



Title of Research:

20-3-10

Establishment of an adverse outcome pathway for the evaluation of developmental neurotoxicity in chemical-induced hypothyroidism

Principal Investigator:

Tsuyoshi Nakanishi (Laboratory of Hygienic Chemistry and Molecular Toxicology, Gifu Pharmaceutical University)

Collaborators:

Daisuke Matsumaru (Laboratory of Hygienic Chemistry and Molecular Toxicology, Gifu Pharmaceutical University)

Summary of Research:

In humans, environmental chemicals that induce hypothyroidism can be a significant risk during pregnancy, since fetal brain development in early pregnancy depends on thyroid hormones supplied by the mother. However, the detailed causal relationship between abnormalities in thyroid function during pregnancy and adverse effects on the development of the baby's brain is unknown. In order to solve such a problem, we focused on differentiation markers of mature neurons and produced reporter transgenic mice (Tg mice) carrying luciferase (Luc2) and LacZ genes downstream of a differentiation marker promoter. In this fiscal year, we verified the usefulness of Tg mice by characterizing the expression of reporter genes in Tg mice. Among the three lines obtained, the highest Luc2 activity was observed in the mature males and females of line #1 at the sites responsible for higher brain functions, including the cerebral cortex. Although, in males, Luc2 activity was also observed in the testes as in brain tissue, Luc2 activity was rarely detected in other organs. In the brain, Luc2 expression peaked immediately after birth and dropped sharply as the age progressed. When the brain slices were X-gal stained to confirm the expression of the LacZ gene, lacZ also showed the same expression pattern as Luc2. These results indicate that tracing luc2 and LacZ expression may provide some understanding of neuronal differentiation. In the future, *in vivo* imaging immediately after birth of this Tg mouse will be performed to verify the usefulness of this mouse, and the adverse effects induced during hypothyroidism during pregnancy will be examined by tracing the expression fluctuations of the reporter genes.

Timeline:

April 1, 2020 – March 31, 2021

Topics:

Oral presentation at JCIA LRI Annual Workshop 2020 "Establishment of an adverse outcome pathway for the evaluation of developmental neurotoxicity in chemical-induced hypothyroidism" (On-line, August 21st, 2020)

Publications:

Ishida K, Minamigawa Y, Mori K, Matsumaru D, Nakanishi T, Establishment of neuronal differentiation tracer mouse for evaluation of developmental neurotoxicity, The 141st Annual Meeting of the Pharmaceutical Society of Japan (Hiroshima), 2021.