Title of Research:

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Development of in vivo fluorescent imaging of neuronal differentiation in zebrafish for developmental neurotoxicity testing

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Summary of Research:

Various chemicals may affect the differentiation of neurons, oligodendrocytes and astrocytes, which may cause neurodevelopmental disorders such as autism and attention deficit hyperactive disorder. *In vivo* models that can be used in both visualization of the neuronal differentiation and quantitative assessment of behavior are highly valuable for developmental neurotoxicity testing. Recently, zebrafish has emerged as an alternative non-mammalian animal model that allows testing of large numbers of subjects while reducing expenses and minimizing the use of mammalian subjects. In this study, we have developed three-color zebrafish exhibiting blue, yellow and red fluorescence in neurons, oligodendrocytes and astrocytes, respectively. Using the zebrafish, we demonstrated that anti-thyroid drugs and thyroid hormone inhibited and stimulated, respectively, the differentiation of oligodendrocytes, which is well consistent with the effects in mammals. Using *in silico* analysis of transcriptome data of mammalian stem cells, we identified sterol regulatory element binding transcription factors (SREBFs) as the key transcription factor in oligodendrocyte differentiation. Using the zebrafish, we were able to demonstrate that chemicals that could inhibit and activate SREBFs impaired and stimulated, respectively, the differentiation of oligodendrocytes. These results suggest that integration of *in silico* prediction and *in vivo* fluorescent imaging of neuronal differentiation in zebrafish can be useful to examine the developmental neurotoxicity of many chemicals and provide a sound basis for human risk assessments.

Timeline:

Mar 2015 ~ Feb 2016

Topics:

Publications:

1) **DNA damage response is involved in the developmental toxicity of mebendazole in zebrafish retina.** Sasagawa S, Nishimura Y, Kon T, Yamanaka Y, Murakami S, Ashikawa Y, Yuge M, Okabe S, Kawaguchi K, Kawase R, Tanaka T. *Frontiers in Pharmacology* 7:257 (2016)
2) **In vivo detection of mitochondrial dysfunction induced by clinical drugs and disease-associated genes using a novel dye ZMJ214 in zebrafish.** Sasagawa S, Nishimura Y, Koiwa J, Nomoto T, Shintou T, Murakami S, Yuge M, Kawaguchi K, Kawase R, Miyazaki T, Tanaka T. *ACS Chemical Biology* 11(2):381-8 (2016)
3) **Using zebrafish in systems toxicology for developmental toxicity testing.** Nishimura Y, Inoue A, Sasagawa S, Koiwa J, Kawaguchi K, Kawase R, Maruyama T, Kim S, Tanaka T. *Congenital Anomalies (Kyoto)*. 56(1):18-27 (2016)
4) **Pharmacological profiling of zebrafish behavior using chemical and genetic classification of sleep-wake modifiers.** Nishimura Y, Okabe S, Sasagawa S, Murakami S, Ashikawa Y, Yuge M, Kawaguchi K, Kawase R, Tanaka T. *Frontiers in Pharmacology* 6:257 (2015)