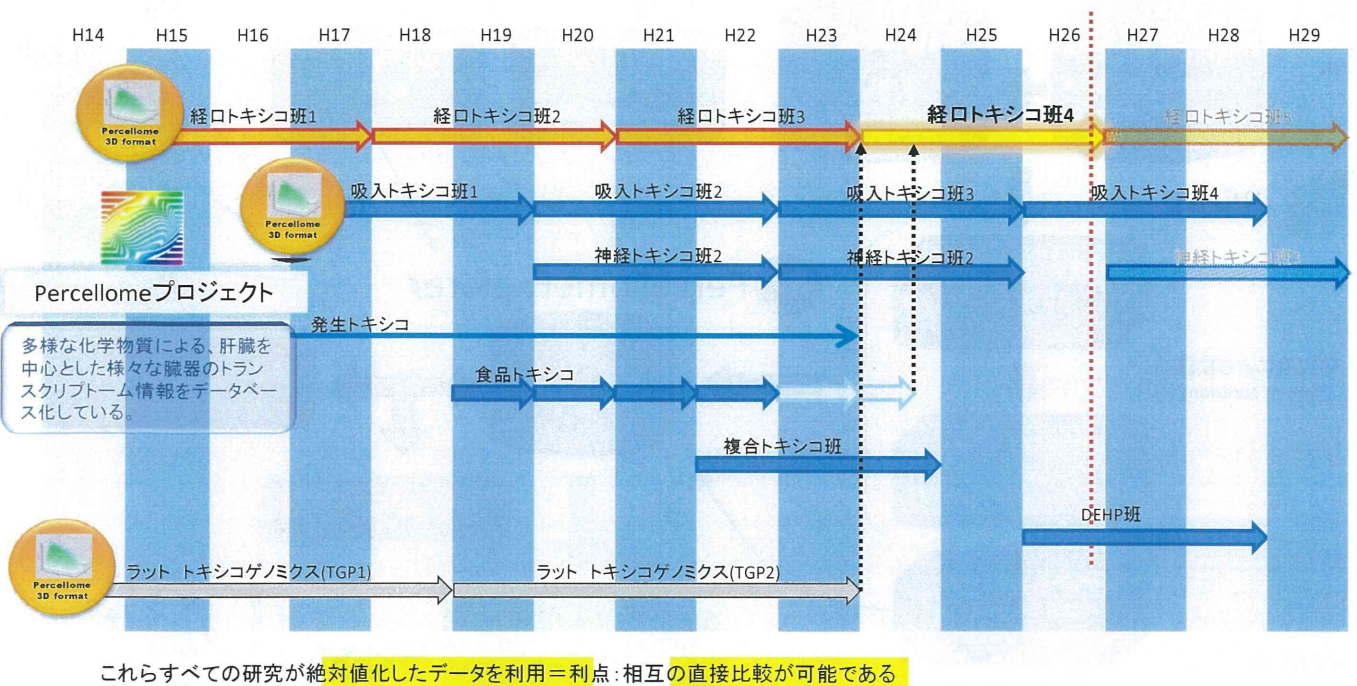


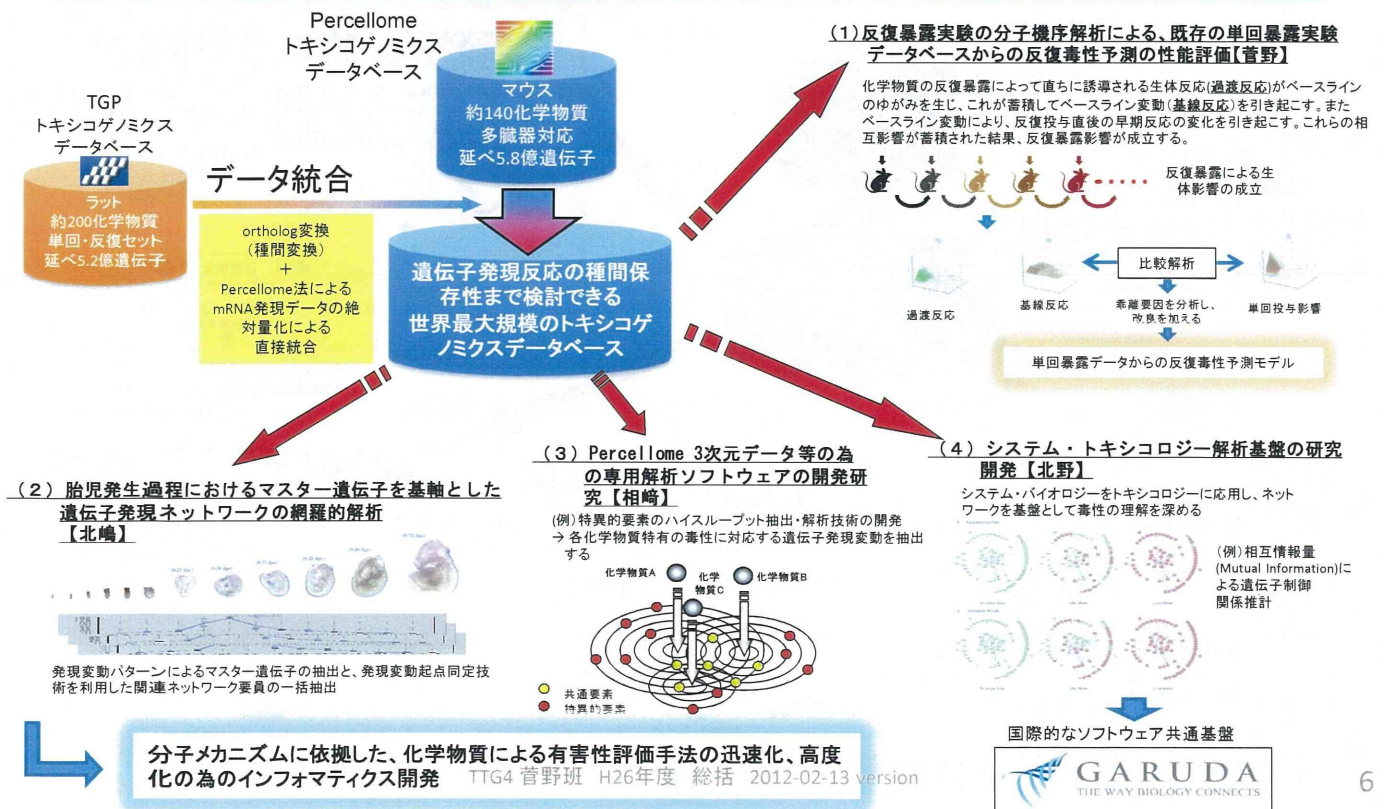
毒性部が展開するトキシコゲノミクス研究



TTG4 菅野班 H26年度 総括 2012-02-13 version

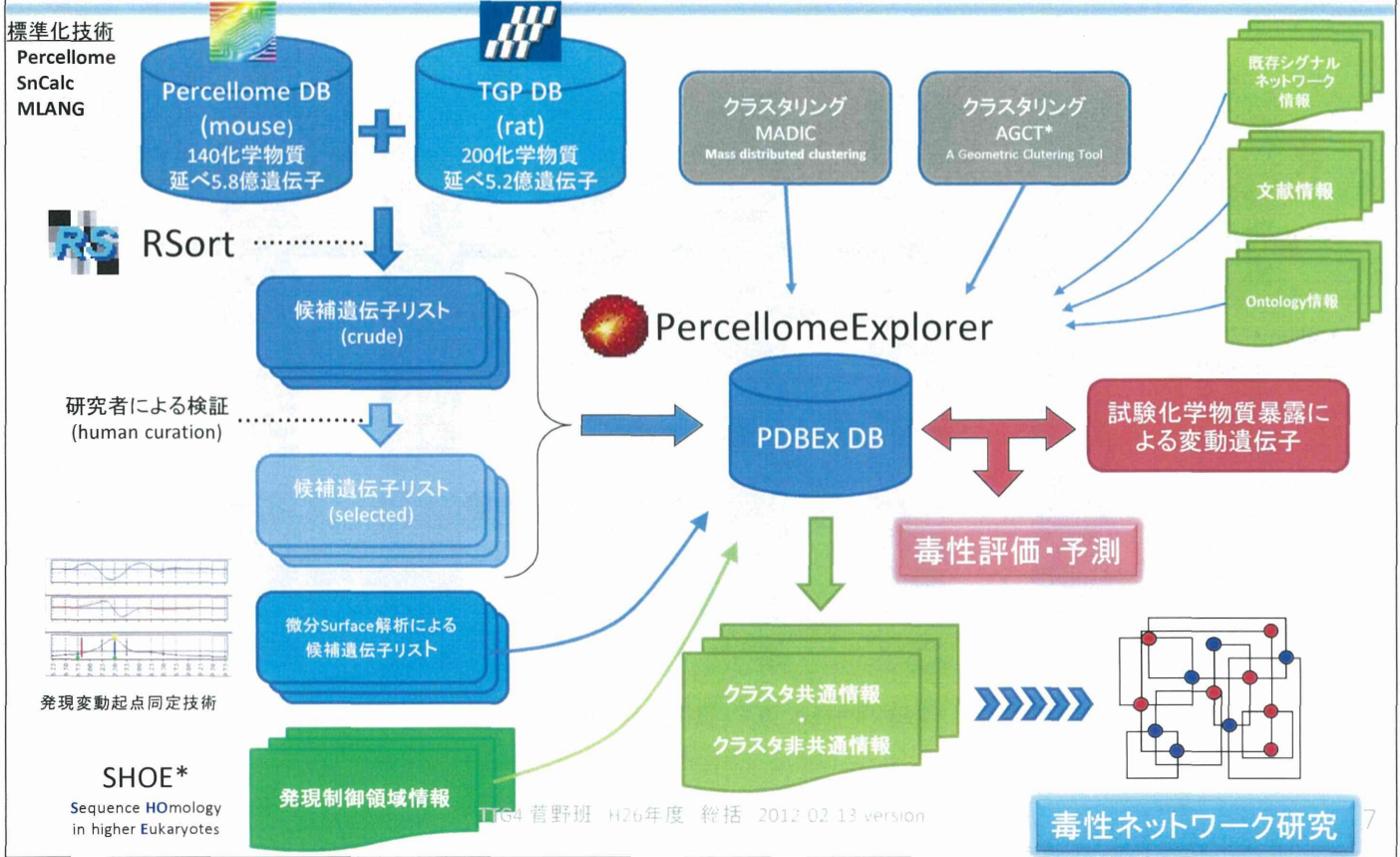
化学物質の有害性評価手法の迅速化、高度化に関する研究

ー 網羅的定量的大規模トキシコゲノミクスデータベースの維持・拡充と毒性予測評価システムの実用化の為のインフォマティクス技術開発ー



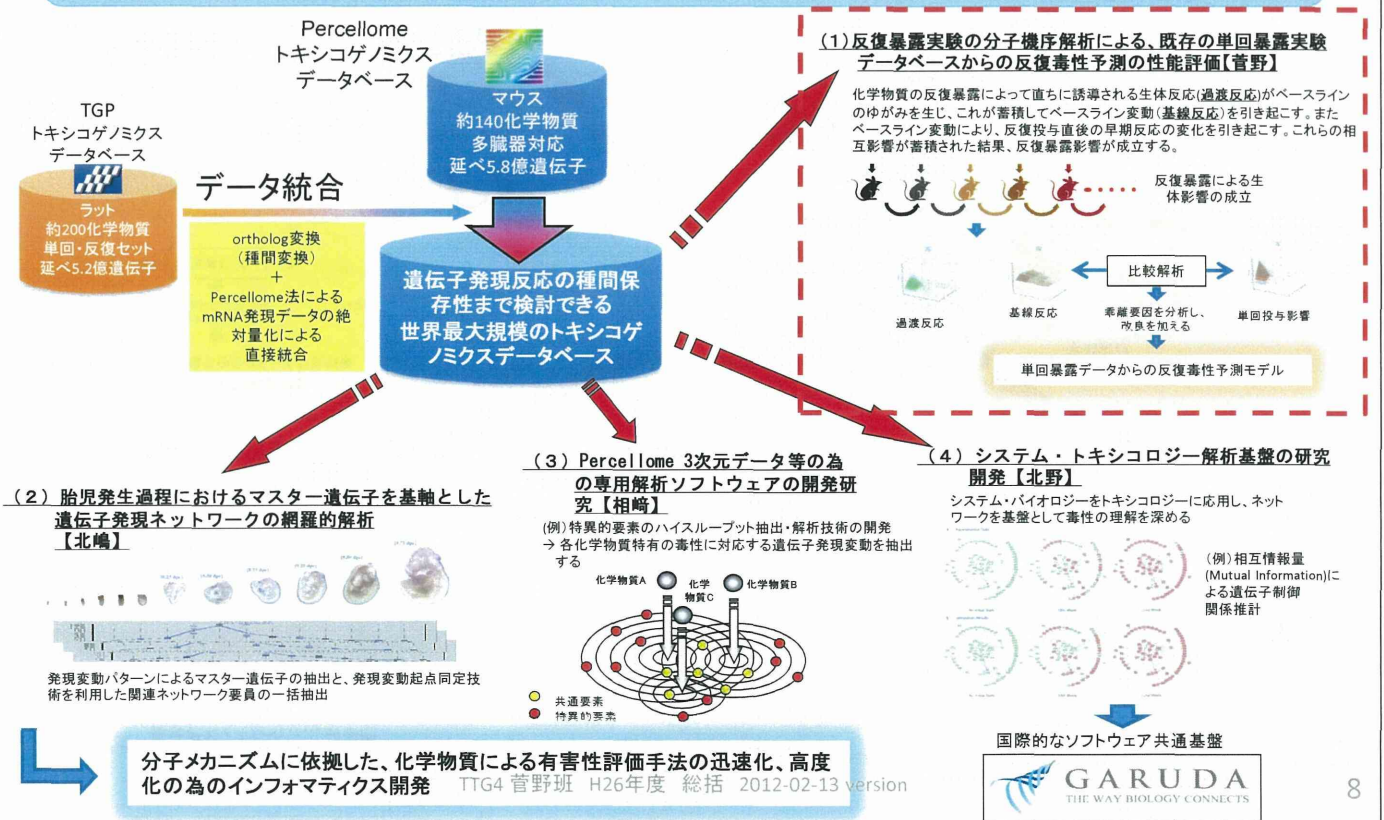
TTG4 菅野班 H26年度 総括 2012-02-13 version

インフォマティクスによる解析の流れ



化学物質の有害性評価手法の迅速化、高度化に関する研究

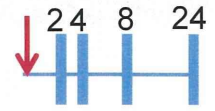
— 網羅的定量的大規模トキシコゲノミクスデータベースの維持・拡充と毒性予測評価システムの実用化の為にインフォマティクス技術開発 —



反復投与の意味の考察

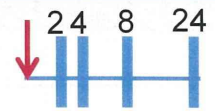
ヒント: 遺伝子改変動物の反応を解析する

野生型マウス



単回投与

遺伝子改変マウス

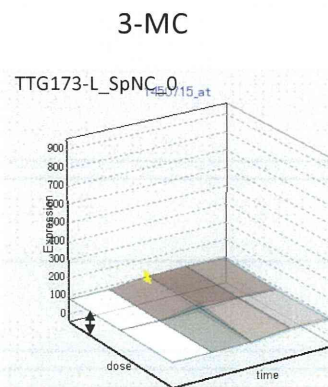
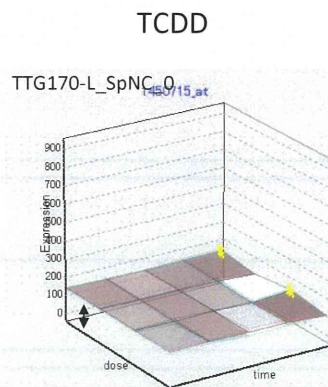


単回投与

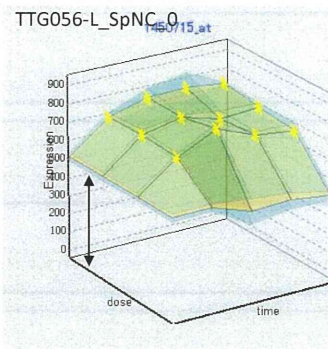
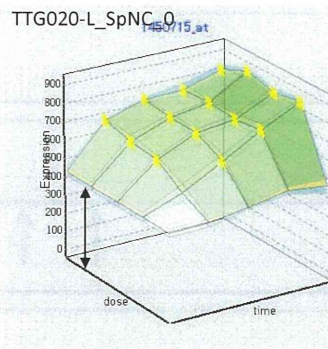
TTG4 菅野班 H26年度 総括 2012-02-13 version

9

AhR KO mouse



Wild type mouse



Cyp1a2
NM_009993

cytochrome P450, family 1, subfamily a, polypeptide 2

TTG4 菅野班 H26年度 総括 2012-02-13 version

10

単回投与 vs 反復投与後の反応

(TTG119-G)

(TTG130-G)

単回投与後の反応 (“TTG1 type”) [0+1]



単回投与

反復投与後の反応 (“TTG2 type”) [14+1]



反復投与 (全群単一用量)

TTG4 菅野班 H26年度 総括 2012-02-13 version

11

A+A' Protocol

[0+1]



[1+1]



[2+1]



[4+1]



[14+1]



TTG4 菅野班 H26年度 総括 2012-02-13 version

12

[0 + 1]

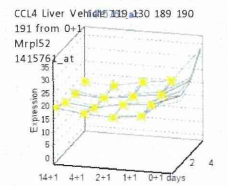
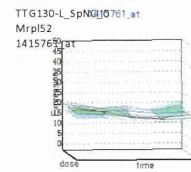
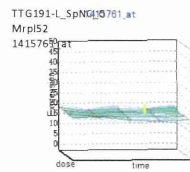
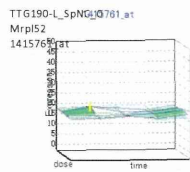
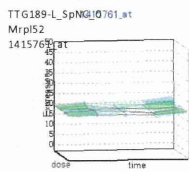
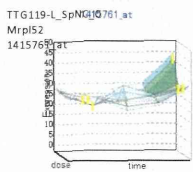
[1 + 1]

[2 + 1]

[4 + 1]

[14 + 1]

Vehicle



四塩化炭素

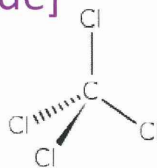
[Carbon tetrachloride]

単回投与

[0, 0.7, 2, 7 mg/kg]

反復後 単回投与

5 mg/kg (for 14 days) + [0, 0.7, 2, 7 mg/kg]



バルプロ酸ナトリウム

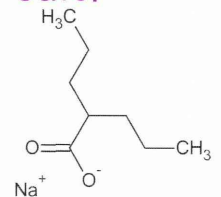
[Valproic acid sodium salt]

単回投与

[0, 50, 150, 500 mg/kg]

反復後 単回投与

100 mg/kg (for 14 days) + [0, 50, 150, 500 mg/kg]



TTG4 菅野班 H26年度 総括 2012-02-13 version

13

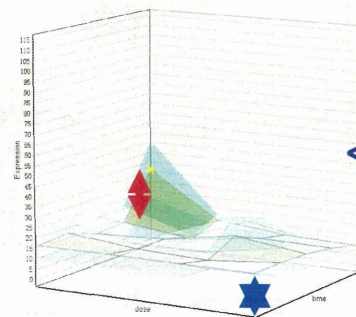
●反復投与が毎回の投与による反応に大きな影響を与える物質

用語定義 Definition

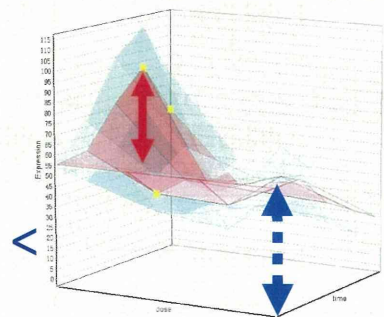
↕ Transient Response
(T-Res)
過渡反応

↕ Baseline Response
(B-Res)
基線反応

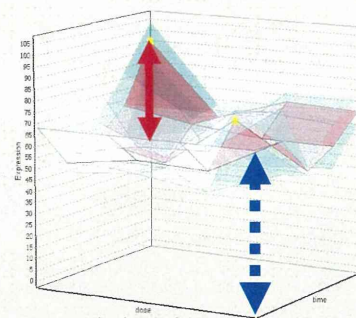
TTG119-L_SpNC_01428817.at



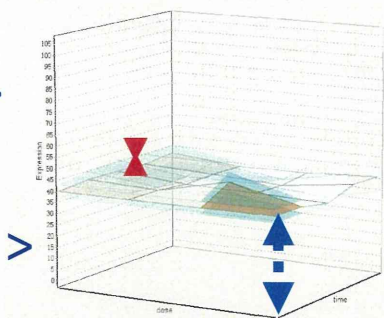
TTG130-L_SpNC_01428817.at



TTG119-L_SpNC_01425501.at



TTG130-L_SpNC_01425501.at



TTG4 菅野班 H26年度 総括 2012-02-13 version

14

Top Canonical Pathways

Name	p-value	Ratio
EIF2 Signaling	1.43E-37	72/185 (0.389)
Oxidative Phosphorylation	1.22E-31	51/109 (0.468)
Mitochondrial Dysfunction	1.34E-28	60/171 (0.351)
Regulation of eIF4 and p70S6K Signaling	8.63E-14	38/146 (0.26)
Acute Phase Response Signaling	2E-10	36/169 (0.213)

Top Upstream Regulators

Upstream Regulator	p-value of overlap	Predicted Activation State
RICTOR	7.17E-75	Activated
HNF4A	1.21E-45	Inhibited
MYCN	6.44E-35	Inhibited
CD 437	1.70E-32	Activated
5-fluorouracil	8.72E-30	Activated

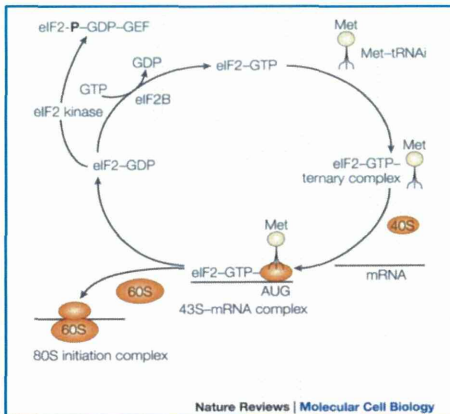
● 基線反応のメカニズムに、『エピジェネティックな制御』を想定

基線反応が低下した化合物

- 四塩化炭素
- クロフィレート
- トリブチル錫

低下した遺伝子のリストが共通であった。

- eIF2回路/ 酸化的リン酸化/ ミトコンドリア
- 上流にRICTOR/ HNF4A

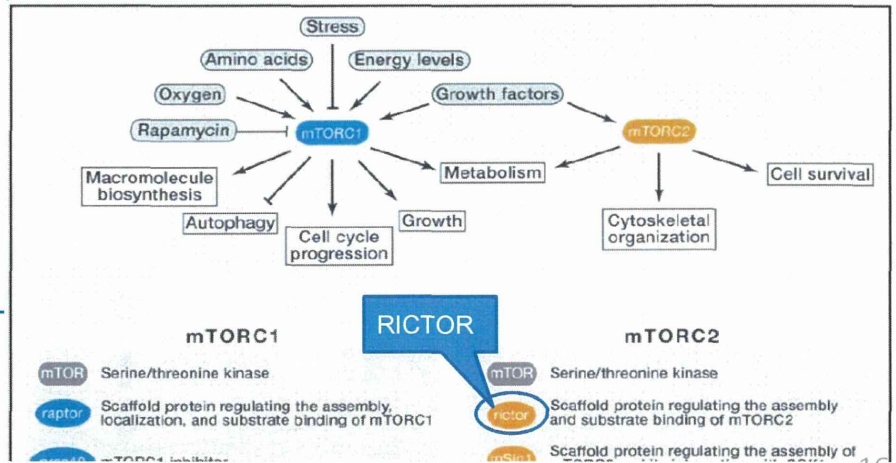


Cell

mTOR Signaling in Growth Control and Disease

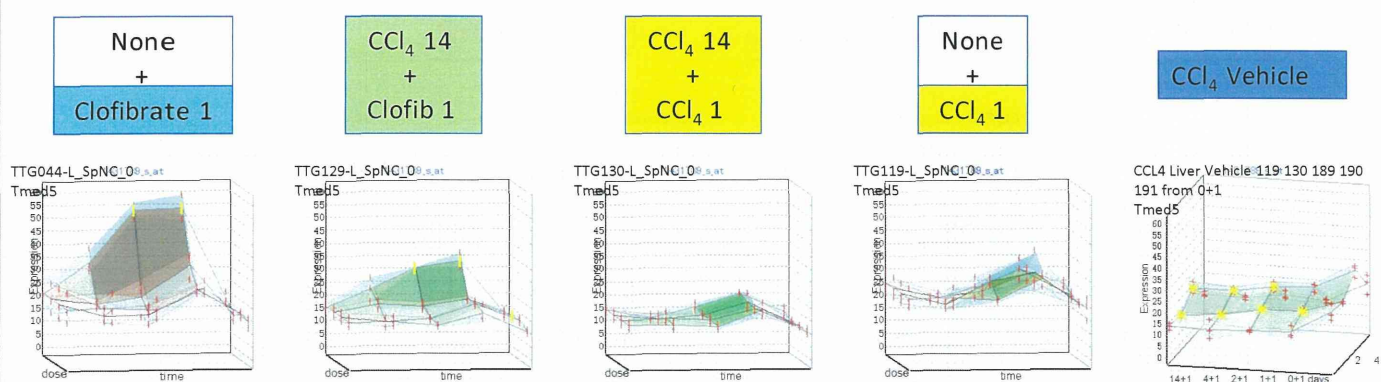
Mathieu Laplante^{1,2,3,4} and David M. Sabatini^{1,2,3,*}

¹Whitehead Institute for Biomedical Research, Nine Cambridge Center, Cambridge, MA 02142, USA
²Howard Hughes Medical Institute, Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
³Koch Center for Integrative Cancer Research at MIT, 77 Massachusetts Avenue, Cambridge, MA 02139, USA



★組み合わせデータの解析

- CCl₄ & CCl₄、Clf、PB、
- VPA & VPA *、Asp、Thalidomide
- Clofibrate & Clf、PCN、ATRA
- TBT & TBT、PB、Clf

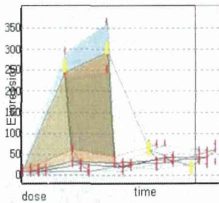


[14+1]

TBT + Clofibrate

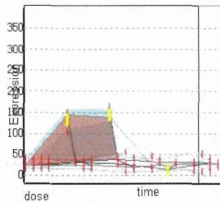
CCl4 + Clofibrate

TTG044-L_SpNC_Q_448700_at
Clofibrate
G0s2



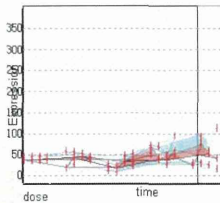
G0/G1 switch gene 2

TTG141-L_SpNC_Q_448700_at
Tributyltin chloride x Clofibrate
G0s2



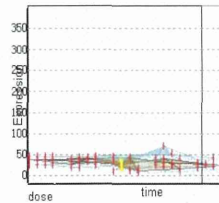
G0/G1 switch gene 2

TTG085-L_SpNC_Q_448700_at
Tributyltin
G0s2



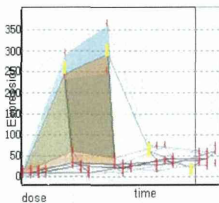
G0/G1 switch gene 2

TTG145-L_SpNC_Q_448700_at
Tributyltin chloride x Tributyltin chloride
G0s2



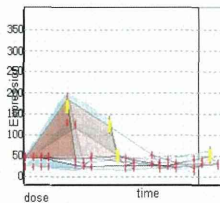
G0/G1 switch gene 2

TTG044-L_SpNC_Q_448700_at
Clofibrate
G0s2



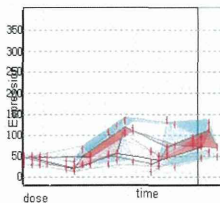
G0/G1 switch gene 2

TTG129-L_SpNC_Q_448700_at
CCl4 x Clofibrate
G0s2



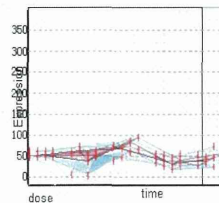
G0/G1 switch gene 2

TTG119-L_SpNC_Q_448700_at
Carbon tetrachloride
G0s2



G0/G1 switch gene 2

TTG130-L_SpNC_Q_448700_at
CCl4 x CCl4
G0s2

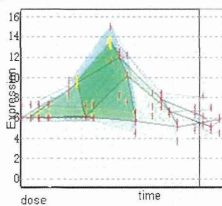


G0/G1 switch gene 2

[14+1]

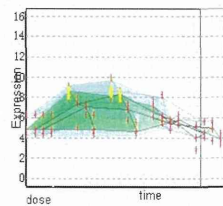
Clofibrate + PCN

TTG090-L_SpNC_Q_429831_at
Pregnenolone Carbonitrile
Pik3ap1



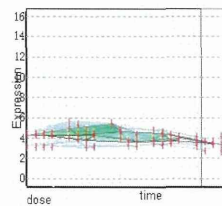
phosphoinositide-3-kinase adaptor protein 1

TTG120-L_SpNC_Q_429831_at
Clofibrate x PCN
Pik3ap1



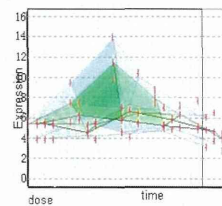
phosphoinositide-3-kinase adaptor protein 1

TTG118-L_SpNC_Q_429831_at
Clofibrate x Clofibrate
Pik3ap1



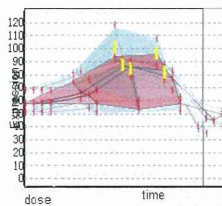
phosphoinositide-3-kinase adaptor protein 1

TTG044-L_SpNC_Q_429831_at
Clofibrate
Pik3ap1



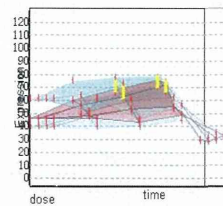
phosphoinositide-3-kinase adaptor protein 1

TTG090-L_SpNC_Q_416793_at
Pregnenolone Carbonitrile
At12



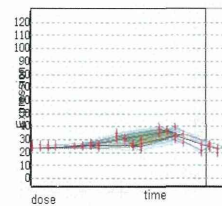
atlastin GTPase 2

TTG120-L_SpNC_Q_416793_at
Clofibrate x PCN
At12



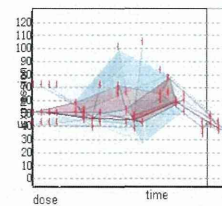
atlastin GTPase 2

TTG118-L_SpNC_Q_416793_at
Clofibrate x Clofibrate
At12



atlastin GTPase 2

TTG044-L_SpNC_Q_416793_at
Clofibrate
At12



atlastin GTPase 2