Title of Research:

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:

This project aims to finalize the AOPwiki entry for AOP 475, proposed to the OECD. During this term, we participated in AOP coaching three times from Dr. Rex FitzGerald, a member of the OECD's Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST).

AOP 475 outlines a pathway involving loss of drebrin (KE_2078) and dendritic spine abnormalities (KE_2242) leading to learning and memory impairments, without neuronal death. To integrate new KEs, we propose several key event relationships (KERs), including: Increased Intracellular Calcium Overload leading to Loss of Drebrin (KER_3091), Loss of Drebrin leading to Dendritic Spine Abnormality (KER_3298), and Dendritic Spine Abnormality leading to Dysfunctional Synapses (KER_3301). Literature and experimental data are being reviewed to validate these links.

To explore the relationship between compounds affecting learning and memory (AO) and drebrin loss (KE3), we conducted experiments using primary rat hippocampal neurons. 7 compounds were tested, with Compound A reducing the number of drebrin clusters without inducing cell death after 1 hour of exposure. Compound B had no effect alone but enhanced the effect of Compound A when co-administered. These findings provide critical evidence supporting the linkage between KE3 (drebrin loss) and AO (memory impairment) in AOP 475.

Timeline:
March 1, 2024 –

Topics:

Publications:
[Original paper] Koganezawa N, Roppongi RT, Sekino Y, Tsutsui I, Higa A, Shirao T. “Easy and Reproducible Low-Density Primary Culture using Frozen Stock of Embryonic Hippocampal Neurons” J Vis Exp. Jan 27;(191). 2023, Video disclosed in Public at April 2024.and another publication
[Conference presentation]
[Lecture]