

Title of Research:

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Development of a combined in vitro/in silico system to predict and evaluate the complex hepatotoxicity of chemical compounds.

Principal Investigator:

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Collaborators:

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Summary of Research:

The aim of study is to develop a system for toxicity evaluation and prediction. In this study, we measured the in vitro reactivity to xenobiotic-responsive nuclear receptors and cytochrome P450s of the chemicals in HESS toxicity database, which contains rat repeated dose toxicity test data of Chemical Substances Control Law-related substances and is available from National Institute of Technology and Evaluation. The results indicate that those biological assay data for nuclear receptors and cytochrome P450s can be used as different types of molecular descriptors from those calculated in silico based on chemical structures. Then, the in vitro assay data and in silico molecular descriptors were subjected separately or in combination to hierarchical clustering and the resulting groupings were compared. The results suggest that the addition of in vitro assay data is useful for grouping chemicals showing similar toxicity properties. Although verification with more large numbers of chemicals is needed, our findings will help to establish a novel toxicity-predicting system based on grouping/categorization and read-across methods.

Timeline:

March 2016 – February 2017

Topics:

None

Publications:

Journal article

1. A Masuda, K Yoshinari, et al.: Construction of the database of rat repeated-dose toxicity tests for the toxicological characterization of hepatocyte hypertrophy. *Yakugaku Zasshi*, 2017 in press.

Oral/poster presentation

1. K Yoshinari, H Oki, T Sasaki, T Hosaka, J Takeshita: New approach for the prediction of repeated-dose toxicity using in vitro and in silico methods in combination with in vivo toxicity database. ICCA-LRI and NIHS Workshop. Jun. 2016, Awaji, Japan.
2. K Yoshinari, H Nakayama, et al.: Attempt on the in silico prediction of rat hepatotoxicity using hierarchical clustering with chemical descriptors. 29th Annual Meeting of the Japanese Society for Alternatives to Animal Experiments. Nov. 2016, Fukuoka.
3. M Watanabe, K Yoshinari, et al.: Biological profiling of chemical compounds based on the inhibition of cytochrome P450 activities. 29th Annual Meeting of the Japanese Society for Alternatives to Animal Experiments. Nov. 2016, Fukuoka.
4. T Sasaki, K Yoshinari, et al.: Inhibitory effects on human cytochrome P450s of chemical compounds and their associations with hepatotoxicity. 137th Annual Meeting of the pharmaceutical Society of Japan. Mar. 2017, Sendai.
5. Y Kitsunai, K Yoshinari, et al.: Search for novel functions of PXR and CAR using in vivo toxicity data. 137th Annual Meeting of the pharmaceutical Society of Japan. Mar. 2017, Sendai.