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Ingenuity Canonical Pathways	-log(p-value)	Ratio	Molecules
Protein Ubiquitination Pathway	1.59E+01	7.78E-02	PSMB3,P
Antigen Presentation Pathway	3.86E+00	9.52E-02	CALR,PD
CMP-N-acetylneuraminate Biosynthesis I (E	3.30E+00	1.11E-01	CMAS,N
Lipid Antigen Presentation by CD1	3.08E+00	1.00E-01	CALR,PD
Colanic Acid Building Blocks Biosynthesis	2.36E+00	5.56E-02	UGDH,G
Adenine and Adenosine Salvage VI	2.15E+00	2.00E-01	ADK
UDP-D-xylose and UDP-D-glucuronate Bios	1.85E+00	1.43E-01	UGDH
Aldosterone Signaling in Epithelial Cells	1.62E+00	2.37E-02	HSP90B1
2-ketoglutarate Dehydrogenase Complex	1.55E+00	1.11E-01	DHTKD1
Heme Degradation	1.55E+00	9.09E-02	BLVRB
GDP-mannose Biosynthesis	1.38E+00	7.69E-02	GMPPA
Hypoxia Signaling in the Cardiovascular Sys	1.09E+00	2.94E-02	HSP90B1
Oleate Biosynthesis II (Animals)	1.05E+00	5.26E-02	UFSP2
Caveolar-mediated Endocytosis Signaling	1.01E+00	2.35E-02	ARCN1,C
γ-glutamyl Cycle	9.91E-01	3.57E-02	GGCT

Rat:  
[PSs induced at any protocol] & BR  
Down (173)

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Upstream Fold	Char	Molecule	T Predicted Activation	Notes	p-value of (Target molecules in d
XBP1		transcripto	Inhibited	-5.275 bias	1.01E-30 ALG12,ARCN1,BET1,
NFE2L2		transcripto	Inhibited	-4.838 bias	5.76E-17 APBA3,COPS5,DNAJ
HNF4A		transcripto			2.77E-10 ADCK3,AP3M1,Apoc
ATF6		transcripto			9.18E-05 DNAJC3,HSP90B1,LM
PLAG1		transcripto			5.78E-03 ATF5,CLTB,CRIP2
THOC1		transcripto			6.61E-03 CALR
ONECUT		transcripto			1.01E-02 ARL1,COPSTA,NUTF
MYCN		transcripto		-0.447	2.15E-02 PDIA4,PSMA7,PSMB
ATF4		transcripto			4.18E-02 APBA3,ATF5,MRPS7
TP53		transcripto		-0.898	4.66E-02 ADCK3,CRIP2,UCI12

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Ingenuity Canonical Pathways	-log(p-value)	Ratio	Molecules
EIF2 Signaling	2.13E+01	7.98E-02	RPL11,RP
Regulation of eIF4 and p70S6K Signaling	6.03E+00	3.43E-02	RPS7,RPS
mTOR Signaling	5.39E+00	2.82E-02	RPS7,RPS
Thyroid Hormone Biosynthesis	2.17E+00	1.43E-01	CTSD
Glioma Invasiveness Signaling	2.12E+00	3.03E-02	CD44,TIM
2-ketoglutarate Dehydrogenase Complex	2.05E+00	1.11E-01	OGDH
Myo-inositol Biosynthesis	2.05E+00	1.25E-01	ISYNA1
Virus Entry via Endocytic Pathways	1.77E+00	1.98E-02	FLNB,AP2
Sucrose Degradation V (Mammalian)	1.75E+00	5.26E-02	ALDOA
Rac Signaling	1.64E+00	1.56E-02	CFL1,CD4
Chondroitin Sulfate Degradation (Metazoa)	1.51E+00	4.35E-02	CD44
Dermatan Sulfate Degradation (Metazoa)	1.48E+00	4.35E-02	CD44
TCA Cycle II (Eukaryotic)	1.31E+00	2.50E-02	OGDH
Gluconeogenesis I	1.30E+00	2.13E-02	ALDOA
Pyrimidine Deoxyribonucleotides De Novo Biosynth	1.28E+00	2.27E-02	NME2
Glycolysis I	1.28E+00	2.44E-02	ALDOA
Wnt/β-catenin Signaling	1.25E+00	1.14E-02	SOX4,CD

Rat:  
[PSs induced at any protocol] & BR  
Up (65)

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Upstream Fold	Char	Molecule	Predicted Activation	Notes	p-value of (Target m
MYCN		transcripto	Activated	3.493	7.37E-22 ALDOA,E
MYC		transcripto	Activated	2.883 bias	2.59E-09 ALDOA,A
HOXD10		transcripto			3.34E-04 CD44,RP
SOX7		transcripto			4.34E-03 SOX4
RFX4		transcripto			4.34E-03 RPL30
Esr1-Estr		complex			6.51E-03 CTSD
KHDRBS		transcripto			8.67E-03 CD44
SIX4		transcripto			8.67E-03 ALDOA
TADA3		transcripto			1.08E-02 CTSD
ASCL2		transcripto			1.51E-02 CTSD
Bcl9-Cbp		complex			1.94E-02 CD44
RFX2		transcripto			1.94E-02 RPL30
FOS		transcripto		0.152 bias	2.17E-02 CD44,RP
CTNNA1		complex			2.37E-02 CD44
BCL10		transcripto			2.58E-02 CD44
SMARCA		transcripto			2.63E-02 CD44,FLI
NSD1		transcripto			3.00E-02 CTSD

## Mouse – Rat comparison

CCL4	Mouse (Max 20mg/kg)			Rat (Max 300mg/kg)	
	Down (induction +)	Up (induction +)	Down (induction -)	Down (induction +)	Up (induction +)
	89	13	1798	173	65
Canonical Pathway	Protein Ubiquitination Pathway		EIF2 Signaling	Protein Ubiquitination Pathway	EIF2 Signaling
			Oxidative Phosphorylation		
			Mitochondrial Dysfunction		
			Acute Phase Response Signaling		
Upstream TF	XBP1	(PAX6)	HNF4A	XBP1	MYCN
	NFE2L2	(XBP1)	MYCN	NFE2L2	MYC
		(SIRT1)	MYC	HNF4A	
			NFE2L2	ATF6	

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## VPA

### Mouse:

- [PSs induced at any protocol] & BR Down
- [PSs induced at any protocol] & BR Up

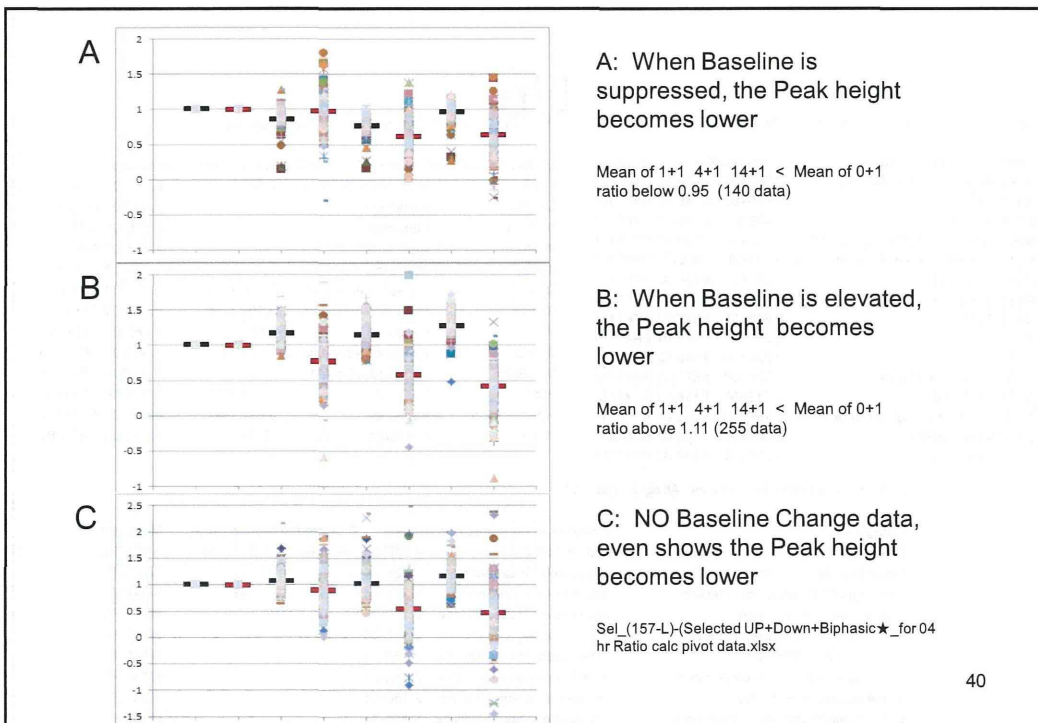
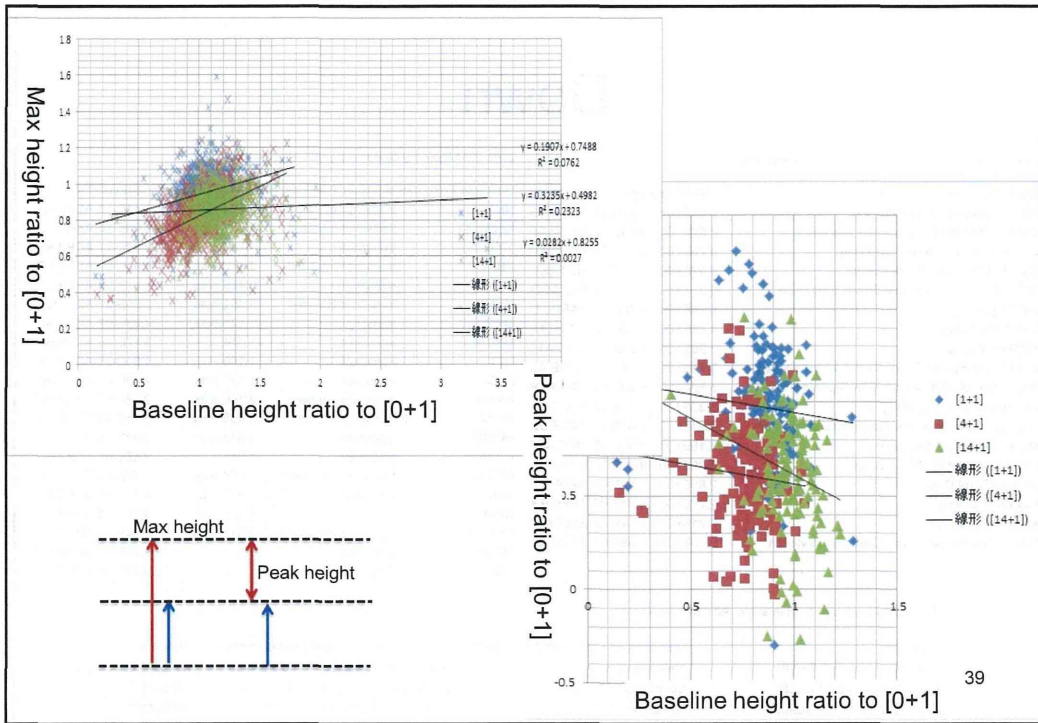
TTG149	TTG2: A)Valproic acid sodium salt, B)Aspirin	A)100mg/kg, B)0, 10, 30, 100mg/kg
TTG150	TTG2: A)Valproic acid sodium salt, B)Thalidomide	A)100mg/kg, B)0, 100, 300, 1000mg/kg
TTG151	TTG2(14d+1d): A)Valproic acid sodium salt, B)Valproic acid sodium salt	A)100mg/kg, B)0, 50, 150, 500mg/kg
TTG157	(0d+1d) Valproic acid sodium salt	0, 50, 150, 500mg/kg
TTG193	TTG4(1d+1d): A)Valproic acid sodium salt, B)Valproic acid sodium salt	A)100mg/kg, B)0, 50, 100, 500mg/kg
TTG194	TTG4(2d+1d): A)Valproic acid sodium salt, B)Valproic acid sodium salt	A)100mg/kg, B)0, 50, 100, 500mg/kg
TTG195	TTG4(4d+1d): A)Valproic acid sodium salt, B)Valproic acid sodium salt	A)100mg/kg, B)0, 50, 100, 500mg/kg

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# Down

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Ingenuity Canonical Pathways	-log(p-value Ratio)	Molecules	Upstream Fold	Char	Molecule	Predicted Activation Notes	p-value of Target	Target
Protein Ubiquitination Pathway	9.35E+00	9.26E-02 PSMB3,B	HNF4A		transcript	Inhibited -3.406 bias	4.44E-16	ACOX2,A
Clathrin-mediated Endocytosis Signaling	7.57E+00	9.60E-02 APOE,AF	NFE2L2		transcript	Inhibited -4.551 bias	8.90E-15	AKR1A1,I
Acute Phase Response Signaling	6.70E+00	9.39E-02 IL6ST,TTI	TP53		transcript	-1.584	2.84E-11	ACP2,AC
Renal Cell Carcinoma Signaling	6.47E+00	1.39E-01 MET,SLC	XBP1		transcript	Inhibited -3.478 bias	4.96E-08	APOA1,B
NRF2-mediated Oxidative Stress Response	6.31E+00	8.72E-02 FTL,SOD	VHL		transcript	0.485 bias	7.61E-08	AHCYL1,
EIF2 Signaling	6.18E+00	8.46E-02 PABPC1,	HNF1A		transcript	Inhibited -3.651 bias	2.25E-07	Akr1c12//
LXR/RXR Activation	4.84E+00	8.63E-02 APOE,TT	MYC		transcript	-0.625 bias	4.69E-07	ACTB,AD
TR/RXR Activation	3.99E+00	8.26E-02 SLC2A1,F	MYCN		transcript	-1.048	3.17E-06	ACTB,B2
IL-12 Signaling and Production in Macrophages	3.74E+00	7.01E-02 APOE,AL	HTT		transcript	1.109	1.04E-05	APOA1,A
Regulation of eIF4 and p70S6K Signaling	3.36E+00	6.29E-02 EIF1AY,R	FOS		transcript	-1.455 bias	2.20E-05	ACP5,AP
Prostate Cancer Signaling	3.33E+00	7.77E-02 PIK3C2A,	NR1H3		ligand-de	Inhibited -2.346 bias	2.28E-05	APOA1,C
Hypoxia Signaling in the Cardiovascular System	3.23E+00	1.03E-01 P4HB,UB	HIF1A		-2 transcript	Inhibited -3.455 bias	2.34E-05	APOE,EC
Macropinocytosis Signaling	3.15E+00	9.09E-02 MET,ARF	PPARA		ligand-de	0.673 bias	2.92E-05	APOA1,A
LPS-stimulated MAPK Signaling	2.96E+00	8.43E-02 IKBKG,PI	FOXA2		transcript	-1.941	3.65E-05	ALB,APO
Methylglyoxal Degradation I	2.85E+00	1.82E-01 HAGH,GI	EPAS1		-2 transcript	Inhibited -2.76 bias	1.57E-04	EGLN3,F
Paxillin Signaling	2.77E+00	6.84E-02 ARF6,PIK	JUN		transcript	-0.827 bias	4.16E-04	ACP5,AP
HIF1 $\alpha$ Signaling	2.71E+00	7.14E-02 SLC2A1,F	NFKBIA		transcript	-0.541 bias	4.35E-04	APOA1,A
NAD Phosphorylation and Dephosphorylation	2.70E+00	1.58E-01 ACP2,AC	PPARGC		transcript	Inhibited -2.946 bias	6.94E-04	C3,COX4
			HIF3A		transcript		9.76E-04	EPAS1,H
			HSF1		transcript	0.2	9.77E-04	CFLAR,H

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Category	Diseases or Functions Annotation	p-Value	Predicted Activation Notes	Molecules	
Liver Necrosis/Cell Death	necrosis of liver	9.62E-08	Increased 3.29 bias	API5,APC	41
Liver Necrosis/Cell Death	apoptosis of liver cells	2.73E-06	Increased 2.645	API5,ARF	
Liver Necrosis/Cell Death	cell death of liver cells	1.69E-05	Increased 2.819	API5,APC	

# Up

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Ingenuity Canonical Pathways	-log(p-value Ratio)	Molecules	Upstream Fold	Char	Molecule	Predicted Activation Notes	p-value of Target	Target
Molecular Mechanisms of Cancer	4.95E+00	7.22E-02 RAC2,RA	TP53		transcript	Activated 4.502	6.11E-08	ACAT1,A
IL-8 Signaling	4.81E+00	8.44E-02 RAF1,RA	JARID2		transcript		3.63E-06	CCND1,C
PTEN Signaling	4.48E+00	1.01E-01 FGFR3,R	ONECUT		transcript		2.39E-05	AGTR1,A
Non-Small Cell Lung Cancer Signaling	4.29E+00	1.20E-01 RAF1,FH	RORA		2 ligand-dej		7.75E-05	APOA4,C
Corticotropin Releasing Hormone Signaling	4.02E+00	8.97E-02 BRAF,GN	RORC		2 ligand-dej		1.08E-04	APOA4,C
Integrin Signaling	3.99E+00	8.65E-02 RAPGEF	CTNNB1		transcript	Activated 3.056 bias	2.24E-04	ACTN4,A
Protein Kinase A Signaling	3.71E+00	6.60E-02 RAF1,Cal	HNF4A		transcript	Activated 2.592 bias	3.27E-04	ABCC3,A
ERK5 Signaling	3.61E+00	1.32E-01 CTF1,FO	HTT		transcript	-0.983	4.58E-04	ALDOA,A
Melanoma Signaling	3.38E+00	1.40E-01 BRAF,RA	SMAD4		transcript	Activated 2.023 bias	4.96E-04	APOA4,A
HGF Signaling	3.32E+00	9.91E-02 RAPGEF	NEUROG		transcript	Inhibited -2.646	6.20E-04	ADD3,CC
Glutaryl-CoA Degradation	3.32E+00	1.67E-01 Acat2/Acc	PML		transcript	0.87 bias	6.95E-04	ANXA4,C
Melatonin Signaling	3.31E+00	1.11E-01 GNAI2,BF	FOS		2 transcript	0.632 bias	6.97E-04	ADAM12,
Tryptophan Degradation III (Eukaryotic)	3.29E+00	1.04E-01 AFMID,Ac	TCF3		transcript	Activated 2.56	8.08E-04	ARSA,BC
ERK/MAPK Signaling	3.26E+00	7.58E-02 RAPGEF						
Glioma Signaling	2.92E+00	8.85E-02 RAF1,Cal						

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Category	Diseases or Functions Annotation	p-Value	Predicted Activation Notes	Molecules	
Liver Steatosis	hepatic steatosis	4.57E-05	Decrease -2.507 bias	ANGPTL1	42
Hepatocellular Carcinoma	hepatocellular carcinoma	1.22E-04	-1.709	ADAM12,	
Liver Hyperplasia/Hyperproliferation	hepatocellular carcinoma	1.22E-04	-1.709	ADAM12,	
Hepatocellular Carcinoma	inoperable hepatocellular c	2.15E-04		BRAF,FG	
Liver Hyperplasia/Hyperproliferation	inoperable hepatocellular c	2.15E-04		BRAF,FG	
Hepatocellular Carcinoma	local hepatocellular carcino	2.15E-04		BRAF,FG	
Liver Hyperplasia/Hyperproliferation	local hepatocellular carcino	2.15E-04		BRAF,FG	
Hepatocellular Carcinoma	unresectable hepatocellula	2.15E-04		BRAF,FG	
Liver Hyperplasia/Hyperproliferation	unresectable hepatocellula	2.15E-04		BRAF,FG	

## 今後の計画

VPAの[1+1]データを加えての解析

Clofibrate の解析

TGP・Rat VPAおよびClofibrateデータの解析

★組み合わせデータの解析

- ・CCl<sub>4</sub> & CCl<sub>4</sub>、Clof、PB、
- ・VPA & VPA \*、Asp、Thalidomide
- ・Clofibrate & Clof、PCN、ATRA
- ・TBT & TBT、PB、Clof

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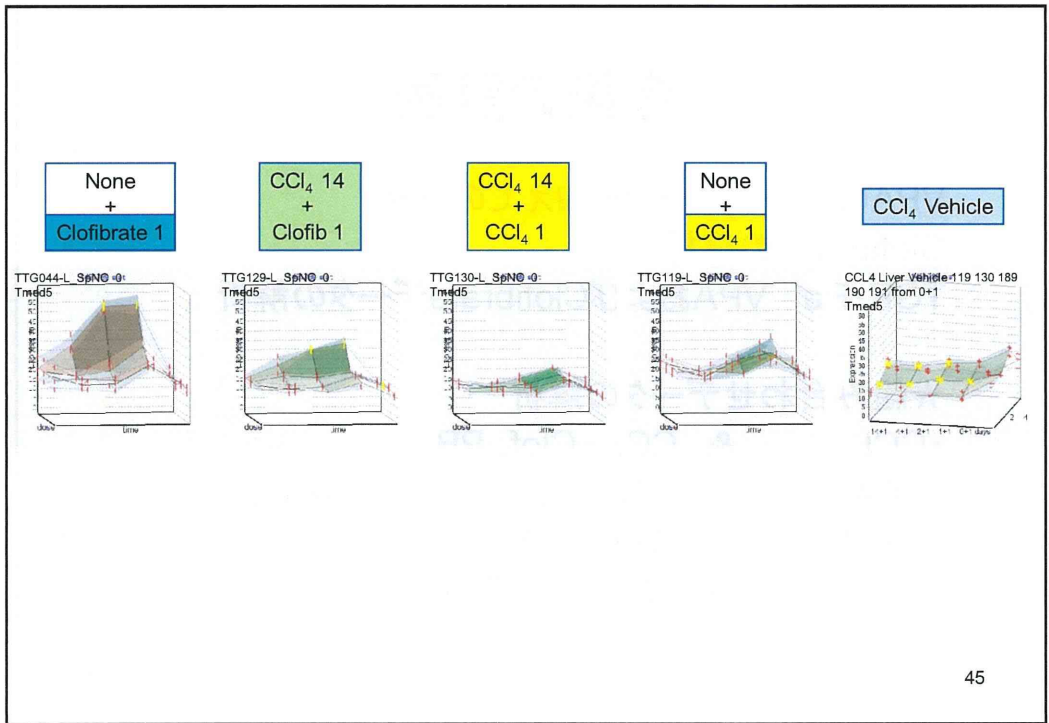
## CCL4

Mouse:

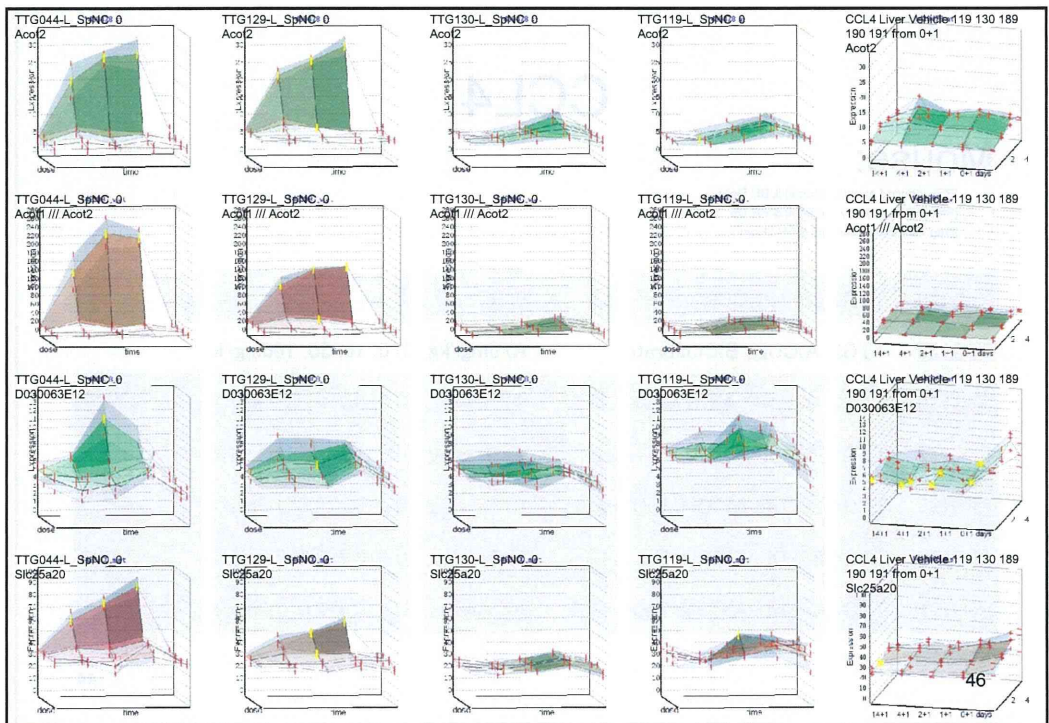
- ・ [PSs induced at any protocol] & BR Down
- ・ [PSs induced at any protocol] & BR Up
- ・ [Regardless of induction] & BR Down
- ・ [Regardless of induction] & BR Up

ITG119	TTG2(0d+1d): CCl4	0, 0.7, 2.0, 7.0 mg/kg
ITG129	TTG2: A)CCl4, B)Clofibrate	A) 5mg/kg, B) 0, 10, 30, 100mg/kg
ITG130	TTG2(14d+1d): A)CCl4, B)CCl4	A) 5mg/kg, B) 0, 0.7, 2.0, 7.0mg/kg
ITG131	TTG2: A)CCl4, B)Phenobarbital	A) 5mg/kg, B) 0, 15, 50, 150mg/kg
ITG189	TTG4(1d+1d): A)CCl4, B)CCl4	A) 5mg/kg, B) 0, 0.7, 2.0, 7.0mg/kg
ITG190	TTG4(2d+1d): A)CCl4, B)CCl4	A) 5mg/kg, B) 0, 0.7, 2.0, 7.0mg/kg
ITG191	TTG4(4d+1d): A)CCl4, B)CCl4	A) 5mg/kg, B) 0, 0.7, 2.0, 7.0mg/kg

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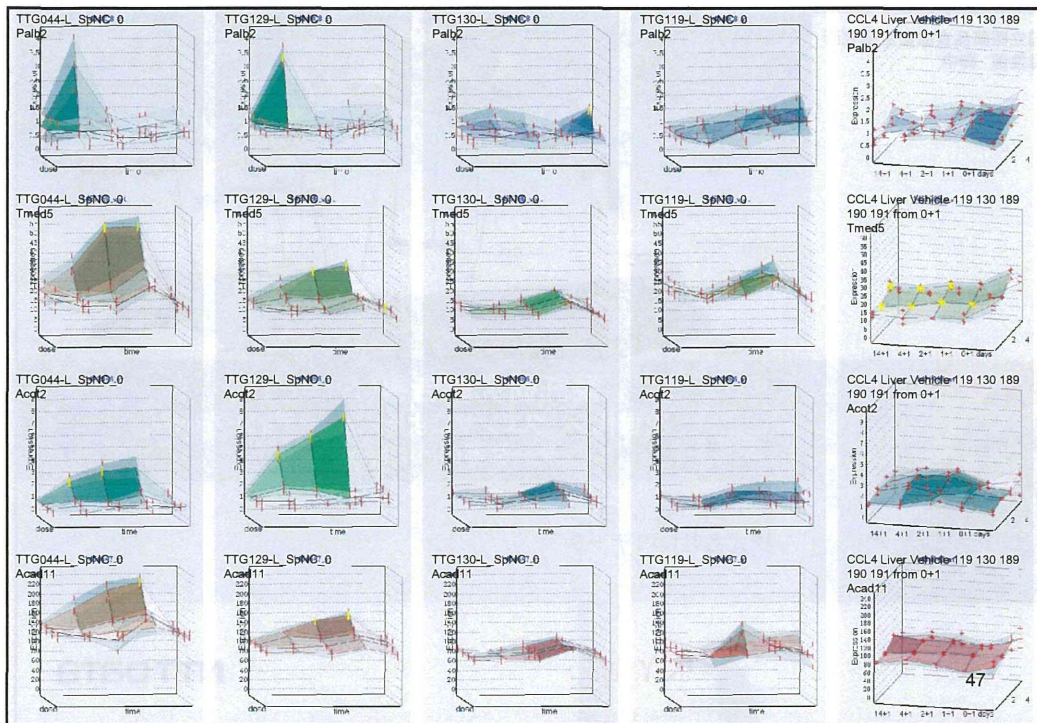


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## まとめ

- 反復投与によるB-ResとT-Resの関係、B-Resの誘導機構に関して、共通的分子メカニズムの存在が示唆された。
- B-Resに2通り以上の機構が存在することが示唆された: Xbp1 および Eif2。
- 組み合わせデータからのネットワーク抽出を加速する。
- 数日反復暴露による慢性影響の高精度予測の可能性が視野に入りつつあると考える。



委託研究報告書(STEP12)  
次世代シーケンサによるノンコーディングRNA  
データ等のin-silico定量化

2014年 1月 31日  
株式会社NTTデータ

TOKYO  
TOYOSU 3-3-3

NTT DATA

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1. 目的

NTT DATA

次世代シーケンサの読み取り速度が向上し、より広いダイナミックレンジでRNAの存在量を計測することが可能になってきた。

本業務では、平成23年度に実施した基礎研究を基に、ノンコーディングRNA (ncRNA) \*を含む200～300塩基程度のRNAシーケンスデータの処理過程において、ゲノム上へのマッピング精度を高め、定量化性能の向上を図る。

\* DNAからRNAに転写されるがタンパク質に翻訳されず、RNAのまま機能を果たしているRNA。様々な機能を担っていることが明らかになりつつある。

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