

F. 研究発表

1. 論文発表

Janesick A, Nguyen TT, Aisaki K, Igarashi K, Kitajima S, Chandraratna RA, Kanno J, Blumberg B. Active repression by RAR γ signaling is required for vertebrate axial elongation. *Development*. (2014);141(11):2260-70.

Tanaka M, Aisaki K, Kitajima S, Igarashi K, Kanno J and Nakamura T, Gene expression response to EWS-FLI1 in mouse embryonic cartilage. *Genomics Data* 2: 296-298, 2014.

Tanaka M, Yamazaki Y, Kanno Y, Igarashi K, Aisaki K, Kanno J, Nakamura T. Ewing's sarcoma precursors are highly enriched in embryonic osteochondrogenic progenitors. *J Clin Invest*. (2014);124(7):3061-74.

Maria Marti-Solano, Ewan Birney, Antoine Bril, Oscar Della Pasqua, Hiroaki Kitano, Barend Mons, Ioannis Xenarios and Ferran Sanz. Integrative knowledge management to enhance pharmaceutical R&D. *Nature Reviews Drug Discovery*. 13, 4, 239-240, Apr. 1, 2014.

Yoshiyuki ASAI; Takeshi ABE, Hideki OKA, Masao OKITA, Ken-ichi HAGIHARA, Samik GHOSH, Yukiko MATSUOKA, Yoshihisa KURACHI, Taishin NOMURA, Hiroaki KITANO. A

Versatile Platform for Multilevel Modeling of Physiological Systems: SBML-PHML Hybrid Modeling and Simulation. *ABE Advanced Biomedical Engineering*. 3, 50-58, May 17, 2014.

Tokiko Watanabe, Eiryo Kawakami, Jason E. Shoemaker, Tiago J.S. Lopes, Yukiko Matsuoka, Yuriko Tomita, Hiroko Kozuka-Hata, Takeo Gorai, Tomoko Kuwahara, Eiji Takeda, Atsushi Nagata, Ryo Takano, Maki Kiso, Makoto Yamashita, Yuko Sakai-Tagawa, Hiroaki Katsura, Naoki Nonaka, Hiroko Fujii, Ken Fujii, Yukihiko Sugita, Takeshi Noda, Hideo Goto, Satoshi Fukuyama, Shinji Watanabe, Gabriele Neumann, Masaaki Oyama, Hiroaki Kitano, and Yoshihiro Kawaoka. Influenza Virus-Host Interactome Screen as a Platform for Antiviral Drug Development. *Cell Host & Microbe*, 16, 6, 795-805, Dec.10, 2014.

Jablonska Agnieszka and Natalia Polouliakh In silico discovery of novel transcription factors regulated by mTOR pathway activities. *Frontier in Cell and Developmental Biology* ISSN: 2296-634X, DOI:10.3389/fcell. 2014.00023 Vol:2 No.23, 1-9 June 3, 2014.

Kanno J, Aisaki K, Igarashi K, Kitajima S, Matsuda N, Morita K, Tsuji M, Moriyama N, Furukawa Y, Otsuka M, Tachihara E, Nakatsu N, Kodama Y.

- (2013) Oral administration of pentachlorophenol induces interferon signaling mRNAs in C57BL/6 male mouse liver. *J Toxicol Sci.* 38(4):643-54.
- Fujimoto, N, Takagi, A, Kanno, J. (2013) Neonatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin increases the mRNA expression of prostatic proteins in C57BL mice. *J Toxicol Sci.* 38(2):279-83.
- Hase, T.; Ghosh, S.; Yamanaka, R.; Kitano, H. Harnessing Diversity towards the Reconstructing of Large Scale Gene Regulatory Networks. *PLOS Computational Biology.* 9(11): e1003361, doi:10.1371/journal.pcbi.1003361, Nov. 21, 2013.
- Yukiko Matsuoka; Hiromi Matsumae; Manami Katoh; Amie J Einfeld; Gabriele Neumann; Takeshi Hase; Samik Ghosh; Jason E Shoemaker; Tiago JS Lopes; Tokiko Watanabe; Shinji Watanabe; Satoshi Fukuyama; Hiroaki Kitano; and Yoshihiro Kawaoka. A comprehensive map of the influenza A virus replication cycle. *BMC Systems Biology.* 7, 97, doi:10.1186/1752-0509-7-97, 2013.
- Yamashita Fumiyoshi; Yukako Sasa; Shuya Yoshida; Akihiro Hisaka; Yoshiyuki Asai; Hiroaki Kitano; Mitsuru Hashida, Hiroshi Suzuki. Modeling of Rifampicin-Induced CYP3A4 Activation Dynamics for the Prediction of Clinical Drug-Drug Interactions from In Vitro Data. *PLOS ONE.* 8, 9, e70330, Sep. 24, 2013.
- Kazuhiro A. Fujita; Marek Ostaszewski; Yukiko Matsuoka; Samik Ghosh; Enrico Glaab; Christophe Trefois; Isaac Crespo; Thanneer M. Perumal; Wiktor Jurkowski; Paul M. A. Antony; Nico Diederich; Manuel Buttini; Akihiko Kodama; Venkata P. Satagopam; Serge Eifes; Antonio del Sol; Reinhard Schneider; Hiroaki Kitano; Rudi Balling. Integrating Pathways of Parkinson's Disease in a Molecular Interaction Map. *Molecular Neurobiology.* DOI 10.1007/s12035-013-8489-4, July 7, 2013.
- Naito, T., Yatsushashi, A.; Kaji, N.; Ando, T., Sato, K.; Moriya, H., Kitano, H., Yasui, T.; Tokeshi, M.; Baba, Y. Parallel Real-Time PCR on a Chip for Genetic Tug-of-War (gTOW) Method. *Analytical Sciences.* 29(3): 367-71, 2013.
- Koji Makanae; Reiko Kintaka; Takashi Makino; Hiroaki Kitano; and Hisao Moriya. Identification of dosage-sensitive genes in *Saccharomyces cerevisiae* using the genetic tug-of-war method. *Genome Research.* 23, 300-311, 2013.
- Natalia Polouliakh; Reprogramming resistant genes: in-depth comparison of gene expressions among iPS, ES and

somatic cells. *Frontier of Physiology* doi:10.3389/fphys.2013.00007, Jan. 30, 2013.

Abe S, Kurata M, Suzuki S, Yamamoto K, Aisaki K, Kanno J, Kitagawa M.(2012) Minichromosome maintenance 2 bound with retroviral Gp70 is localized to cytoplasm and enhances DNA-damage-induced apoptosis. *PLoS One*. 7(6):e40129.

Swedenborg E, Kotka M, Seifert M, Kanno J, Pongratz I, Rüegg J.(2012) The aryl hydrocarbon receptor ligands 2,3,7,8-tetrachlorodibenzo-p-dioxin and 3-methylcholanthrene regulate distinct genetic networks. *Mol Cell Endocrinol.* Mol Cell Endocrinol. 362(1-2):39-47. doi: 10.1016/j.mce.2012.05.006

Igarashi K, Kitajima S, Aisaki K, Tanemura K, Taquahashi Y, Moriyama N, Ikeno E, Matsuda N, Saga Y, Blumberg B, Kanno J.(2012) Development of humanized steroid and xenobiotic receptor mouse by homologous knock-in of the human steroid and xenobiotic receptor ligand binding domain sequence. *J Toxicol Sci*. 37(2):373-80.

Crespo, I.; Roomp, K.; Jurkowski, W.; Kitano, H.; del Sol, A. Gene regulatory network analysis supports inflammation

as a key neurodegeneration process in prion disease. *BMC Systems Biology*, 6:132, 2012.

Shoemaker, J.; Fukuyama, S.; Einfeld, A. J.; Muramoto, Y.; Watanabe, S.; Watanabe, T.; Matsuoka, Y.; Kitano, H.; Kawaoka, Y. Integrated network analysis reveals a novel role for the cell cycle in 2009 pandemic influenza virus-induced inflammation in macaque lungs. *BMC Systems Biology*, 6:117, 2012.

Shoemaker, J. E., Lopes, T. J., Ghosh, S., Matsuoka, Y., Kawaoka, Y., Kitano, H. CTen: a web-based platform for identifying enriched cell types from heterogeneous microarray data. *BMC Genomics*, 13 (1): 460, 2012.

Martijn P. van Iersel, Alice C. Villegier, Tobias Czauderna, Sarah E. Boyd, Frank T. Bergmann, Augustin Luna, Emek Demir, Anatoly Sorokin, Ugur Dogrusoz, Yukiko Matsuoka, Akira Funahashi, Mirit I. Aladjem, Huaiyu Mi, Stuart L. Moodie, Hiroaki Kitano Nicolas Le Novere, and Falk Schreiber. Software support for SBGN maps: SBGN-ML and LibSBGN. *Bioinformatics*. 28 (15): 2016-21, 2012. doi: 10.1093/bioinformatics/bts270, published online May 10, 2012.

Carl-Fredrik Tiger, Falko Krause, Gunnar Cedersund, Robert Palmér, Edda

Klipp, Stefan Hohmann, Hiroaki Kitano and Marcus Krantz. A framework for mapping, visualisation and automatic model creation of signal-transduction networks. *Molecular Systems Biology*. 8: 578, April 24, 2012.

2. 学会発表

Jun Kanno, Ken-ichi Aisaki, Satoshi Kitajima, Percellome Toxicogenomics, 50th Congress of the European Societies of Toxicology (EUROTOX2014)(2014.9.9) Edinburgh, UK, poster

Jun Kanno, Ken-ichi Aisaki, Satoshi Kitajima, Percellome toxicogenomics project as the 3R-toxicology and the foundation of in vitro- and in silico-toxicology, the 9th World Congress on Alternatives and Animal Use in the Life Sciences (WC9) (2014.8.27), Prague, Czech Republic, Oral

相崎健一、北嶋 聡、菅野 純、遺伝子発現から見た毒性学—Percellome トキシコゲノミクスの進捗—、第 36 回日本中毒学会総会・学術集会(2014.7.25) 東京、シンポジウム

北嶋 聡、小川幸男、大西 誠、相磯成敏、相崎健一、五十嵐勝秀、高橋祐次、菅野 純、シックハウス症候群レベルの極低濃度吸入暴露時の海馬 Percellome トキシコゲノミクス—化学構造が異なる 3 物質の比較—、第 41 回日本毒性学会学術年会 (2014.7.3) 神戸、口演

菅野 純、相崎健一、北嶋 聡、Percellome Project の進捗—新型反復暴露による慢性毒性の予測に向けての分子背景の解析—、第 41 回日本毒性学会学術年会 (2014.7.2) 神戸、シンポジウム

北嶋 聡、種村健太郎、菅野 純、毒性の網羅的把握のための遺伝子発現ネットワーク描出と動的バイオマーカー抽出、第 41 回日本毒性学会学術年会(2014.7.2)神戸、シンポジウム

Jun Kanno, Progress in Japanese Percellome Project and incorporation of TGP data, 11th International Conference of Environment Mutagens (11th ICEM), (2013.11.4) , Fos do Iguassu, Brazil, invited

Jun Kanno, Percellome Toxicogenomics, A Quantitative and Comprehensive Approach for Basic and Applied Toxicology. ICT2013 The XIII International Congress of Toxicology, (2013.7.2), Seoul, Korea, distinguished lecture

菅野 純、"Percellome Project ケミカルバイオロジーの視点からのトキシコゲノミクス—Percellome Project の進捗とその応用性—"、第 40 回日本毒性学会学術年会、2013 年 6 月 18 日、千葉、シンポジウム

菅野 純、網羅的絶対量化遺伝子発現解析による外来物質生体影響の動的ネットワーク

マーカー抽出 : Percellome Project、第 102 回日本病理学会総会、2013 年 6 月 7 日、札幌、シンポジウム

菅野 純、創薬とトキシコゲノミクスー Percellome Project の進捗とその応用性ー、医薬基盤研究所公開セミナー、大阪、2012 年 10 月 30 日、招待

Satoshi KITAJIMA, Ken-ichi AISAKI, Katsuhide IGARASHI and Jun KANNO, Application of Percellome Toxicogenomics approach to food safety in case of a flavor, estragole, The 6th International Congress of Asian Society of Toxicology(2012.7.20) Sendai, Symposium

北嶋 聡、相崎健一、五十嵐勝秀、菅野 純、食品の安全性確認に向けた Percellome トキシコゲノミクスの適用ー香料エストラゴールの場合ー、第 39 回日本毒性学会学術年会、2012 年 7 月 17 日、仙台、一般口演

菅野 純、Percellome Project : 組織、臓器、種を跨いで、第 39 回日本毒性学会学術年会、2012 年 7 月 17 日、仙台、シンポジウム

Jun Kanno, Modernization and Harmonization of Toxicology; an Approach by Percellome Toxicogenomics, 2012 Global Summit on Regulatory Science - Modernizing Toxicology (2012.5.11) Hangzhou, People's Republic of China, Invited

北嶋 聡,小川幸男, 大西 誠 ,相磯成敏,相崎健一,五十嵐勝秀, 高橋祐次, 菅野 純 シックハウス症候群レベルの極低濃度暴露の際の海馬における Percellome 法による吸入トキシコゲノミクス、第 40 回日本毒性学会学術年会(2013.6.18)

Kitajima S, Aisaki K, Igarashi K, Kanno J. Application of Percellome Toxicogenomics approach to food safety: A flavor, estragole appears to be a PPAR-alpha agonist. The XIII International Congress of Toxicology 2013 (ICT 2013)] (2013.7.3.), Seoul, Korea

Tanemura K, Igarashi K, Furukawa Y, Otsuka M, Aisaki K, Kitajima S, Sato E, Kanno J. Delayed Effects on CNS Induced by Disturbance of Neural Activity during Development - Behavioral Impairment in Male Adult Mice Induced by Postnatal Oral Intake of Acephate. The XIII International Congress of Toxicology 2013 (ICT 2013)] (2013.7.3.), Seoul, Korea

北嶋 聡、高橋 祐次、五十嵐 勝秀、相崎 健一、菅野 純、Percellome 網羅的定量的トキシコゲノミクス、平成 24 年度公益社団法人日本実験動物学会 維持会員懇談会 (2012.11.16)

田中美和、山崎ゆかり、菅野陽平、五十嵐勝秀、相崎健一、菅野 純、中村卓郎、ユーストイング肉腫モデルマウスを用いた発生起原の同定と遺伝子発現解析、第 101 回日本病

理学会総会、2012年4月27日、東京、一般口演

種村健太郎、古川佑介、大塚まき、五十嵐勝秀、相崎健一、北嶋 聡、佐藤英明、菅野純、発生-発達期の神経シグナルかく乱による遅発中枢影響解析-幼弱期マウスへのイボテン酸投与による成熟期の脳高次機能障害について-、2012年7月17日、仙台、シンポジウム

富永貴志、富永洋子、五十嵐勝秀、種村健太郎、菅野 純、中島欽一、妊娠期投与による胎生期バルプロ酸暴露マウスは学習記憶異常と海馬抑制系の減弱を示す、第39回日本毒性学会学術年会、2012年7月19日、仙台、一般口演

Satoshi KITAJIMA, Ken-ichi AISAKI, Katsuhide IGARASHI and Jun KANNO, Application of Percellome Toxicogenomics approach to food safety in case of a flavor, estragole, The 6th International Congress of Asian Society of Toxicology(2012.7.20) Sendai, Symposium

Katsuhide Igarashi, Noriko Moriyama, Kentaro Tanemura, Maki Otsuka, Yusuke Furukawa, Hirotugu Asano, Kinichi Nakashima and Jun Kanno, Glucocorticoid Receptor (GR) enhances the astrocytic differentiation of neural stem cells via LIF-STAT3-GFAP pathway by a ligand dependent binding of GR to STAT3 at the STAT3 responsive element

of GFAP promoter, 15th International Congress on Hormonal Steroids and Homones & Cancer (2012.11.16) Kanazawa, poster

Kitano, H. Frontiers of Systems Biology and Software Platform. Presentation at L'ORÉAL, L'ORÉAL Research & Innovation, Aulnay-sous-Bois, France, Apr. 22, 2014. (invited)

Kitano, H, Multiscale disease systems modelling. 7th Noordwijkerhout Symposium on Pharmacokinetics, Pharmacodynamics and Systems Pharmacology: "SYSTEMS PHARMACOLOGY IN DRUG DISCOVERY AND DEVELOPMENT", NH Conference Centre Leeuwenhorst, Noordwijkerhout, the Netherlands, Apr. 24, 2014. (invited)

北野宏明. システム毒性学の戦略とプラットフォーム技術. 第41回日本毒性学会学術年会 シンポジウム: 毒性オミクス-遺伝子発現ネットワークを標的とした、治療、毒性、及びそれらの評価の新動向-, 神戸国際会議場, July 2, 2014. (invited)

Ghosh, S.; Kitano, H. Garuda: Fly to the future of biology. ISMB 2014, John B. Hynes Memorial Convention Center, Boston, USA, July 14, 2014.

Kitano, H. Systems Drug Discovery and Software Platform. Unlocking unique

clinical research roadmaps using a systems approach, ICSB 2014, Melbourne Convention and Exhibition Centre, Sep. 15, 2014.

Kitano, H. Systems Biology and Applications. ICSB 2014, Melbourne Convention and Exhibition Centre, Sep. 16, 2014. (invited)

Kitano, H. Garuda Platform: An integrated software solution for data-driven medical sciences. World Health Summit 2014, Federal Foreign Office, Berlin, Germany, Oct. 20, 2014. (invited)

Kitano, H. Systems drug discovery and Neuro-degenerative diseases. CHDI's 8th Annual Huntington's Disease therapeutics Conference: A Forum for Drug Discovery & Development, Molino Stucky Hilton Hotel, Venice, Italy, Apr. 9, 2013. (invited)

Kitano, H. Systems Biomedicine for Drug Discovery and Personalized Healthcare. Seminar at Institute for Infocomm Research(I2R), Institute for Infocomm Research(I2R), Singapore, Apr. 12, 2013. (invited)

Kitano, H. Systems Biology: past, present, future. Talk at AIBN at the University of Queensland, Australian Institute for Bioengineering and Nanotechnology,

University of Queensland, Brisbane, Australia, May 9, 2013. (invited)

Kitano, H. Systems biology in the context of systems and precision engineering. Talk at Australian Institute of Marine Science(AIMS), AIMS, Townsville, Australia, May 10, 2013. (invited)

北野宏明. システムトキシコロジープラットフォームフォーラム. 第40回日本毒性学会学術年会シンポジウム7「毒性オミクス」, 幕張メッセ, 千葉, June18, 2013. (invited)

Kitano, H. Systems biology and systems biomedicine: integrative systems sciences and biomedical sciences. 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Osaka International Convention Center, Osaka, July 7, 2013. (invited keynote)

Kitano, H. Systems Biology Platform for Drug Discovery. Talk at Imperial College, London, UK, July 30, 2013. (invited)

Kitano, H. Systems Biology and Software Platform. Nature Publishing Group Asian Academic Publishing team meeting, Sheraton Miyako Hotel, Sep. 6, 2013. (invited)

Kitano, H. Garuda Platform: An integrated inter-operability for biomedical software and data resources.

COMBINE 2013, Institut Curie, Paris, France, Sep. 16, 2013. (invited)

北野宏明. システムバイオロジーを活用したバイオマーカー評価. 日経バイオテク/日経バイオテク ONLINE プロフェッショナルセミナー「実例から学ぶクリニカルバイオマーカー時代の到来」, コクヨホール, Oct. 2, 2013. (invited)

Kitano, H. Systems Drug Discovery and Systems Biomedicine. Systems Biology Seminar co-hosted by Garvan Institute and UNSW, Garvan Institute, Sydney, Oct. 11, 2013. (invited)

北野宏明. システムバイオロジーを活用したバイオマーカー評価. 講演@東北メディカルメガバンク機構. Nov. 1, 2013. (invited)

北野宏明. Systems drug discovery and its software platform システム創薬とソフトウェアプラットフォーム. セミナー@武田薬品工業株式会社 湘南研究所, Dec. 3, 2013. (invited)

北野宏明. 多階層生体機能学：モデル創薬から臨床推論サポートまで. 金沢医科大学第15回KMU研究推進セミナー, 金沢医科大学病院, Dec.4, 2013. (invited)

北野宏明. Current Status and Perspectives on Systems Drug Discovery. システム創薬の現状と今後の展望. アスピオファーマ社内セミナー, アスピオファーマ

株式会社, Dec. 24, 2013. (invited)

Natalia Polouliakh and Hiroaki Kitano "Discovery of gene network by clustering and promoter analysis. The Journal of Toxicological Sciences ISBN:0388-1350 Vol:37 (Supplement 1) S31. The Japanese Society of Toxicology.

Kitano, H. Will engineering play the lead role in drug discovery in 2030? BioMelbourne breakfast, Cinema 1, Melbourne, Australia, June 5, 2012.(invited)

Kitano, H. Software Platform for Systems Drug Discovery. Bio-IT World Asia Conference 2012, Marina Bay Sands, Singapore, June 8, 2012. (invited)

Kitano, H. Systems Drug Design and Garuda Software Platform. Network Biology SIG: On the Analysis and Visualization of Network in Biology (NetBio SIG), ISMB 2012, Long Beach Convention Center, USA, July 13, 2012. (invited)

Kitano, H. HD-Physiology, Garuda, and Computational drug side-effects prediction. Talk at FDA, FDA, Silver Spring, USA, July 17, 2012. (invited)

Kitano, H. Biological Robustness. Seminar at University of Toronto, University of Toronto, Canada, Aug. 20,

2012. (invited)

Kitano, H. Systems Biology powered by Artificial Intelligence. PRICAI-2012: 12th Pacific Rim International Conference on Artificial Intelligence (via skype, invited), Pullman Hotel, Kuching, Malaysia, Sep. 7, 2012. (invited)

Kitano, H. VPH in industrial research. VPH 2012, Savoy Place, London, UK, Sep. 20, 2012. (invited)

北野宏明. システム創薬と Garuda プラットフォームの概要. BioJapan 2012, パシフィコ横浜, Oct. 11, 2012, (invited)

Kitano, H. Systems biomedicine and their computational platforms. FOSBE 2012, Institute for Advanced Biosciences, Keio University, Oct. 21, 2012. (invited keynote)

北野宏明. システムバイオロジー概論. 第6回 KAST システムバイオロジー講座, かながわサイエンスパーク, Nov. 2, 2012. (invited)

Kitano, H. "Systems Toxicology", An invited Talk at DSTO, Defence Science and Technology Organisation (DSTO), Department of Defence, Australian Government, Melbourne, Australia, Dec. 4, 2012. (invited)

北野宏明. Data-Driven Network-Based

Biomarker Discovery. 第35回日本分子生物学会年会 バイオテクノロジーセミナー, 福岡国際会議場, Dec. 12, 2012. (invited)

G. 知的所有権の取得状況

1. 特許取得

特許第 5177712 号、2013 年 1 月 18 日登録、特許権者：国立医薬品食品衛生研究所、NTT データ、発明者：菅野純、相崎健一ら、「競合的ハイブリダイゼーションにおける遺伝子データの補正方法及び補正装置」

2. 実用新案登録

なし

3. その他

なし

(資料 1) 総合報告資料

厚生労働科学研究費補助金(化学物質リスク研究事業)

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 -

(H24-化学-指定-006)

国立医薬品食品衛生研究所・安全性生物試験研究センター・毒性部
菅野 純

1



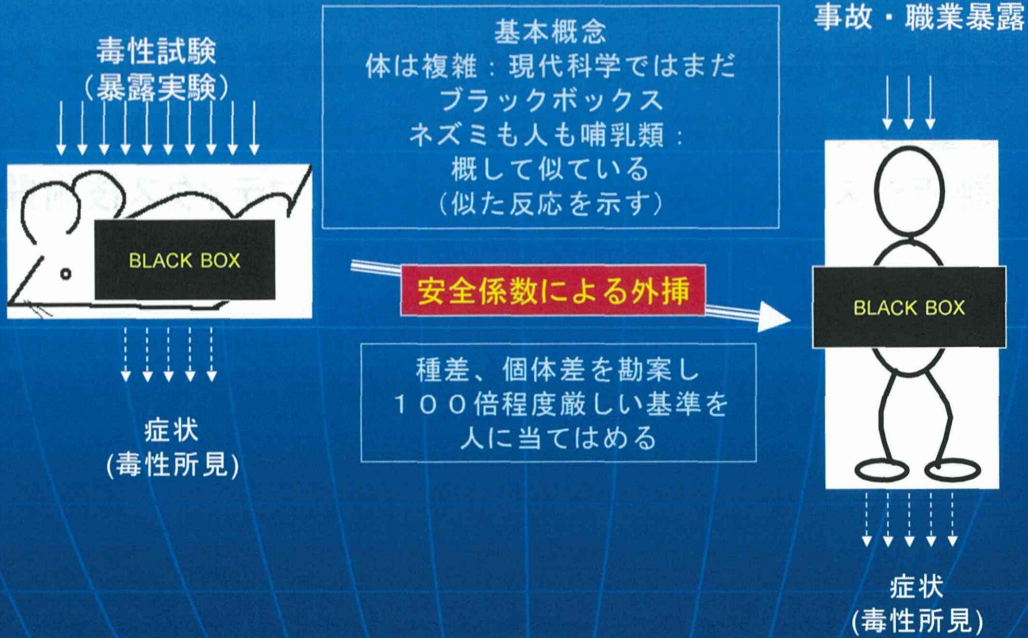
Percellome Project

トキシコゲノミクスを必要とする理由 (研究目的と期待される成果)

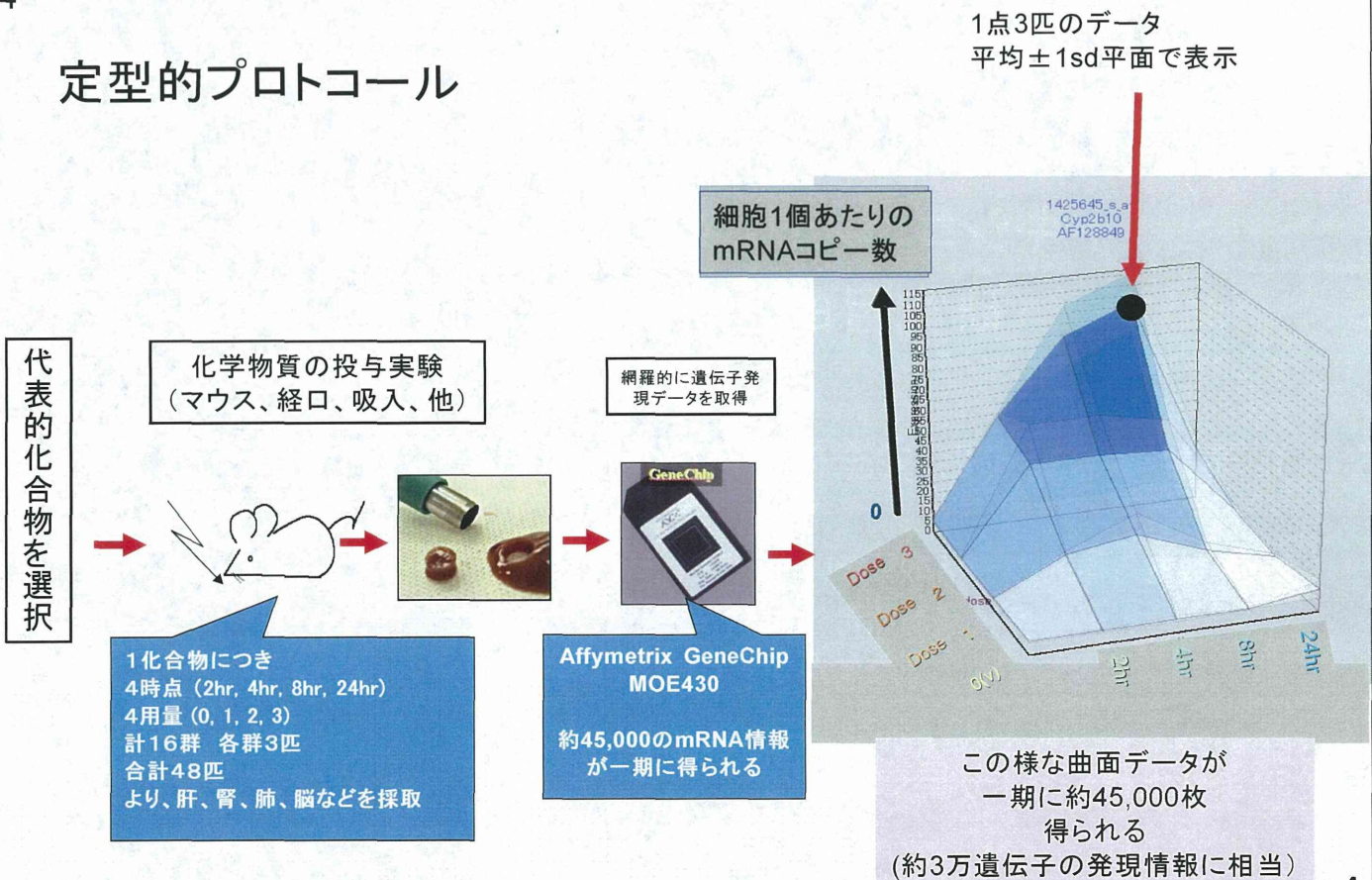
1. 毒性学の近代化:安全係数からの脱却
2. 多数ある標的の一括取り扱い
多種類ある毒性試験法
(2年かかるもの、億単位の経費のかかるもの)
3. より正確に、より早く、より安く(3Rにも貢献)

2

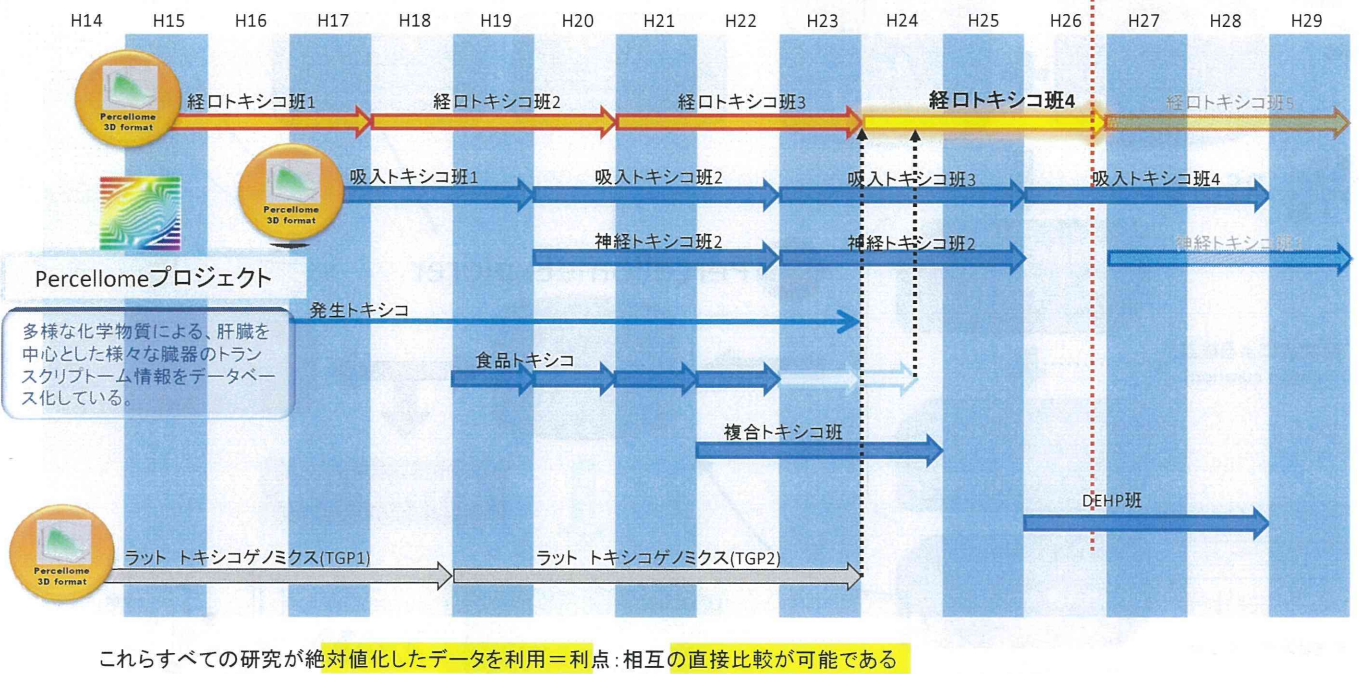
動物実験(毒性試験) 齧歯類(ラット・マウス)などを用いる =人の身代わりとして



定型的プロトコール



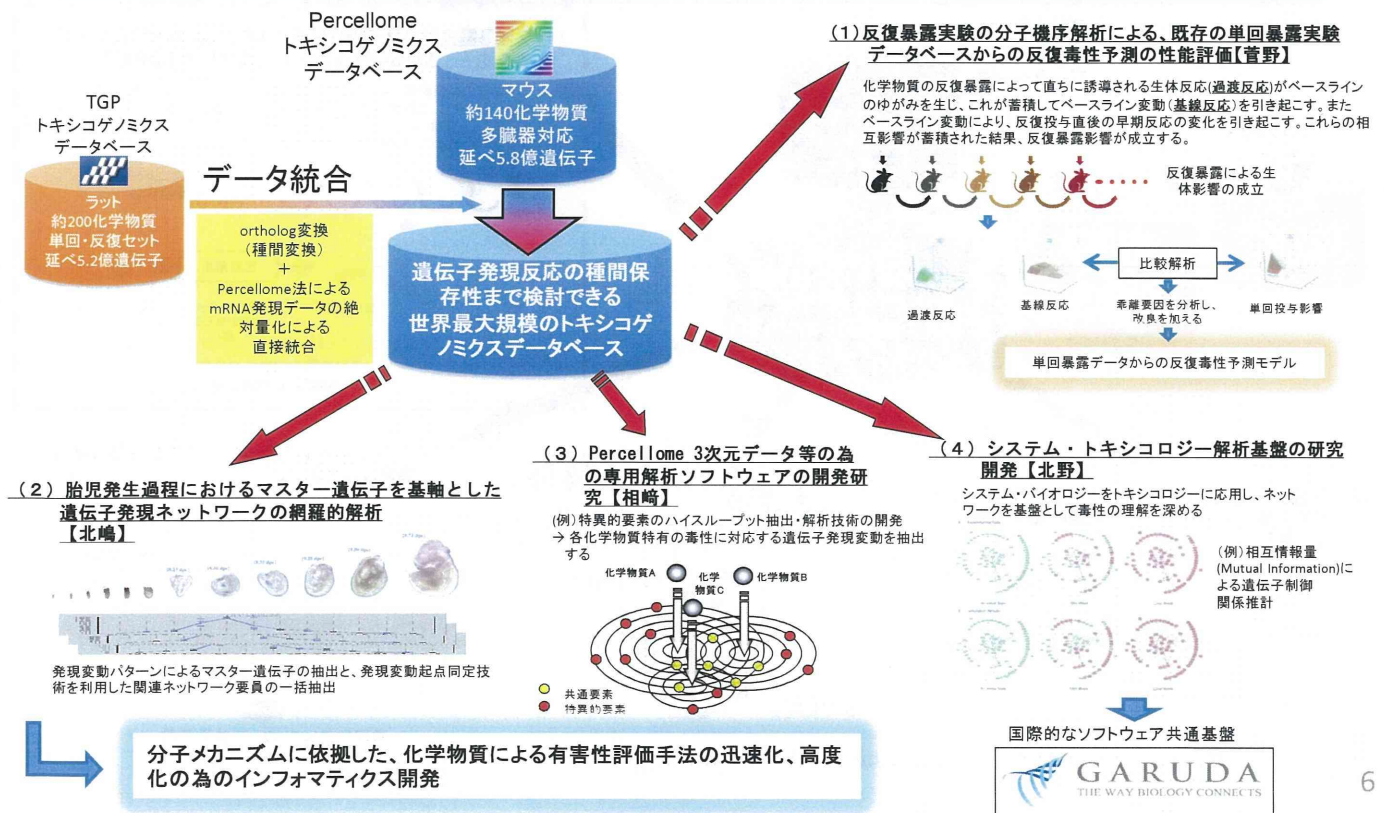
毒性部が展開するトキシコゲノミクス研究



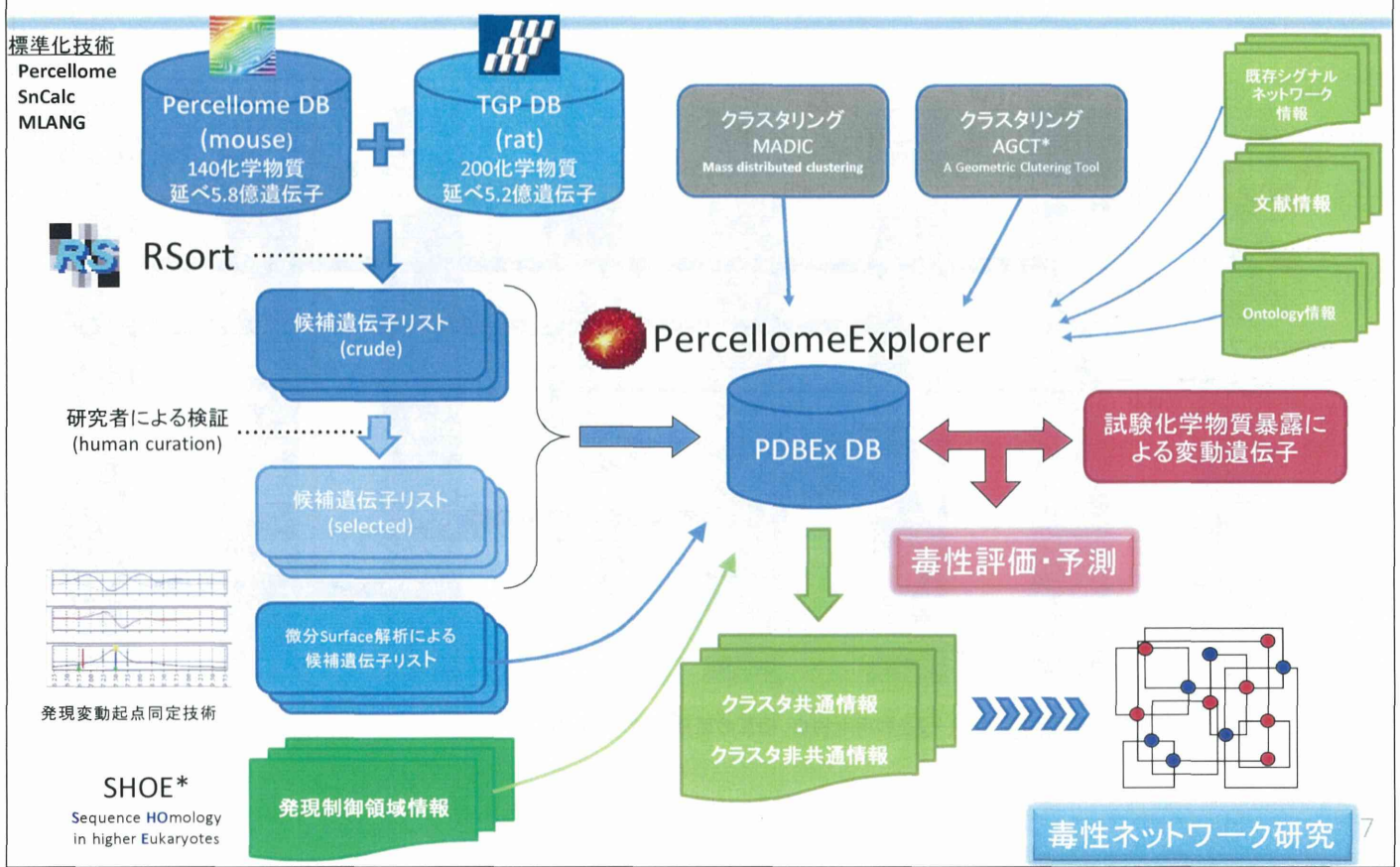
これらすべての研究が絶対値化したデータを利用=利点:相互の直接比較が可能である

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

一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

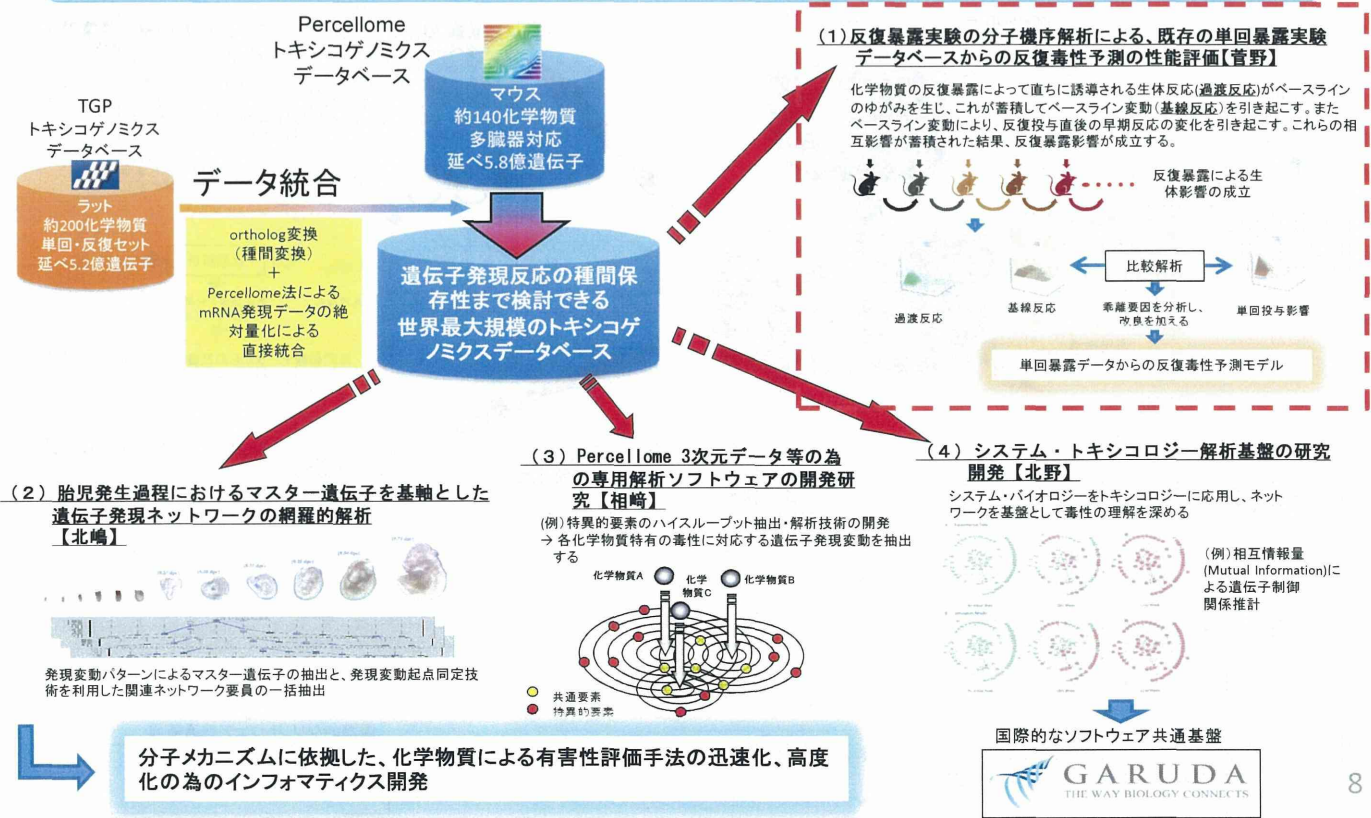


インフォマティクスによる解析の流れ



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

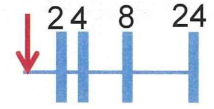
— 網羅的定量的大規模トキシコゲノミクスデータベースの維持・拡充と毒性予測評価システムの実用化の為のインフォマティクス技術開発 —



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

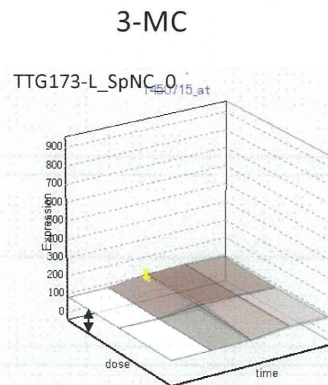
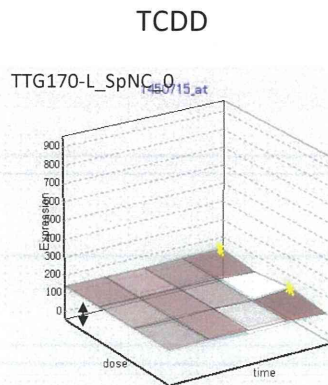
遺伝子改変マウス



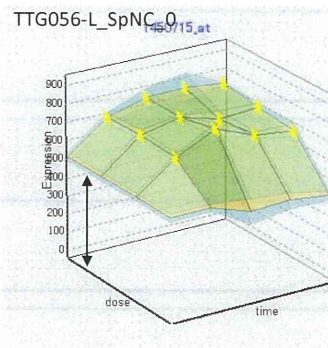
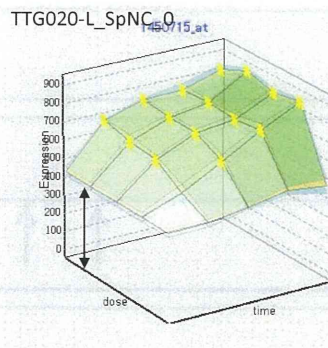
単回投与

9

AhR KO mouse



Wild type mouse



Cyp1a2

NM_009993

cytochrome P450, family 1, subfamily a, polypeptide 2

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)

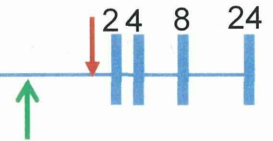
11

A+A' Protocol

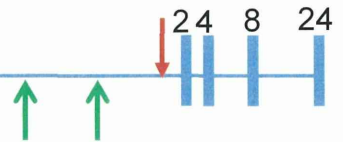
[0 + 1]



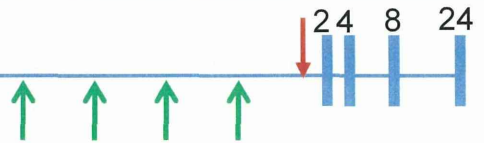
[1 + 1]



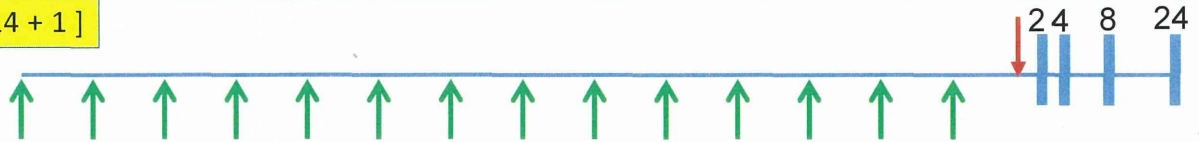
[2 + 1]



[4 + 1]



[14 + 1]



12

[0 + 1]

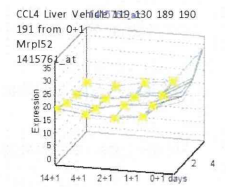
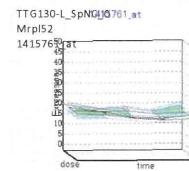
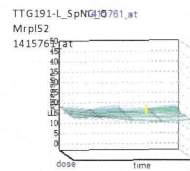
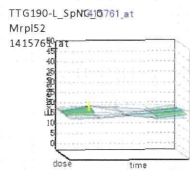
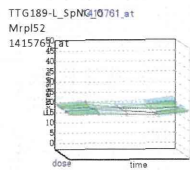
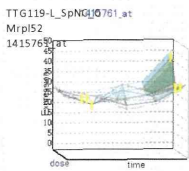
[1 + 1]

[2 + 1]

[4 + 1]

[14 + 1]

Vehicle



四塩化炭素

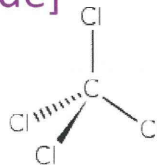
[Carbon tetrachloride]

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

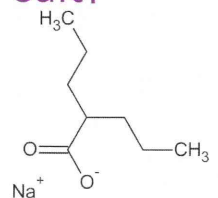
[Valproic acid sodium salt]

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]



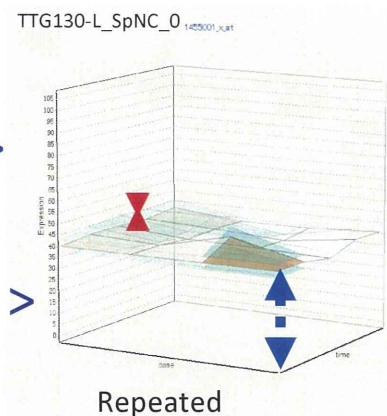
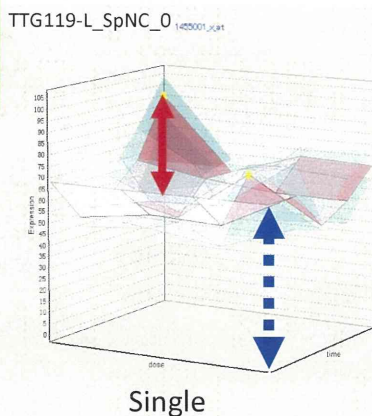
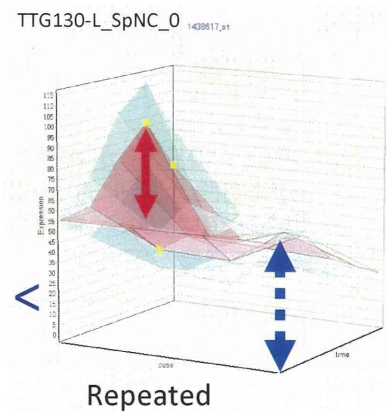
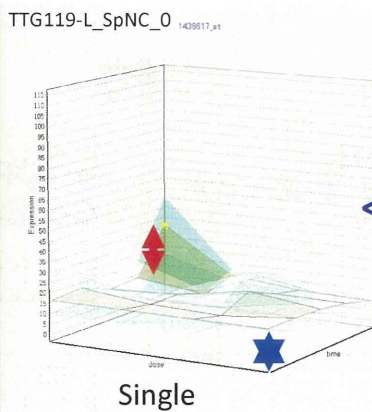
13

●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



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

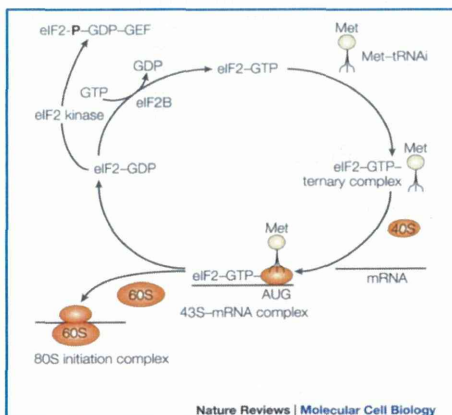
● 基線反応のメカニズムに、『エピジェネティックな制御』を想定

基線反応が低下した化合物

- 四塩化炭素
- クロフィブレート
- 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

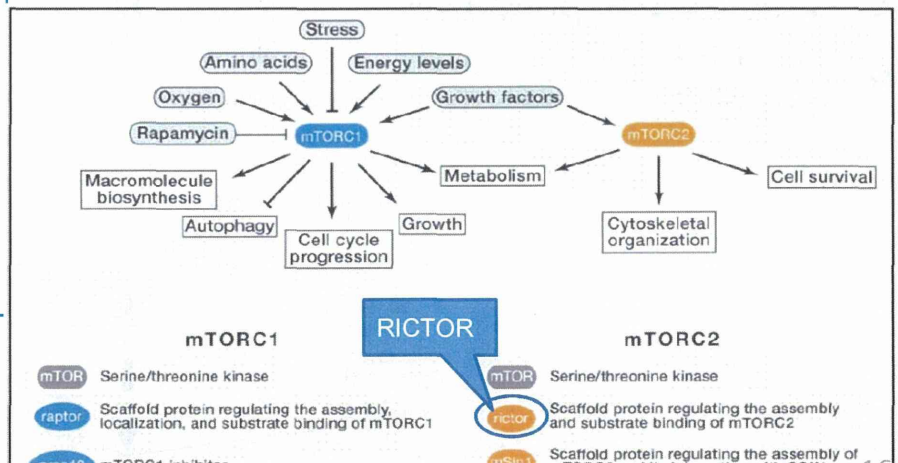


Cell

mTOR Signaling in Growth Control and Disease

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

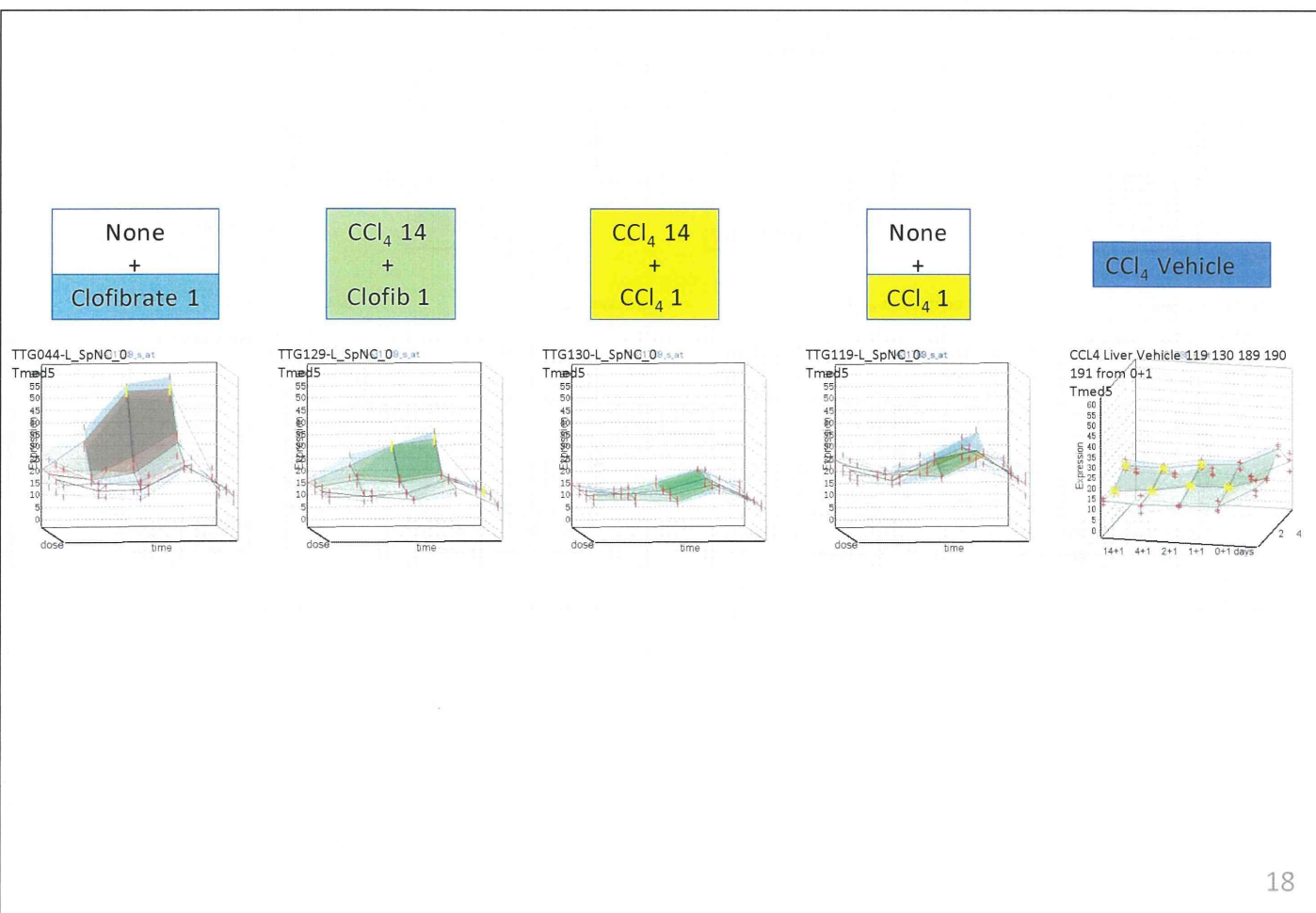
¹Whitehead Institute for Biomedical Research, Nine Cambridge Center, Cambridge, MA 02142, USA
²Howard Hughes Medical Institute, Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
³Koch Center for Integrative Cancer Research at MIT, 77 Massachusetts Avenue, Cambridge, MA 02139, USA
⁴Department of Cell Biology, Harvard Medical School, Boston, MA 02115, 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

17



18

[14+1]

TBT + Clofibrate

CCl4 + Clofibrate

