Title of Research:

13_PT01-03

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:

N/A

Summary of Research:

Nuclear receptors are the group of transcription factors that are activated by a wide variety of chemicals and are involved in hepatotoxicity. The aim of this study is to develop a new method for the prediction of chemical-induced hepatotoxicity, based on a combined use of data analysis technology and the chemical properties for nuclear receptor activation, which can be assessed by in vitro assays. In this research term, we extracted in vitro toxicity data (liver, blood chemistry) from a publicly available database, HESS-DB (NITE, Japan) to build a database for the association study. In addition, we performed reporter assays of 5 rat nuclear receptors (AHR, CAR, PXR, PPARα, LXRα) for 190 chemical compounds selected from HESS-DB. To obtain physicochemical properties of these compounds, 3764 molecular descriptors from 19 different categories were calculated using the software Dragon. We are currently performing association studies among in vivo toxicity, the results of in vitro assays and chemical properties obtained in silico. Moreover, we have established a metabolism-integrated in vitro reporter gene assay to improve the in vivo and in vitro correlation.

Timeline:

November 1st, 2013 – February 28th, 2015

Topics:

N/A

Publications:

Invited lectures:

1. Mechanistic analysis, assessment and prediction of chemical-induced hepatotoxicity using a database of in vivo toxicity and in vitro assays. Yoshinari, K., CBI 2013 Annual Meeting. October 2013, Tokyo.
2. In vitro and in silico studies of nuclear receptors toward the prediction of chemical-induced hepatotoxicity. Yoshinari, K., 2013 Seminar for QSAR for chemicals. March 2014, Tokyo.

Meeting presentations:

1. Development of metabolism-integrated in vitro reporter gene assay. Yoshinari, K., Nakajima, H., Noomote, C. The 26th Annual Meeting of Japanese Society for Alternatives to Animal Experiments. December 2013, Kyoto, Japan.
2. Establishment of reporter gene assay equipped with metabolic system. Noomote, C, Nakajima, H., Yoshinari, K. The 134th Annual Meeting of the Pharmaceutical Society of Japan. March 2014, Kumamoto, Japan.