



**Title of Research:**

Proposal of a new AOP for the neurotoxicity and developmental neurotoxicity assessment of glutamate receptor binding agonists that cause learning and memory impairment.

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**Summary of Research:**

When the actin-binding protein drebrin which forms dendritic spines of neurons is eliminated by NMDA-type glutamate activity, the spines become thinner and eventually disappear. Loss of dendritic spines impairs learning and memory. In this study, we developed an image analysis algorithm that automatically counts the number of drebrin immunostained clusters in 3-weeks cultured rat fetal hippocampal-derived neurons. Next, we measured changes in the number of drebrin clusters caused by chemical substances. This research resulted in a proposal submitted an Adverse Expression Pathway (AOP) to OECD. The AOP started from the binding of the compound to the NMDA-type glutamate receptor as a molecular initiation event (MIE) , and end at the impairment of learning and memory as the adverse event (AO). The new proposal was registered as Wiki475. We will collect evidence to complete AOP-Wiki475 in the future.

**Timeline:**

March 1, 2020 –

**Topics:**

Poster presentation in 2022 ICCA-LRI & NITE Workshop "Proposal of a new AOP for the neurotoxicity and developmental neurotoxicity assessment of glutamate receptor binding agonists that cause learning and memory impairment."

**Publications:**

Mase S, Mitsuoka T, Koganezawa N, Shirao T, Sekino Y, "Drebrin cluster analysis using cultured hippocampal neurons"ISRN-2022, Web, March 2022

Sekino Y., "The neurochemistry of addiction and strategies for substance abuse prevention" 69th Annual meeting of Hokkaido Pharmaceutical Sciences, Web, May 2022

Shogo Mase, Toshinari Mitsuoka, Noriko Koganezawa, Hiroyuki Yamazaki, Yuuichi Kato, Izuo Tsutsui, Hiroshi Kawabe, Tomoaki Shirao, Yuko Sekino "Quantitative analysis of developmental neurotoxicity using drebrin immunocytochemical images of cultured rat hippocampal neurons" The 49th Annual Meeting of the Japanese Society of Toxicology, Sapporo, June 2022

Shogo Mase, Toshinari Mitsuoka, Noriko Koganezawa, Hiroyuki Yamazaki, Yuuichi Kato, Izuo Tsutsui, Hiroshi Kawabe, Tomoaki Shirao, Yuko Sekino, "High-content analysis using drebrin immunocytochemical images of cultured rat hippocampal neurons" Japan Basic and Clinical Pharmacology Week 2022, Dec 2022

Yuko Sekino, "Collecting Evidence for Enlightenment Activities to Prevent Illegal Drug Use by Youth" Research Report on Subsidies for the Ministry of Health, Labor and Welfare Administration Promotion Research Project (FY2022)