

Title of Research:

13_PT01-03-2

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

Kouichi Yoshinari (University of Shizuoka)

Collaborators:

Hiroyuki Kojima (Hokkaido Institute of Public Health)

Summary of Research:

The aim of this study is to develop an in vitro/in silico system for toxicity evaluation and prediction, using the chemicals' biological properties based on the in vitro reactivity to xenobiotic-responsive nuclear receptors in combination with the physicochemical properties shown as chemical descriptors. Especially, we have developing an prediction system for rat repeated dose toxicity (RDT) using a HESS database, which contains RDT test data of Chemical Substances Control Law-related substances and is available from National Institute of Technology and Evaluation, and a rat RDT test database of pesticides, which has been constructed by our group. In this system, we are using a grouping (read-across) method based on hierarchical clustering. In this research period, with HESS database compounds we have found that groupings only with chemical descriptors show relatively high accordance with groupings with RDT test data (Rand index: ~0.8). Meanwhile, some concerns and problems have been raised including the importance of the selection of descriptors and toxicity findings and the insufficiency of in vitro assay data. These points need to be solved and cleared in the next year. For the analysis with pesticides, the database construction and in vitro reporter assays of 4 nuclear receptors were completed. After calculation of descriptors, grouping analysis with these toxicity data, in vitro assay data and descriptors will be performed in the next year.

Timeline:

March 2015 – February 2016

Topics:

None

Publications:

Invited lecture

1. K. Yoshinari: Development of a combined in vitro/in silico system to predict and evaluate the complex hepatotoxicity of chemical compounds. in "What Will Work? Future Approaches and Technologies for Assessing Chemical Safety", 2015 ICCA-LRI & U.S. EPA Workshop. June, 2015. New Orleans, LA, USA.
2. K. Yoshinari: Role of nuclear receptors in chemical toxicity and its application to toxicity prediction. 2015 LRI Annual Meeting, August, 2015. Tokyo.
3. K. Yoshinari: Development of an in vitro/in silico combined system for the toxicity prediction. CBI Annual Meeting 2015. October, 2015. Tokyo.
4. K. Yoshinari: A new approach to the prediction of repeated dose toxicity. The 28th Annual Meeting of the Japanese Society for Alternatives to Animal Experiments. December, 2015. Yokohama.
5. K. Yoshinari: Role of xenobiotic-responsive nuclear receptors in hepatotoxicity. 13th Meeting of the Asia Pacific Federation of Pharmacologists. February, 2016. Bangkok, Thailand.

Oral/poster presentation

1. M. Masuda, K. Yoshinari: Toxicological characterization of hepatocyte hypertrophy using public data of in vivo toxicity tests. The 135th Annual Meeting of the Pharmaceutical Society of Japan. March, 2015. Kobe.

Development and assessment of new risk assessment methods

2. K. Yoshinari, M. Masuda, A. Masuda, M. Sekimoto, K. Nemoto: Toxicological characterization of hepatocyte hypertrophy using rat 2-year repeated dose toxicity/carcinogenicity tests. The 42nd Annual Meeting of the Japanese Society of Toxicology. June, 2015. Kanazawa.
3. A. Masuda, M. Masuda, M. Sekimoto, K. Nemoto, K. Yoshinari: Construction of the database of rat 90-day repeated dose toxicity tests and its application to toxicological characterization of hepatocyte hypertrophy. The 42nd Annual Meeting of the Japanese Society of Toxicology. June, 2015. Kanazawa.
4. K. Yoshinari, A. Masuda, M. Masuda: Construction of toxicity database of rat repeated dose toxicity tests and its application to toxicological characterization of hepatocyte hypertrophy. Forum 2015 Pharmaceutical Health Science & Environmental Toxicology. September, 2015. Kobe.
5. A. Masuda, M. Masuda, K. Yoshinari: Toxicological characterization of hepatocyte hypertrophy for the safety evaluation of food contaminants: Analysis using in vivo toxicity test data of pesticides. The 1st Forum of Regulatory Sciences for Young Scientists. September, 2015. Funabashi.
6. K. Yoshinari, H. Nakajima: In vitro and in silico analyses of the association of hepatocyte hypertrophy with nuclear receptor activation and enzyme induction. 30th the Japanese Society for the Study of Xenobiotics Annual Meeting. November, 2015. Tokyo.