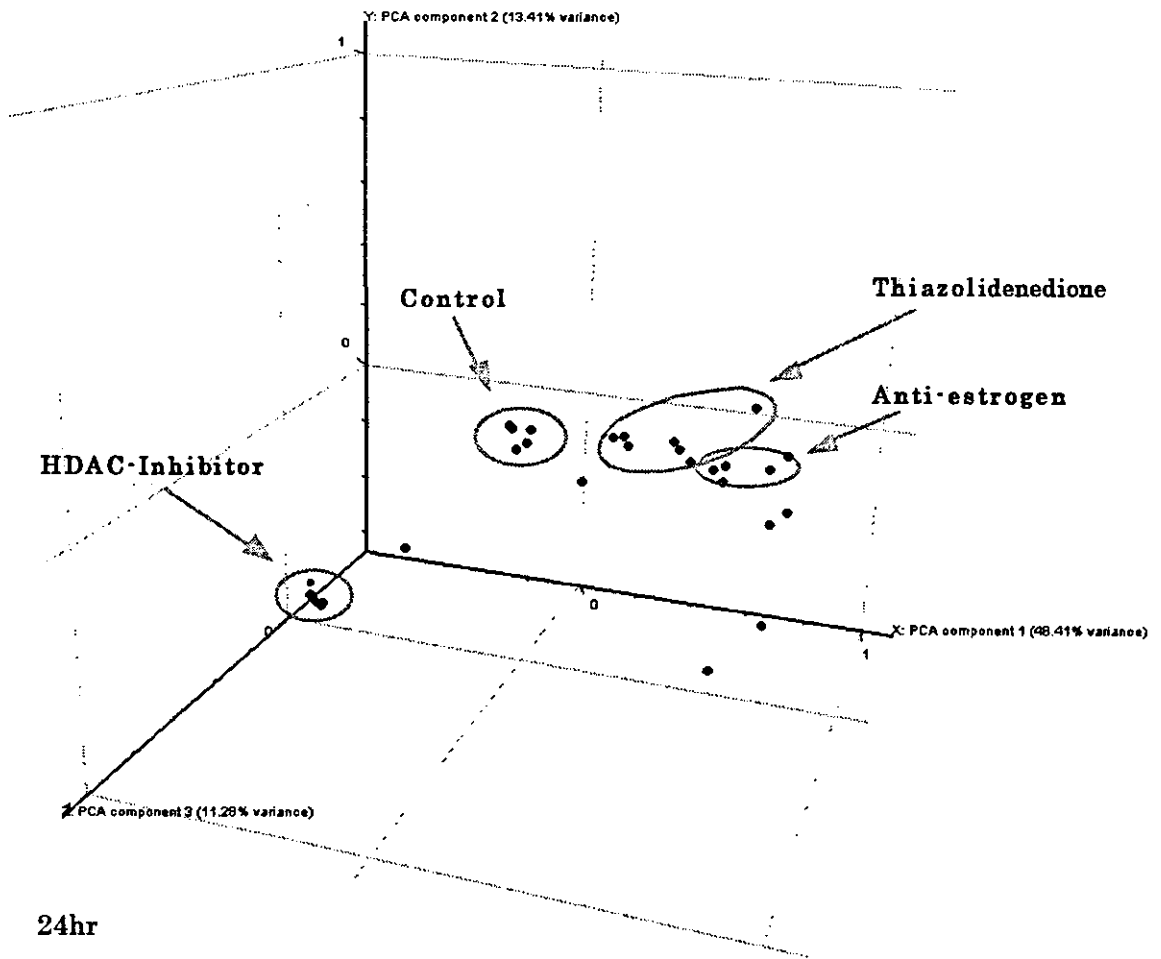


図 4. 主成分分析による遺伝子発現パターンの解析結果

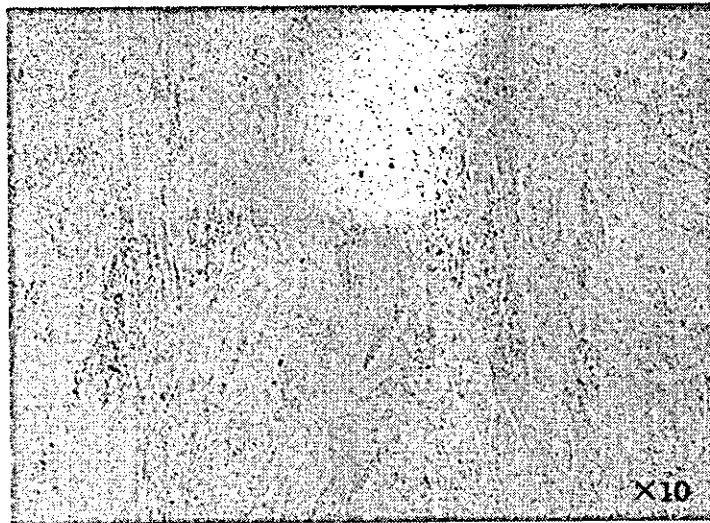


図 5. Human renal cortical cell (10%コンフルエント)

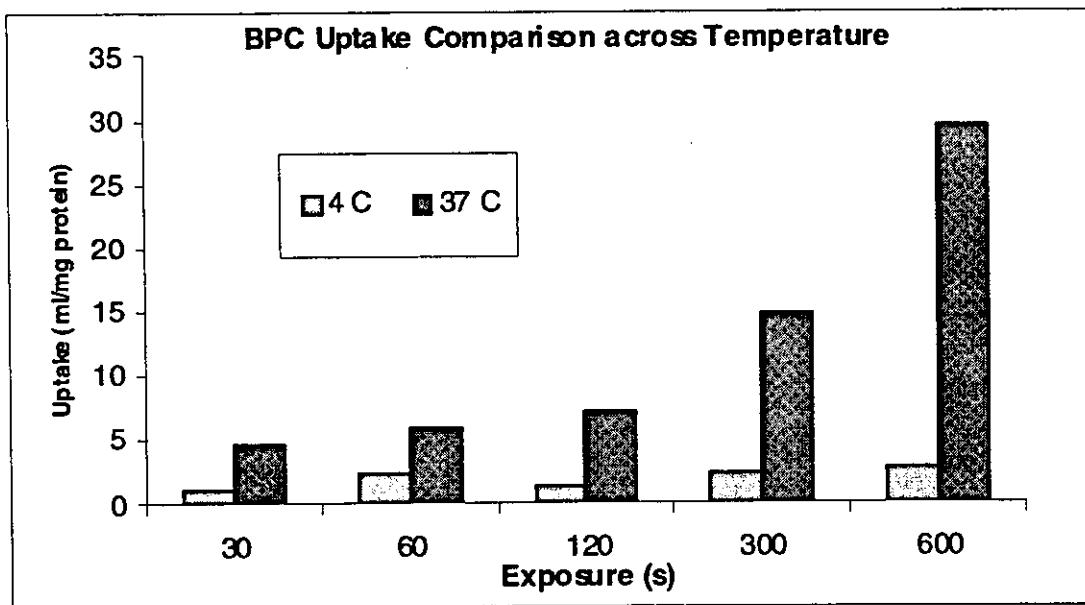


図 6. トランスポーターの取り込み活性試験の結果

資料 2

実験動物データのヒトへの外挿を目指した基本手法の確立に関する研究の図表

表1 アリストロキア酸によりマウス各臓器にて発現の変化した遺伝子数

	Spleen		G.Stomach		Liver		Bladder		F.Stomach		Kidney		
	6hr	6hr	24hr	6hr	24hr	6hr	24hr	6hr	24hr	6hr	24hr	48hr	
Up	10	15	6	101	6	8	10	13	47	218	26	48	
Down	5	48	8	116	2	15	17	9	67	243	33	107	

表2 アリストロキア酸にて臓器間で異なった動きを示した遺伝子

Gene Title	Spleen		Glandular Stomach		Liver		Bladder		F.Stomach		Kidney															
	6hr Ratio	24hr Ratio	6hr Ratio	24hr Ratio	6hr Ratio	24hr Ratio	6hr Ratio	24hr Ratio	6hr Ratio	24hr Ratio	6hr Ratio	24hr Ratio	48hr Ratio													
major urinary protein group 1 gene	2.47	P	0.53	P	1.59	P	1.46	P	1.08	P	0.08	A	0.41	A	0.18	P	0.18	P	0.70	P	0.90	P	1.16	P		
adaptor protein complex AP-1, sigma 1	0.79	P	2.07	P	1.05	P	0.87	P	1.13	P	1.25	P	1.08	P	0.98	P	1.03	P	0.47	P	1.04	P	0.97	P		
adipocyte complement related protein albumin 1	2.98	P	1.34	P	1.07	P	1.03	A	1.54	M	0.56	P	0.33	P	1.39	P	1.23	P	0.85	A	2.10	P	1.48	P	1.21	P
B lymphoma Mo-MLV insertion region 1 basic leucine zipper and W2 domains 1	2.60	P	0.03	A	5.46	P	1.47	P	1.17	P	0.18	A	0.89	A	0.49	A	0.47	A	2.01	P	1.48	P	1.48	P	0.98	P
BCL2/adenovirus E1B 19kDa-interacting protein 3-like cDNA sequence BC028585	0.79	P	1.21	P	0.92	P	1.42	P	1.22	P	1.21	P	1.17	P	1.08	P	0.76	P	2.97	P	0.35	P	1.33	P		
complement component 1, r subcomponent	0.80	P	0.99	P	0.99	P	1.19	P	1.01	P	1.29	P	0.94	P	1.56	P	1.19	P	2.72	P	0.44	P	0.73	P		
cysteine and glycine-rich protein 1 deleted in polyposis 1-like 1	0.91	P	1.14	P	1.08	P	2.18	P	0.94	P	1.11	P	0.78	P	0.93	P	0.65	P	2.46	P	0.45	P	0.58	P		
expressed sequence AWS49877	1.17	P	1.21	P	1.29	P	1.15	P	1.17	P	0.58	P	0.77	P	1.14	P	1.18	P	1.20	M	2.87	M	1.28	P		
immunoglobulin kappa chain variable 8 (V8)	0.31	M	0.40	M	1.37	P	2.84	P	1.11	P	0.90	P	0.85	P	0.53	P	0.82	P	1.18	M	2.87	M	1.28	P		
isopentenyl-diphosphate delta isomerase kangal 1 (suppression of tumorigenicity 6, prostate)	0.68	P	1.31	P	1.01	P	0.51	A	1.21	P	0.99	P	1.04	P	0.97	P	0.78	P	0.35	P	1.78	P	1.19	P		
keratin complex 1, acidic, gene 10	1.30	A	0.50	P	0.52	A	1.89	P	1.13	P	0.78	P	0.46	P	0.80	P	0.50	A	1.72	P	1.13	P	1.19	P		
keratin complex 2, basic, gene 4	1.04	P	1.12	P	0.80	P	1.63	P	0.84	P	1.46	P	0.83	P	0.89	P	0.83	P	2.75	P	0.39	P	0.71	P		
lipocalin-like 4	1.33	P	0.98	P	1.07	P	1.25	P	0.86	P	1.43	P	0.94	P	1.92	P	2.72	P	0.73	P	0.53	P	0.89	P		
major urinary protein 4	0.73	P	0.97	P	1.02	P	0.82	P	1.11	P	1.17	P	0.89	P	0.91	P	0.95	P	0.41	P	1.32	P	2.13	P		
major urinary protein 5	1.00	P	2.60	P	0.58	P	1.34	P	1.47	P	1.05	P	0.74	P	0.86	P	0.84	P	1.86	P	0.71	P	0.77	P		
major urinary protein 5	1.58	A	3.52	P	0.43	P	0.73	A	0.95	A	1.01	P	1.41	P	0.88	P	0.71	P	1.04	A	0.71	A	1.25	A		
major urinary protein 5	2.00	P	1.20	P	1.18	P	1.80	P	1.14	P	0.84	P	0.40	P	1.40	P	1.21	P	1.76	P	0.82	P	0.58	P		
major urinary protein 5	0.98	P	0.13	P	1.81	P	1.80	P	1.12	P	0.19	A	0.86	A	0.54	A	2.27	A	0.83	A	0.83	A	0.91	P		
matrix gamma-carboxylated glutamate (glu) protein	1.53	P	0.29	P	1.66	P	1.50	P	1.19	P	0.30	A	1.10	A	0.71	A	0.31	A	3.99	P	0.97	A	2.28	P		
megakaryoblastic leukemia 1 homolog (human)	0.81	P	0.63	P	0.94	P	2.29	P	1.38	P	1.20	P	1.20	P	1.08	P	1.66	P	1.80	P	0.90	P	0.42	P		
myosin light polypeptide 1, alkali, strial, embryonic	0.92	P	0.78	P	0.77	P	0.44	P	2.77	P	1.06	P	1.19	P	1.20	P	1.10	P	0.59	P	0.93	P	0.96	P		
nascent polypeptide-associated complex alpha polypeptide	0.74	P	0.44	P	0.99	P	3.85	P	0.71	A	0.64	P	1.02	P	0.86	P	1.04	P	1.54	M	1.00	A	1.18	P		
nascent polypeptide-associated complex alpha polypeptide	1.38	P	0.75	P	1.02	P	1.47	P	1.02	P	1.31	P	0.76	P	0.71	P	0.40	P	3.34	P	1.56	P	1.63	P		
nascent polypeptide-associated complex alpha polypeptide	1.05	M	1.12	P	0.31	A	0.85	A	1.06	A	0.48	A	0.54	A	4.06	P	0.50	P	0.97	A	1.79	A	1.08	A		
nascent polypeptide-associated complex alpha polypeptide	1.87	P	1.88	P	0.95	P	1.47	P	1.18	P	1.17	P	0.78	P	1.30	P	0.58	P	2.12	P	0.87	P	0.85	P		
nascent polypeptide-associated complex alpha polypeptide	0.96	M	1.12	P	0.78	P	2.16	P	1.46	P	0.74	P	0.58	P	0.85	P	3.40	P	0.47	P	1.67	P	0.31	P		
RIKEN cDNA 1110020A08 gene	1.40	P	2.28	P	0.89	P	0.52	P	1.04	P	2.00	P	0.79	P	1.03	P	1.14	P	1.87	P	0.86	P	0.40	P		
RIKEN cDNA 1700056017 gene	1.08	P	0.50	P	1.19	P	1.92	P	0.92	P	1.03	P	1.01	P	0.87	P	1.27	P	2.40	P	0.32	P	0.55	P		
RIKEN cDNA 220008D09 gene	0.90	A	0.39	A	2.88	P	0.34	A	1.81	A	0.82	A	1.00	A	0.50	A	0.50	A	0.68	A	1.03	A	0.97	A		
RIKEN cDNA 8030623C06 gene	1.00	A	1.40	P	1.85	P	1.02	A	1.38	A	1.02	P	0.45	P	1.12	P	1.86	P	1.34	A	1.55	A	3.38	P		
RIKEN cDNA 8130415E20 gene	0.65	P	1.21	P	0.84	P	1.51	P	0.79	P	1.14	P	1.09	P	1.01	P	1.11	P	3.97	P	0.42	P	1.29	P		
serine (or cysteine) proteinase inhibitor, clade A, member 1a	1.32	P	0.14	M	1.93	P	1.43	P	1.17	P	0.43	A	0.89	A	0.77	M	0.73	A	1.85	P	0.73	P	2.14	P		
serine (or cysteine) proteinase inhibitor, clade A, member 1b	1.24	P	0.07	A	3.24	P	1.39	P	1.18	P	0.13	A	0.84	A	0.38	A	0.39	A	1.23	P	0.78	P	1.82	P		
serine (or cysteine) proteinase inhibitor, clade A, member 1d	1.75	P	0.07	A	2.75	P	1.40	P	1.21	P	0.16	P	0.68	A	0.70	P	0.47	P	1.30	P	0.74	P	1.59	P		
serine (or cysteine) proteinase inhibitor, clade A, member 1e	1.81	P	0.04	A	4.74	P	1.45	P	1.18	P	0.13	A	0.52	A	0.38	A	1.02	P	0.72	P	0.72	P	1.48	P		
sterol-C4-methyl oxidase-like	1.49	P	0.85	P	1.10	P	2.46	P	0.83	P	0.98	P	0.49	P	1.13	P	0.45	P	1.54	P	0.96	P	0.84	P		
ubiquitin-conjugating enzyme E2D 2	0.80	P	1.07	P	0.97	P	1.85	P	1.04	P	1.15	P	1.28	P	0.83	P	1.41	P	3.41	P	0.43	P	0.84	P		
UV radiation resistance associated gene	0.87	P	0.64	A	0.98	A	0.74	A	1.04	A	0.48	P	2.77	P	0.68	A	1.00	A	1.03	M	1.75	A	0.68	A		

※ 発現上昇 発現抑制

図1 各薬物処理によりTK6細胞で発現が変化した遺伝子数

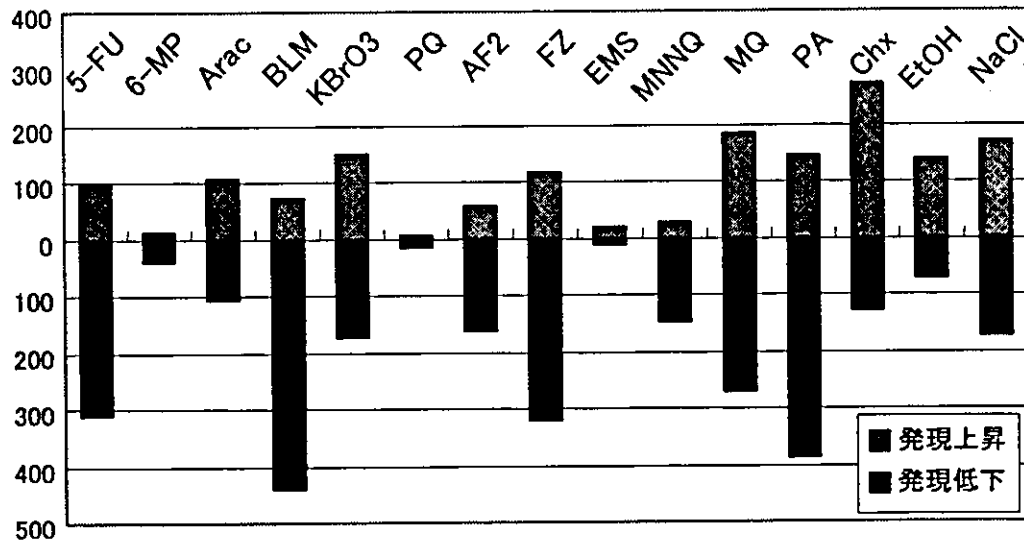


表5 15化合物間で共通性を持って変化した遺伝子

Gene Title	SFU	6MP	AraC	BLM	KBrO ₃	FZ	PQ	AF2	EMS	MNNG	MQ	NaCl	PA	Chx	EtOH
activating transcription factor 3	1.93	1.15	5.95	2.28	1.26	4.09	1.06	8.08	1.57	1.57	7.18	0.82	1.43	3.99	7.88
protein phosphatase 1D Mg-dependent	2.55	1.19	4.45	3.27	1.56	2.50	1.15	2.54	1.53	1.26	2.38	2.46	1.42	1.28	1.63
heterogeneous nuclear ribonucleoprotein D p21	2.67	0.95	1.26	0.95	0.66	2.73	1.10	2.61	1.38	1.02	2.60	2.52	2.35	2.17	0.85
PCF11p homolog	1.12	0.95	11.14	4.45	9.22	1.10	1.23	5.98	1.55	1.30	2.98	1.45	0.96	0.66	1.17
eukaryotic translation initiation factor 5A	3.44	1.02	0.71	1.11	1.66	3.53	0.89	1.29	0.90	0.68	4.75	2.04	2.02	4.65	2.84
protein phosphatase 1, regulatory subunit 15A	3.73	2.72	1.16	4.40	1.62	3.75	1.49	0.80	1.25	0.93	1.21	1.02	3.22	0.86	1.70
thioredoxin interacting protein	0.73	1.22	1.34	0.74	0.83	2.35	0.96	1.77	1.24	0.98	3.54	2.63	0.56	3.56	2.32
protein phosphatase 1, regulatory subunit 15A	2.39	1.08	2.56	1.84	1.29	1.11	0.79	1.31	1.18	1.15	1.32	0.96	1.77	8.22	3.23
F-box and leucine-rich repeat protein 11	0.77	0.91	1.76	0.44	0.53	2.32	1.05	1.85	1.54	1.24	3.94	2.58	0.14	4.25	2.14
KIAA0669	2.04	1.30	0.79	1.74	1.38	2.12	0.78	1.08	1.44	1.37	1.29	2.91	3.03	2.86	3.54
cystathionase (cystathionine gamma-lyase)	2.52	1.23	0.98	1.15	1.17	2.32	1.00	1.11	1.81	0.70	2.01	1.74	1.52	2.66	1.91
solute carrier family 38, member 2	1.31	1.36	2.12	1.40	0.92	3.86	0.70	2.15	1.06	0.84	4.35	1.00	3.60	1.11	3.51
bromodomain containing 2	1.72	1.13	1.36	1.55	1.55	2.23	0.86	1.33	0.94	0.51	2.72	4.69	1.91	0.51	2.24
opioid receptor, sigma 1	1.06	0.56	1.20	0.84	1.23	0.93	1.23	2.43	1.27	1.22	3.08	2.74	1.01	3.63	1.41
beta 5-tubulin	1.78	0.64	0.52	0.61	2.76	1.84	0.33	0.90	0.52	0.85	0.99	3.29	0.54	1.85	2.82
enolase 1, (alpha)	0.57	0.52	1.11	0.55	1.77	0.49	0.94	1.15	0.97	1.18	1.25	1.78	0.55	1.05	0.80
stress-induced-phosphoprotein 1	0.35	0.48	0.87	0.38	2.10	0.32	1.04	1.24	1.01	1.17	1.16	2.10	0.29	1.22	1.10
calnexin	0.21	0.32	0.93	0.18	2.04	0.28	1.04	1.38	0.98	0.99	0.91	2.30	0.34	1.98	1.12
growth arrest and DNA-damage-inducible, beta	0.44	0.58	0.99	0.61	2.58	0.41	0.93	1.02	1.22	1.30	1.28	1.80	0.49	1.36	1.27
tumor necrosis factor, alpha-induced protein 3	0.26	0.93	1.07	0.24	0.76	0.24	1.01	1.30	0.78	1.14	2.27	0.72	0.19	4.31	1.86
phosphodiesterase 4B	0.35	1.45	2.88	1.16	0.75	0.41	1.07	0.90	1.33	1.01	1.26	2.00	0.46	1.99	0.86
DEAD (Asp-Glu-Ala-Asp) box polypeptide 3	0.26	0.82	4.30	2.84	1.21	0.56	0.96	0.66	0.81	0.82	0.11	0.55	0.58	4.00	1.92
chromosome 9 open reading frame 16	0.39	1.24	0.83	0.39	1.89	0.35	1.08	0.90	1.02	1.01	0.83	2.57	0.44	1.05	1.30
chemokine (C-C motif) ligand 3	0.12	0.93	1.31	0.21	0.78	0.11	1.34	2.52	0.90	1.70	0.86	1.27	0.09	1.07	0.64
inhibitor of DNA binding 3	0.44	1.32	2.25	1.19	0.91	0.52	1.09	0.49	0.92	0.96	1.51	0.27	0.55	0.97	0.18
H2B histone family, member S	0.52	0.65	3.06	1.00	0.73	0.28	0.94	0.89	0.93	1.08	0.44	0.28	0.62	0.93	0.84
SEC23 interacting protein	0.33	1.39	0.59	0.23	0.95	0.50	1.21	1.25	1.23	1.30	0.85	1.34	0.27	19.25	0.48
heat shock 70kDa protein 1A	0.81	0.69	0.74	0.76	2.67	0.99	0.99	0.85	0.45	0.18	0.43	1.61	1.22	2.24	1.45
transgelin 2	0.26	1.48	0.73	0.36	1.19	0.25	1.29	2.89	1.33	1.34	1.43	0.78	0.30	0.27	0.29
phenylalanine-tRNA synthetase-like	0.23	0.33	0.51	0.32	2.03	0.24	0.82	1.27	0.82	0.98	1.04	1.69	0.27	1.14	0.91
exosome complex exonuclease RRP41	0.25	0.83	1.08	0.28	1.02	0.13	1.10	1.00	1.14	1.15	0.43	1.02	0.21	1.18	1.20
abhydrolase domain containing 6	0.29	0.99	0.74	0.29	0.52	0.26	0.88	1.03	0.93	1.27	0.22	0.81	0.29	0.74	0.73
exosome complex exonuclease RRP41	0.45	0.77	0.55	0.21	0.89	0.34	1.08	0.69	0.88	1.11	0.42	0.96	0.21	0.76	0.85
MCM3 associated protein	0.35	0.87	0.90	0.22	0.73	0.25	1.06	0.85	0.97	1.35	0.33	0.68	0.15	0.63	0.65
ribosome binding protein 1 homolog	0.42	0.80	0.89	0.38	0.83	0.32	1.03	0.73	0.97	1.15	0.86	1.02	0.31	0.42	0.80
splicing factor, arginine/serine-rich 1	0.14	0.86	1.11	0.06	0.39	0.19	1.01	1.46	0.98	1.52	1.43	0.50	0.18	0.70	0.69
cyclin-dependent kinase 9	0.39	0.95	1.33	0.40	1.15	0.32	0.93	0.99	1.15	1.22	1.01	1.18	0.44	0.55	0.72
arrestin, beta 2	0.30	1.10	0.98	0.24	0.62	0.31	1.05	0.85	0.87	1.08	0.35	0.45	0.31	0.99	0.60
hypothetical protein FLJ20399	0.38	0.89	0.83	0.37	0.71	0.43	0.77	0.82	0.94	0.90	0.70	1.05	0.39	0.40	0.82
interferon regulatory factor 4	0.69	0.84	1.03	0.36	0.75	0.51	1.02	0.84	1.09	1.14	0.02	0.42	0.27	0.69	0.50
G protein-coupled receptor 43	0.30	0.81	0.62	0.37	1.30	0.25	1.09	0.53	1.32	1.27	0.97	0.72	0.31	0.35	0.39
Epstein-Barr virus induced gene 2	0.09	0.99	1.02	0.21	0.82	0.09	1.20	0.30	1.02	1.13	0.31	1.03	0.18	1.09	0.90
testis zinc finger protein	0.42	1.10	0.44	1.40	1.10	0.44	0.90	0.34	1.09	0.55	0.22	0.63	0.87	0.33	0.49
v-myc viral oncogene homolog	0.28	0.93	0.53	0.40	0.39	0.20	0.76	0.29	0.56	0.88	0.15	0.56	0.65	1.17	0.80
v-myc viral oncogene homolog	0.29	0.95	0.46	0.66	0.55	0.28	1.08	0.60	0.97	1.25	0.57	0.33	0.45	0.40	0.21

※ 発現上昇 発現低下

表6 遺伝子傷害性物質のみで共通性を持って発現変化した遺伝子

Gene Title	5FU	6MP	AraC	BLM	KB-O ₃	PQ	AF2	FZ	EMS	MNNG	MQ	NaCl	PA	Chx	EtOH
p21	1.12	0.95	11.14	4.45	3.22	1.23	5.38	1.10	1.55	1.30	2.98	1.45	0.96	0.66	1.17
testis zinc finger protein	0.28	0.93	0.53	0.40	0.39	0.76	0.29	0.20	0.56	0.88	0.15	0.56	0.65	1.17	0.80
growth arrest and DNA-damage-inducible, alpha	1.38	1.11	6.26	1.74	1.18	1.17	3.97	1.73	1.27	0.94	2.62	0.78	0.50	1.60	1.86
solute carrier family 7	2.29	1.11	1.60	1.23	1.47	1.10	1.71	2.48	1.35	0.85	5.38	0.95	1.98	0.49	1.84
calreticulin	3.32	1.94	0.83	3.18	1.11	0.86	0.75	3.40	0.79	0.97	1.14	1.07	2.44	0.82	0.85
hypothetical protein FLJ90005	1.66	0.79	3.44	2.02	1.02	0.90	2.99	1.43	1.16	1.09	2.77	0.97	1.04	1.88	1.36
thyroid peroxidase autoantibody light chain variable region	0.71	0.99	0.84	1.48	1.63	1.85	2.43	1.04	0.74	1.85	1.60	1.55	1.11	1.10	1.27
60S Ribosomal Protein L7	1.94	1.87	0.60	1.38	1.87	0.81	0.99	2.12	1.96	0.69	1.09	0.70	1.76	1.11	1.21
BTG3 associated nuclear protein	2.69	1.79	1.00	2.33	0.94	1.27	0.90	1.85	0.98	1.04	1.19	0.82	1.60	1.82	1.74
prostate differentiation factor	0.85	1.04	68.32	4.18	1.50	1.47	7.39	1.11	1.23	2.87	1.16	1.13	0.70	0.71	1.02
dihydrofolate reductase	2.61	1.78	1.01	1.98	0.81	0.92	1.28	2.95	1.00	0.86	1.11	1.08	1.82	0.62	0.95
calnexin	0.44	0.56	0.99	0.61	2.56	0.93	1.02	0.41	1.22	1.30	1.28	1.80	0.49	1.36	1.27
SEC23 interacting protein	0.81	0.69	0.74	0.76	2.67	0.99	0.65	0.99	0.45	0.18	0.43	1.61	1.22	2.24	1.45

表7 定量的RT-PCRデータとGeneChipデータの比較 (RT-PCR / GeneChip)

Sample	PLAB	P21	ATF3	GADD45	PPM1D	EIF5A	PSMD11	MGC450	CMP	LTA	CDC	SLC	GPR43	CCL2	TZFP
6-MP	1.2/1.0	1.6/1.0	1.4/1.2	1.0/1.1	1.1/1.2	1.1/2.7	1.2/1.0	1.1/1.2	1.1/1.0	0.8/1.6	0.9/1.3	0.9/1.3	1.2/1.0	1.1/0.7	1.1/0.9
5-FU	0.6/0.9	1.3/1.1	1.9/1.9	0.8/1.4	2.1/2.6	1.3/3.7	1.1/2.1	2.0/1.5	1.4/1.5	0.6/1.2	1.1/1.7	0.8/1.2	0.4/0.1	0.3/0.1	0.5/0.3
FZ	1.0/1.1	0.9/1.1	4.1/4.1	1.1/1.7	1.3/2.8	1.3/5.8	1.1/2.1	1.0/2.5	1.0/2.3	0.7/0.9	0.9/1.2	0.8/1.4	0.5/0.1	0.4/0.5	0.8/0.2
BLM	1.28/4.2	4.9/4.5	2.8/2.3	3.9/1.7	3.9/3.3	1.9/4.4	1.2/1.3	1.6/1.0	1.0/1.3	0.9/1.4	1.0/1.0	1.0/1.6	1.0/0.2	0.9/1.5	1.3/0.4
KB-O ₃	4.1/1.5	3.3/3.2	2.2/1.3	3.0/1.2	1.9/1.6	1.4/1.8	1.3/1.1	1.8/1.0	1.2/1.0	0.9/0.7	1.1/1.3	1.1/1.0	0.9/0.6	0.7/0.7	1.4/0.4
PQ	1.5/1.5	1.2/1.2	1.0/1.1	1.3/1.2	1.1/1.2	0.8/1.5	1.0/0.8	0.9/1.5	0.5/0.5	0.8/0.8	0.7/0.9	0.9/1.0	0.7/1.2	1.0/1.1	0.1/0.8
EMS	2.0/1.2	1.5/1.8	0.9/1.8	1.2/1.3	1.5/1.3	1.3/1.3	1.1/1.3	1.1/1.8	0.8/0.4	0.7/0.3	0.9/0.9	1.0/0.9	0.6/1.0	1.0/1.0	0.1/0.8
AraC	194.6/68.3	135.1/1.1	6.6/4.0	24.1/6.3	3.7/4.6	1.6/1.2	2.1/0.9	6.9/3.0	0.5/0.7	0.9/0.7	0.5/0.5	0.6/0.6	0.5/1.0	0.5/0.4	0.3/0.5
MQ	1.3/1.2	2.1/3.0	4.2/1.2	3.4/2.8	2.2/2.4	1.7/1.2	2.4/2.8	4.8/5.1	0.4/0.7	0.4/0.2	0.5/1.0	0.3/0.9	0.1/0.3	0.2/0.3	0.8/0.2
AF2	1.25/7.4	4.5/5.4	4.1/6.1	7.3/4.0	4.0/2.8	2.8/0.8	4.3/2.7	8.1/6.0	0.4/0.8	0.3/0.1	0.5/0.5	0.7/1.0	0.2/0.3	0.2/0.1	0.2/0.3
MNNG	1.8/2.9	1.0/1.3	0.9/1.8	1.1/0.9	1.0/1.3	1.0/0.9	1.1/1.2	0.9/1.6	0.8/0.8	0.8/0.4	0.8/0.4	0.9/0.9	0.6/1.1	1.2/0.7	0.3/0.9
PA	0.5/0.7	0.9/1.0	3.2/1.4	0.2/0.5	1.5/1.4	1.3/5.2	1.3/1.7	3.6/2.9	1.3/1.2	1.1/1.5	1.2/2.0	1.4/1.2	1.3/0.2	0.9/1.4	0.8/0.7
NaCl	1.3/1.1	1.0/1.5	10.1/0.8	3.9/0.8	4.2/2.5	1.1/1.0	1.1/1.4	0.6/0.9	1.1/1.5	1.2/1.4	1.3/0.9	0.8/0.8	0.8/1.0	0.6/0.7	1.0/0.6
EtOH	0.5/1.0	1.1/1.2	1.9/1.9	0.3/1.8	2.8/1.6	1.3/1.7	1.4/0.7	4.6/0.7	1.3/1.0	1.1/1.2	1.2/1.5	1.1/1.2	1.1/0.9	0.6/0.8	2.9/0.8
chx	1.0/0.7	1.1/0.7	7.1/4.0	10.5/1.8	3.5/1.3	1.4/0.9	1.8/1.0	1.1/2.0	1.9/0.7	1.8/1.4	1.7/1.5	1.5/1.0	1.2/1.1	0.5/0.4	6.8/1.2

up regulated in genechip up regulated in RT-PCR (sample/control>2)
 down regulated in genechip down regulated in RT-PCR (sample/control<0.5)

表8 RT-PCR法を用いた用量、経時変化に関する詳細な検討

	dose (ug/ml)	time (hr)	PLAB	P21	ATF3	PPM1D	EIF5A	PSMD11	MGC450	CMP	LTA	CDC	SLC	GPR43	CCL2
			209	4	6.9	4.1	1.6	1.4	1.2	1.2	1.1	0.9	0.9	1.1	1.0
KB-O ₃	417.5	1	1.2	0.8	1.3	0.5	0.9	1.1	0.7	1.2	0.9	1.6	0.9	1.3	1.0
		4	10.7	6.0	2.2	1.3	1.0	1.1	1.0	0.7	0.9	0.9	0.7	1.0	0.8
		8	23.2	5.1	6.8	2.3	0.9	0.9	0.9	0.9	0.8	0.8	0.8	0.7	0.4
EMS	835	4	22.2	9.4	3.0	1.6	1.0	1.0	0.9	0.8	0.6	0.8	0.8	0.9	0.4
		4	0.6	1.4	2.1	1.2	0.9	1.1	1.2	0.7	0.4	1.1	0.8	0.6	0.3
		1	0.6	0.8	2.3	0.5	1.0	1.2	0.9	1.0	1.0	1.5	0.9	1.0	0.6
PQ	150	4	1.1	1.5	2.0	1.3	1.3	1.1	1.1	0.9	0.8	1.4	1.2	1.1	0.7
		8	1.0	1.7	1.4	1.2	0.7	0.7	0.8	1.1	0.5	0.8	0.9	0.4	0.1
		4	0.7	1.7	2.7	1.2	0.8	0.9	1.2	1.2	0.5	1.3	0.8	0.5	0.3
MNNG	0.0025	4	0.7	0.9	1.3	0.6	0.9	0.9	1.1	0.7	0.6	1.2	1.3	0.8	0.8
		1	0.5	1.0	1.4	0.8	0.7	0.9	1.5	0.7	0.7	0.9	0.8	0.7	0.4
		4	0.9	1.7	3.3	1.5	1.2	1.2	1.1	1.5	0.5	1.3	0.9	0.8	0.3
ENU	10	4	0.5	0.9	1.1	1.2	0.9	0.9	0.7	1.1	0.7	1.4	0.9	0.5	0.2
		4	0.7	1.3	2.9	1.0	1.0	1.1	0.9	1.2	0.4	1.2	0.9	0.6	0.3
		1	0.6	1.0	1.9	0.4	0.8	0.9	0.9	0.9	0.8	1.2	0.7	1.0	0.6
ENU	20	4	1.0	2.5	1.9	1.3	0.8	0.9	1.0	0.7	0.4	0.8	0.7	0.5	0.3
		8	1.0	1.7	1.9	1.2	0.6	0.7	0.8	1.2	0.5	0.8	0.8	0.4	0.2
		4	2.9	4.3	3.3	1.5	0.8	1.0	0.8	1.0	0.4	1.0	0.8	0.6	0.3

up regulated in RT-PCR (sample/control>2)
 down regulated in RT-PCR (sample/control<0.5)

表 10 グリタゾン化合物に共通して変化した遺伝子の機能分類

4hr	24hr	72hr
drug metabolism & excretion (6)	cell cycle (7)	lipid metabolism (5)
PPAR response transcription (5)	lipid metabolism (7)	cell cycle (4)
signal pathway (6)	signal pathway (7)	signal pathway (3)
lipid metabolism (5)	oxidoreductase (3)	oxidative stress (3)
oxidoreductase (4)	Inflammatory (2)	transcription (2)
stress response (2)	GST (2)
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表 11 トログリタゾンに特異的に発現変化した遺伝子

Pioglitazone				Rosiglitazone				Troglitazone				Gene Name														
20 mg/kg		200 mg/kg		20 mg/kg		200 mg/kg		20 mg/kg		200 mg/kg			log ₂ T score													
1h	4h	24h	72h	1h	4h	24h	72h	1h	4h	24h	72h															
0.39	1.47	0.51	0.80	1.12	0.70	1.15	1.49	0.36	0.64	0.59	0.78	0.29	0.78	0.78	1.23	0.55	1.11	0.85	0.23	2	2	chemokine (C-X-C motif) ligand 1				
1.43	2.48	0.36	0.50	1.17	1.57	0.64	0.70	0.73	1.96	0.83	0.51	1.70	1.75	0.49	0.51	0.66	0.96	0.97	0.53	3	3	aromatase 2				
3.04	1.08	1.34	2.31	3.08	0.77	0.93	2.95	1.54	1.04	1.17	2.36	2.11	0.91	1.43	2.28	0.44	0.97	0.81	2.57	2.31	0.99	0.54	2.88	3	3	RKEN cDNA 2700043D08 gene
1.26	1.25	0.57	1.84	1.47	0.99	0.52	1.21	1.39	1.78	0.82	1.41	1.31	0.59	0.51	1.45	0.69	0.94	2.79	1.29	1.04	1.09	0.59	1.74	2	2	Tnfr-induced adipose-related protein
0.63	0.96	0.81	1.84	1.42	0.64	1.13	1.26	1.96	1.02	0.78	1.36	1.24	0.83	0.83	1.78	2.21	2.27	1.49	2.76	0.94	0.96	1.00	1.21	2	2	Kruppel-like factor 9
0.95	1.56	0.98	1.04	1.52	1.28	1.21	0.81	1.55	2.01	0.99	0.80	1.19	1.06	1.29	1.31	0.90	2.17	0.85	0.86	0.82	0.97	0.97	0.60	2	2	coractin
1.11	0.77	0.48	0.83	1.15	0.58	0.78	0.29	1.53	0.67	0.84	0.62	1.76	0.70	0.35	0.58	1.32	2.94	2.28	0.67	1.10	0.73	0.83	0.49	2	2	slc41a2
1.21	1.14	1.39	0.25	1.00	1.27	1.73	0.54	1.05	1.63	1.67	1.12	1.02	1.01	1.41	0.73	1.16	0.98	3.19	0.41	1.23	0.98	1.54	0.39	2	2	Down syndrome critical region homolog 1 (DSCR1)
9.59	0.32	1.12	0.80	2.85	0.92	0.41	0.38	3.18	0.93	0.33	0.38	3.66	0.96	1.47	0.45	0.66	0.71	1.02	0.24	0.76	1.29	0.63	1.67	2	2	RKEN cDNA 1700010AD0 gene
2.03	0.78	0.65	1.32	2.48	0.54	1.11	0.88	2.04	0.55	0.87	0.90	2.19	0.85	0.74	1.06	2.67	0.82	0.86	0.95	2.67	0.52	0.74	0.54	2	2	ATP binding protein associated with cell di
2.03	1.83	0.18	1.25	0.57	1.29	0.89	0.59	0.63	1.68	2.24	0.88	0.77	1.41	0.10	1.18	3.13	2.77	0.65	0.73	0.71	1.29	0.25	1.09	5	4	serum amyloid A 2
1.68	0.68	0.25	1.00	0.56	2.03	0.74	0.74	0.42	1.81	1.24	1.02	0.71	1.49	0.13	1.49	1.93	1.03	0.72	0.65	3.78	1.46	0.26	0.76	4	3	serum amyloid A 2
2.02	2.02	0.64	0.89	0.80	1.30	1.02	0.82	1.10	1.77	0.23	1.00	0.54	1.61	1.14	0.73	1.21	0.93	0.16	1.50	3.93	1.31	0.79	1.38	4	3	lipocain 2
9.92	1.47	1.00	1.80	0.30	0.27	0.73	1.25	0.97	1.33	0.95	0.65	8.17	0.71	0.73	1.10	1.02	0.93	0.17	0.87	7.16	1.17	0.75	0.78	2	2	RKEN cDNA 4933427L07 gene
1.70	2.07	1.42	1.67	1.56	0.25	1.10	0.86	1.68	2.14	0.92	1.48	2.03	1.53	0.58	0.93	1.33	1.29	1.44	1.20	1.10	0.96	0.27	0.26	2	2	ATP synthase mitochondrial F1 complex as
0.84	0.71	0.93	1.32	0.85	0.96	1.02	1.29	0.53	0.78	1.04	1.18	0.52	0.79	2.17	1.40	0.44	0.71	1.34	1.44	0.43	0.73	1.14	0.69	2	2	Down syndrome critical region homolog 5 (DSCR5)
0.96	0.90	0.53	0.66	1.81	0.82	0.48	0.47	0.91	0.83	0.58	0.84	1.51	0.99	0.96	0.84	1.31	0.40	0.58	0.77	1.17	0.59	0.43	0.58	2	2	heat shock protein 16
0.41	0.47	0.82	0.52	0.58	0.81	1.11	0.69	0.51	0.41	0.87	0.94	0.33	1.12	1.56	0.48	0.35	0.52	1.28	0.43	0.38	0.69	0.85	0.93	3	2	solute carrier family 14 (urea transporter)
1.21	1.14	1.39	0.25	1.00	1.27	1.73	0.54	1.05	1.83	1.67	1.12	1.02	1.01	1.41	0.73	1.16	0.66	3.19	0.41	1.23	0.98	1.54	0.39	3	2	Down syndrome critical region homolog 1 (DSCR1)
0.70	0.81	0.85	0.51	0.29	1.54	0.89	0.41	0.34	0.48	0.12	0.34	0.45	1.03	1.35	0.65	0.27	1.05	1.46	0.44	0.07	0.56	1.23	1.14	3	2	lysosomal-associated protein transmembr
0.84	0.75	0.71	0.58	0.82	1.15	0.71		1.90	0.45	0.51	0.54	0.23	1.14	0.98		1.73	0.19	0.54	0.97	2.83	0.91	0.82	0.31	3	2	multiple inositol polyphosphate histidine ph
0.54	0.52	0.58	0.10	0.92	0.79	0.83	0.58	0.45	0.06	0.20	0.08	2.45	0.43	1.06	0.71	0.11	0.34	0.24	0.57	1.06	1.39	0.97	0.52	3	2	zinc finger protein 207

表 12 トログリタゾンに特徴的に変化した遺伝子の機能分類

4hr	24hr	72hr
cell growth (12)	mitochondrion function (7)	signal pathway (12)
immune and inflammatory (12)	transcription (7)	mitochondrion function (10)
transcription (12)	Inflammatory (5)	Inflammatory (7)
ion transporter (10)	signal pathway (5)	transcription (5)
stress response (6)	oxidoreductase (4)	acute phase protein (4)
signal pathway (6)	structural molecular (4)	cell growth and apoptosis (4)
lipid metabolism (5)	oxidative stress (3)	ion transporter (4)
oxidoreductase (5)	amyloid (3)	lipid metabolism (4)
protein translation (4)	cell growth (2)	ubiquitin (4)
apoptosis (3)	acute phase protein (2)	oxidoreductase (3)
structural molecular (3)	oxidative stress (2)
acute phase protein (2)		structural molecular (2)
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