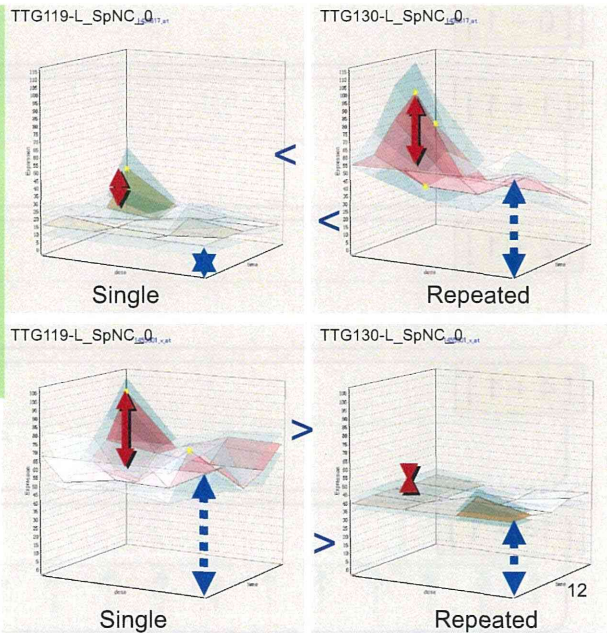


● 反復投与が毎回の投与による反応に大きな影響を与える物質

用語定義 Definition

↕ Transient Response (T-Res)  
過渡反応

↕ Baseline Response (B-Res)  
基線反応



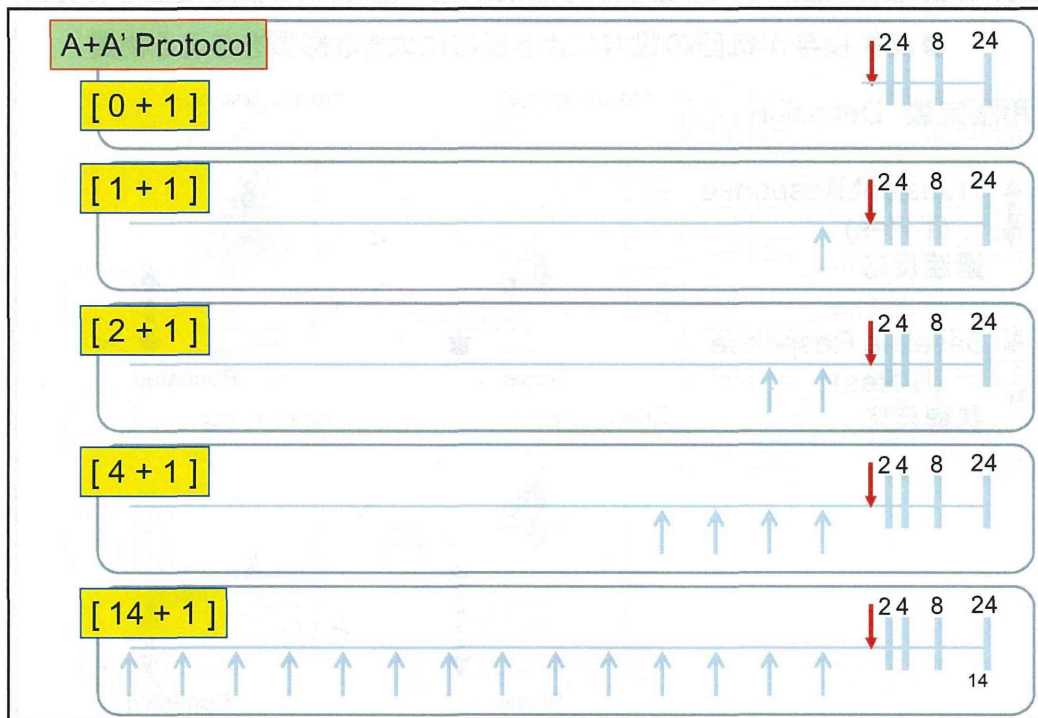
# CCL4

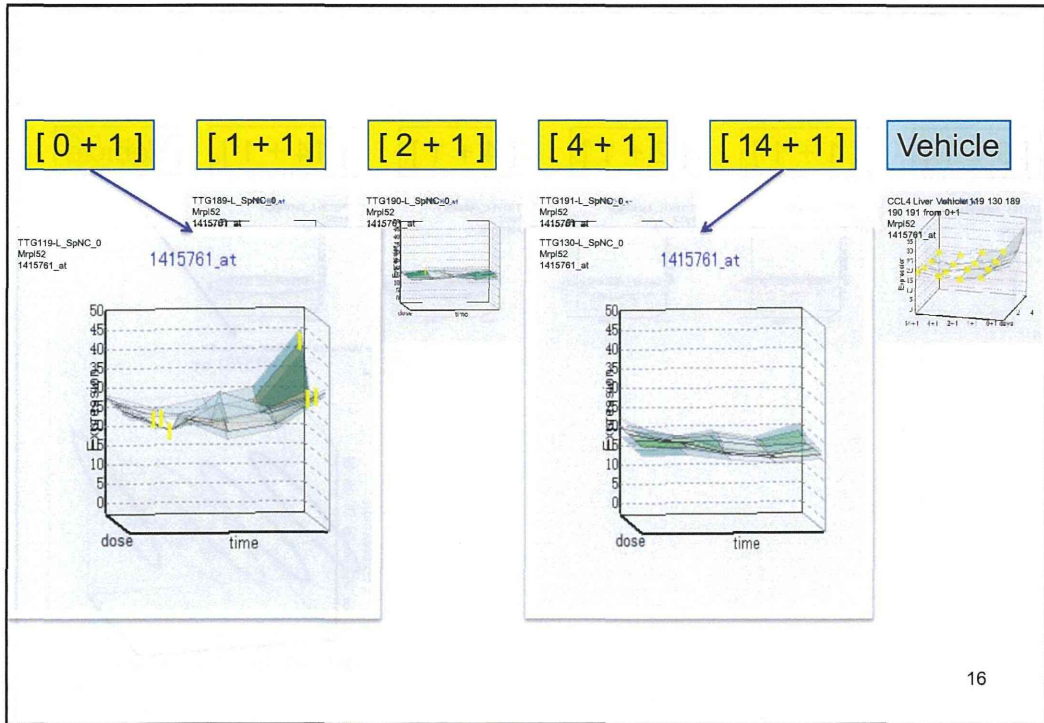
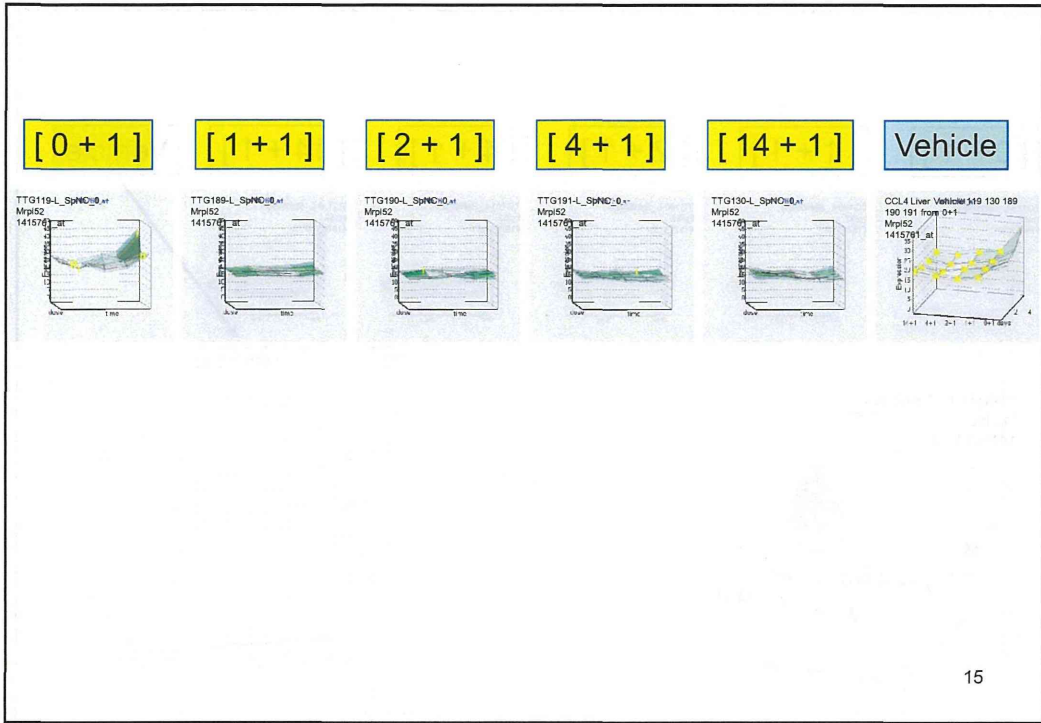
## Mouse:

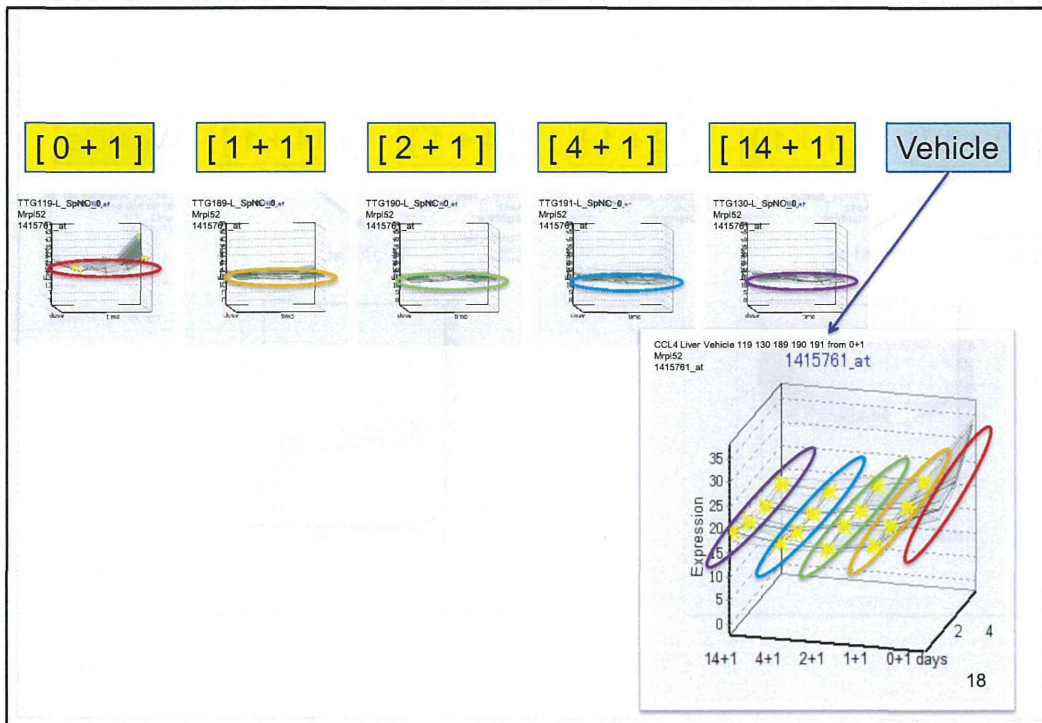
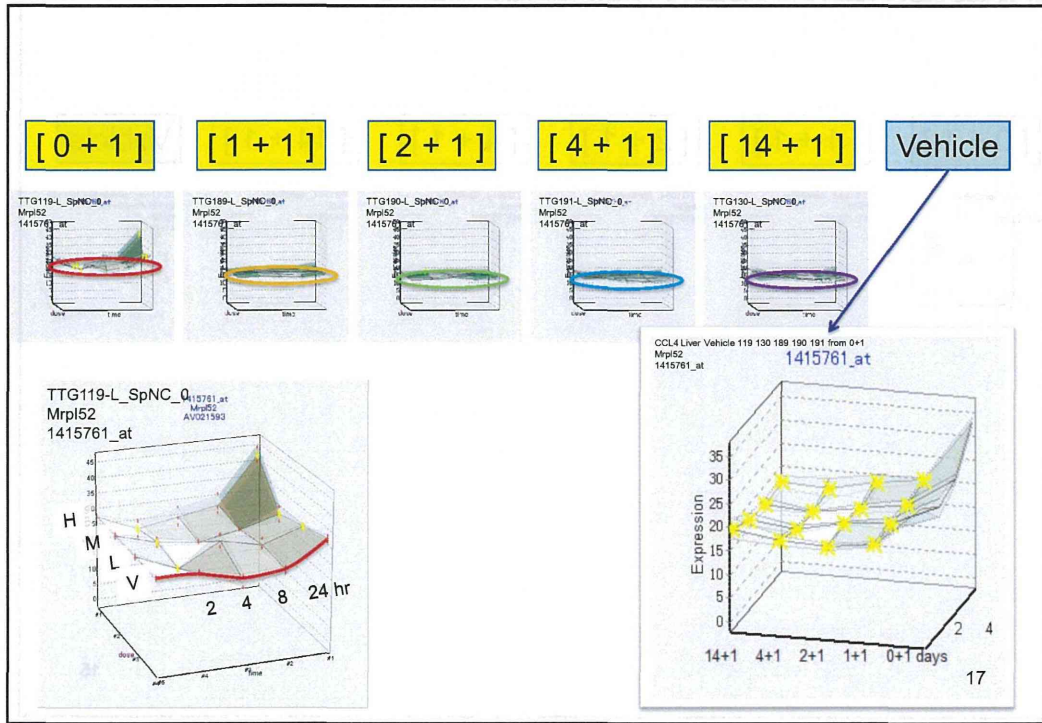
- [PSs induced at any protocol] & BR Down
- [PSs induced at any protocol] & BR Up
- [Regardless of induction] & BR Down
- [Regardless of induction] & BR Up

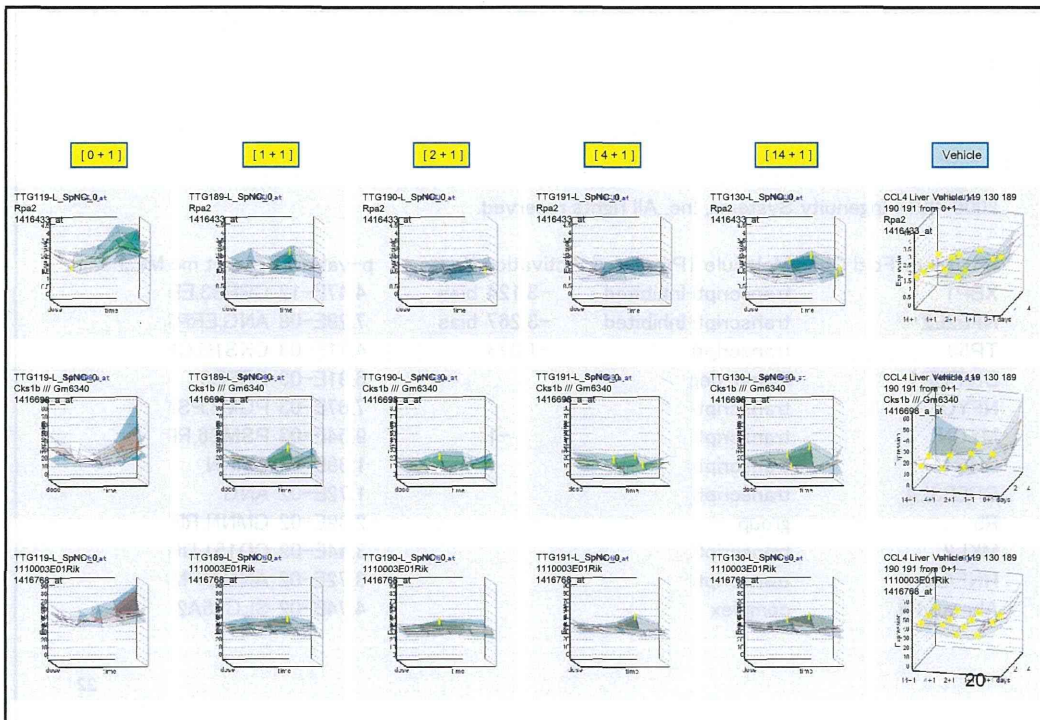
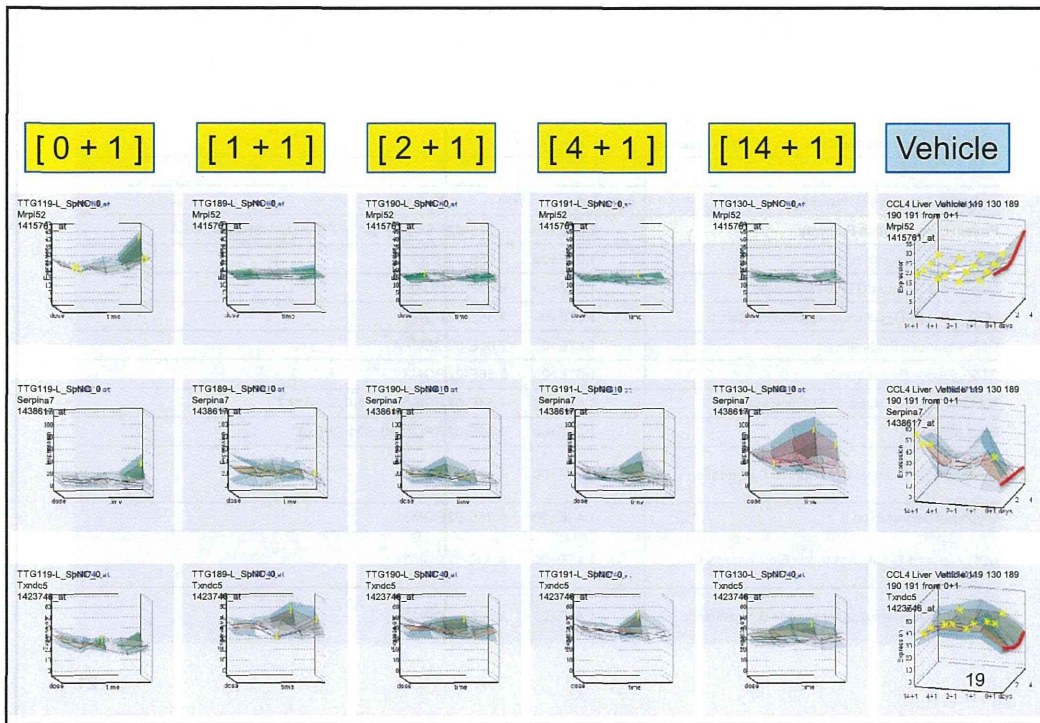
<a href="#">TTG119</a>	TTG2(0d+1d): CCl4	0, 0.7, 2.0, 7.0 mg/kg
<a href="#">TTG129</a>	TTG2: A)CCl4, B)Clofibrate	A) 5mg/kg, B) 0, 10, 30, 100mg/kg
<a href="#">TTG130</a>	TTG2(14d+1d): A)CCl4, B)CCl4	A) 5mg/kg, B) 0, 0.7, 2.0, 7.0mg/kg
<a href="#">TTG131</a>	TTG2: A)CCl4, B)Phenobarbital	A) 5mg/kg, B) 0, 15, 50, 150mg/kg
<a href="#">TTG189</a>	TTG4(1d+1d): A)CCl4, B)CCl4	A) 5mg/kg, B) 0, 0.7, 2.0, 7.0mg/kg
<a href="#">TTG190</a>	TTG4(2d+1d): A)CCl4, B)CCl4	A) 5mg/kg, B) 0, 0.7, 2.0, 7.0mg/kg
<a href="#">TTG191</a>	TTG4(4d+1d): A)CCl4, B)CCl4	A) 5mg/kg, B) 0, 0.7, 2.0, 7.0mg/kg

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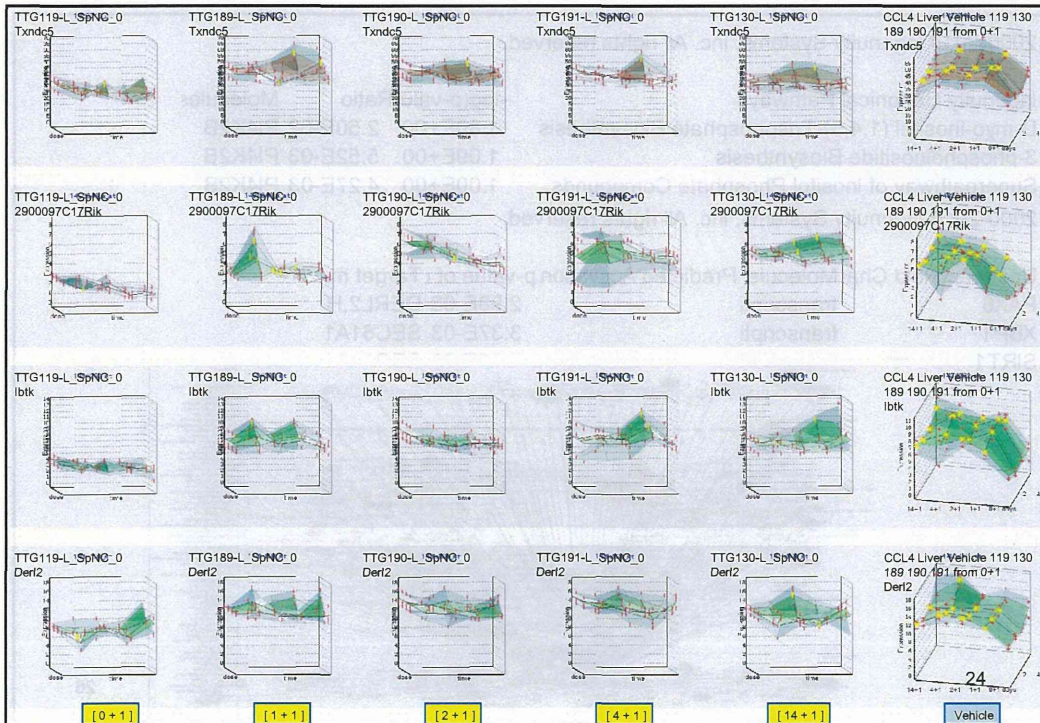
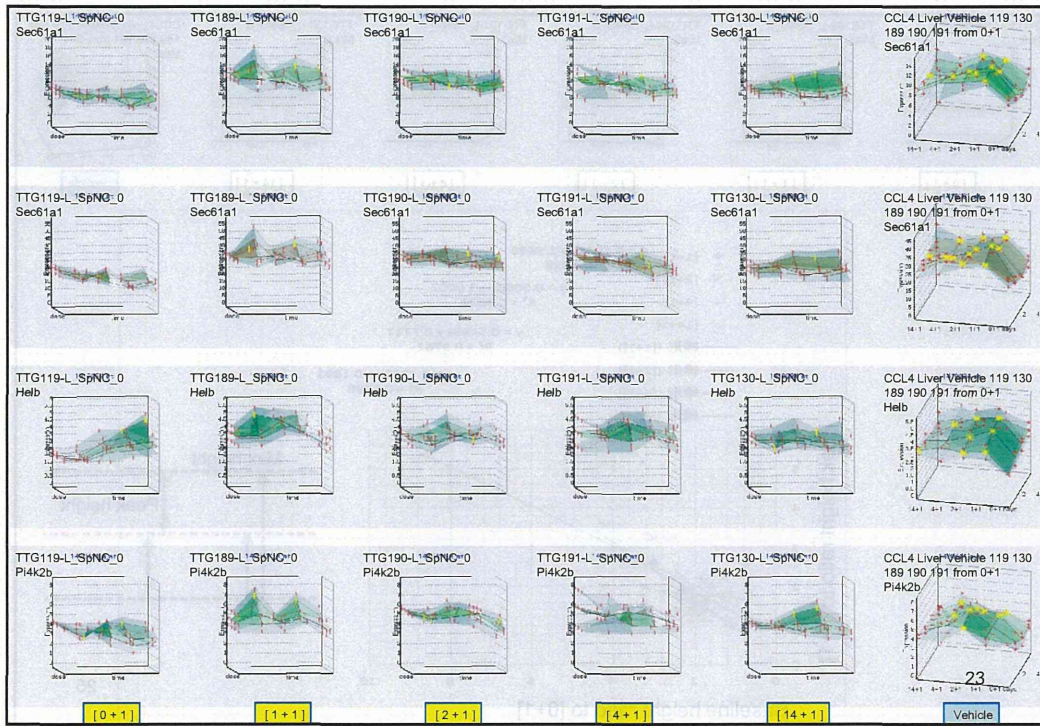
Ingenuity Canonical Pathways	-log(p-value)	Ratio	Molecules
Protein Ubiquitination Pathway	2.66E+00	1.85E-02	PSMB3,PSMC6,PSMD12,HSPB8,PSMB6
Spermidine Biosynthesis I	1.97E+00	1.25E-01	SRM
Oxidized GTP and dGTP Detoxification	1.97E+00	9.09E-02	DDX6
UDP-N-acetyl-D-glucosamine Biosynthesis II	1.67E+00	5.88E-02	PGM3
GDP-mannose Biosynthesis	1.67E+00	7.69E-02	GMPPA
GDP-glucose Biosynthesis	1.61E+00	5.56E-02	PGM3
NRF2-mediated Oxidative Stress Response	1.57E+00	1.54E-02	ERP29,HSPB8,SLC35A2
EIF2 Signaling	1.55E+00	1.49E-02	RPL21,RPS21,RPL13
Glucose and Glucose-1-phosphate Degradation	1.55E+00	4.35E-02	PGM3
Glycogen Degradation II	1.45E+00	6.25E-02	PGM3
UDP-N-acetyl-D-galactosamine Biosynthesis II	1.45E+00	4.00E-02	PGM3
Dolichyl-diphosphooligosaccharide Biosynthesis	1.41E+00	2.50E-02	DPM2

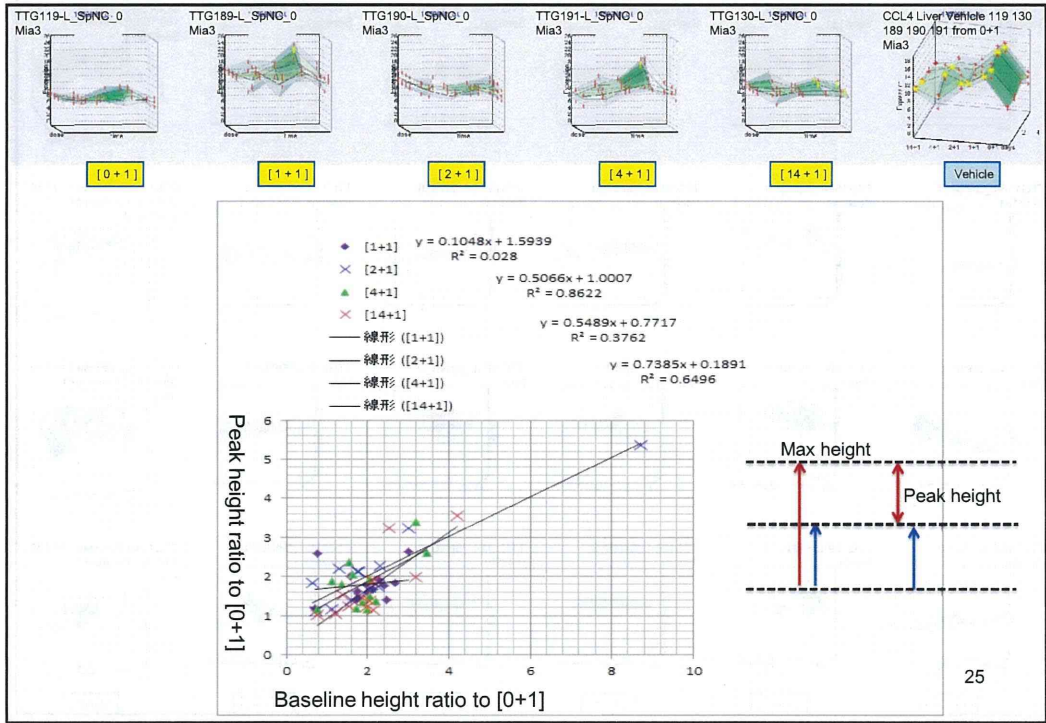
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Upstream	Fold Chan	Molecule	1Predicted	Activation	Notes	p-value of Target	mo	Mechanist
XBP1		transcripti	Inhibited	-3.124	bias	4.47E-12	CREB3,ER	
NFE2L2		transcripti	Inhibited	-3.267	bias	7.29E-08	ANG,ERP2	
TP53		transcripti		-1.373		4.71E-03	CKS1B,CF	
DNTTIP1		ligand-dec				6.91E-03	CREB3	
NFYC		transcripti				7.67E-03	PGM3,PSM	
MYCN		transcripti		-1		9.54E-03	PSMB6,RF	
PHC1		transcripti				1.38E-02	GMNN	
CREB3L4		transcripti				1.72E-02	ANG	
Rb		group				2.39E-02	GMNN,RP	
MKL2		transcripti				3.44E-02	CD151,DH	
HNF4A		transcripti				3.72E-02	ANG,DPM	
Ahr-aryl h		complex				4.74E-02	SLC35A2	

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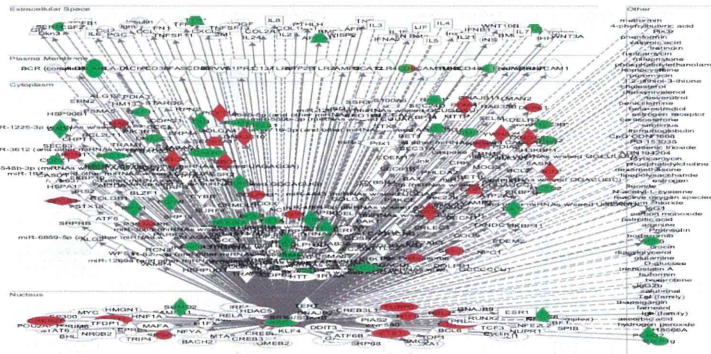


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Ingenuity Canonical Pathways	-log(p-value)	Ratio	Molecules
D-myo-inositol (1,4,5)-Trisphosphate Biosynthesis	1.80E+00	2.50E-02	PI4K2B
3-phosphoinositide Biosynthesis	1.09E+00	5.52E-03	PI4K2B
Superpathway of Inositol Phosphate Compounds	1.00E+00	4.27E-03	PI4K2B

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Upstream Fold Change	Molecule	Predicted Activation	p-value of Target	Target
PAX6	transcript	2.98E-03	DERL2, H	
XBP1	transcript	3.37E-03	SEC61A1	
SIRT1	transcript	3.37E-03	SEC61A1	





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Ingenuity Canonical Pathways	-log(p-val)	Ratio
EIF2 Signaling	3.52E+01	3.53E-01
Oxidative Phosphorylation	3.51E+01	4.58E-01
Mitochondrial Dysfunction	3.08E+01	2.93E-01
Acute Phase Response Signaling	9.93E+00	2.04E-01
Regulation of eIF4 and p70S6K Signaling	9.77E+00	1.94E-01
Protein Ubiquitination Pathway	7.24E+00	1.56E-01
LXR/RXR Activation	5.30E+00	1.65E-01
NRF2-mediated Oxidative Stress Response	4.57E+00	1.44E-01
Ethanol Degradation II	4.39E+00	2.33E-01
Coagulation System	4.15E+00	2.63E-01
mTOR Signaling	4.10E+00	1.31E-01
Noradrenaline and Adrenaline Degradation	4.04E+00	1.89E-01
Urea Cycle	3.56E+00	2.00E-01
Clathrin-mediated Endocytosis Signaling	3.55E+00	1.31E-01
Intrinsic Prothrombin Activation Pathway	3.42E+00	2.16E-01
Hypoxia Signaling in the Cardiovascular System	3.41E+00	1.91E-01
Extrinsic Prothrombin Activation Pathway	3.39E+00	2.73E-01

Mouse:  
[Regardless of induction] & BR  
Down

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Upstream	Fold Chan	Molecule 1	Predicted	Activation	Notes	p-value of Target mo
HNF4A			transcripti	Inhibited	-4.325 bias	2.47E-47 ABT1,ACA
MYCN			transcripti	Inhibited	-5.881	1.51E-32 ACTB,ALC
MYC			transcripti	Inhibited	-4.098 bias	3.96E-18 ACTB,ADP
NFE2L2			transcripti	Inhibited	-5.927 bias	1.24E-14 AKR1A1,A
PPARA			ligand-dep		-0.743 bias	1.84E-10 ACAA1,AC
MED30	-2		transcripti			5.34E-08 COX5B,N[
NRF1			transcripti	Inhibited	-3.049 bias	7.15E-07 CD47,CO
HNF1A			transcripti	Inhibited	-4.645 bias	2.82E-06 ADH1C,AF
Tcf 1/3/4			group	Inhibited	-2.2 bias	5.67E-06 AHSJ,ALF
TP53	-2		transcripti	Inhibited	-2.562	1.71E-05 ACAA2,AC
RNA polyn			complex			2.03E-05 APOM,AR
SMARCB1			transcripti	Inhibited	-3.163 bias	2.43E-05 APOC4,C/
ESRRA			ligand-dep	Inhibited	-4.477 bias	1.14E-04 ALDOB,Al
HTT			transcripti		-0.739	4.37E-04 ALDOB,Al
PAX3			transcripti			5.48E-04 ASSJ,C8C
ONECUT1			transcripti			6.35E-04 AWP,API

## TGP rat CCL4

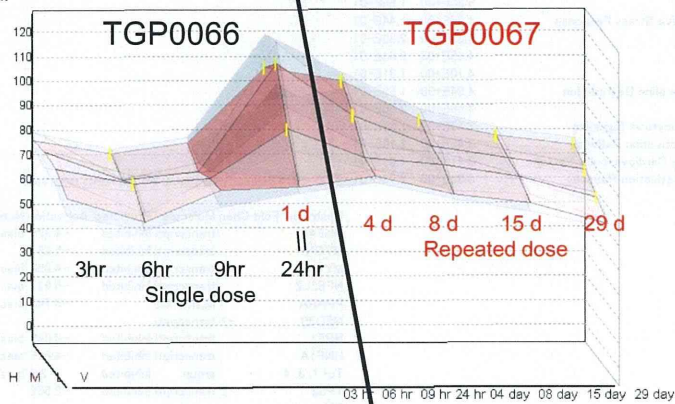
TGP0066  
type: single  
vehicle: corn oil  
dosage: 0, 30, 100, 300mg/kg  
time: 3, 6, 9, 24hr

TGP0067  
type: repeat  
vehicle: corn oil  
dosage: 0, 30, 100, 300mg/kg  
time: 4, 8, 15, 29day

★Sampled at 24hr timing

TGP0067 + 0066L\_SN  
Mettl9  
1376589\_at

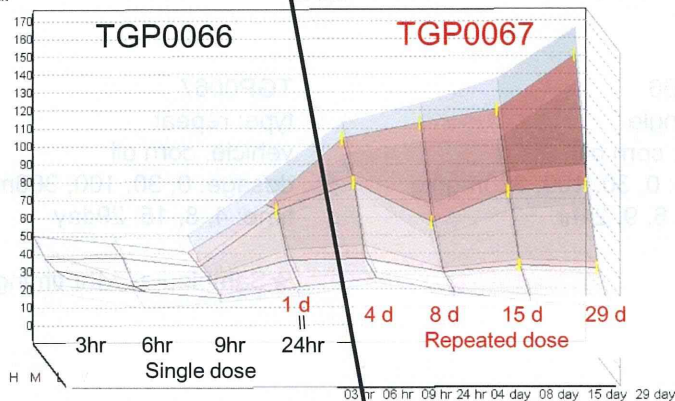
1178589\_at  
Mettl9  
B0380345



Desensitization  $\hat{=}$  Reduced Baseline Response<sub>29</sub>

TGP0067 + 0066L\_SN  
Reep5  
1371481\_at

371481\_at  
Reep5  
B1274372



Hypersensitization  $\hat{=}$  Elevated Baseline Response<sub>30</sub>