Title of Research:

23-6-03

A Validation Study for approval of AOP475 that proposes a New Approach Method for OECD TG on Neurotoxicity and Developmental Neurotoxicity.

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Summary of Research:

The aim of this research is to finalize the AOPwiki entry for AOP475 proposed to the OECD. During this term, we participated in AOP coaching and incorporated intracellular Ca^{2+} overload, dendritic spine abnormality, and decreased neuronal network function into the Key Event (KE). We are currently gathering literature to link KE1 to KE4 and examining papers to connect KE4 to KE6. Experiments utilizing frozen rat neurons for primary culture and live rats were carried out to demonstrate the relationship between risk compounds of Impairment of Learning and Memory (AO) and Loss of Drebrin (KE3). Nine compounds were administered to cultured neurons, fixed, and immunocytochemically stained for drebrin and MAP2. Neuronal cell death was observed after 1 and 7 days of treatment with Compound A, but not at 1 hour. However, the number of high-intensity drebrin clusters was significantly reduced even at 1 hr. After a single oral dose of Compound B and Compound C to pregnant rats on gestation day 15, changes in drebrin expression were detected in the hippocampus and neocortex of the offspring (6 weeks). Changes in localization and expression of drebrin are useful indicators for risk assessment of compounds.

Timeline:

March 1, 2023 –

Topics:

Oral presentation at LRI research report meeting (25th Aug. 2023)

Publications:

[Original paper] Lin Waka, Shiomoto Shusaku, Yamada Saki, Watanabe Hikaru, Kawashima Yudai, Eguchi Yuichi, Muramatsu Koichi, Sekino Yuko “Dendritic spine formation and synapse maturation in transcription factor-induced human iPSC-derived neurons.” iScience. 26(4):106285, 2023, and another publication

[Conference presentation] Yuko Sekino, Izuo Tsutsui, Tomoaki Shirao, Shihori Tanabe “Impairment of learning and memory via loss of drebrin from dendritic spines of neurons.” The 97th Annual Meeting of the Japanese Pharmacological Society, Kobe, December 2023, and five other publications.

【Lecture】Yuko Sekino, "Actin cytoskeleton in synapses controls memory," The 46th Annual Meeting of the Japanese Neuroscience Society, Luncheon Seminar, Sendai, August 1, 2023.