

## Neurotoxicant Disruption of Astroglial Differentiation

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Glial cells play essential roles in homeostasis, the development of the central nervous system (CNS), and the pathophysiology of disease and neurotoxicity. A recent hypothesis suggests that glial cells are CNS progenitor cells that can asymmetrically divide to give rise to neurons, glia and other CNS cell types. SVG cells, an immortalized human astroglial cell line derived from primary fetal brain cells, provide a novel model of the developing human CNS to investigate the mechanisms of action of neurotoxicants. SVG cells exhibit dramatic morphological changes and display neuronal, radial glial, astrocytic, and oligodendrocytic characteristics based on morphology and cell-specific marker expression following the induction of differentiation by co-treatment with the cAMP inducer, forskolin (fsk) and the phosphodiesterase inhibitor, 3-isobutyl-1-methylxanthine (IBMX). In the present multidisciplinary proposal we will test the hypothesis that retinoic acid (RA) and methylmercury (MeHg), two chemically distinct developmental neurotoxicants with different modes of action, alter SVG differentiation, morphology and cell-specific marker expression by disrupting pre-programmed global gene expression. Environmentally relevant doses of RA and MeHg will be included. Data will be analyzed using multiple statistically rigorous strategies in order to compare the relative utility of different methods of identifying significant changes in global gene expression, and to establish associations between global gene expression patterns, cell-specific marker expression and morphogenesis. Results from these studies will identify specific signal transduction pathways and critical regulatory gene expression networks that are disrupted by RA and MeHg during SVG cell differentiation, thus indicating potential causal relationships to developmental neurotoxic lesions and dysmorphogenesis. Moreover, these studies will further characterize the SVG cell line as an innovative CNS cell model that can be used for elucidating the cell specific mechanisms of action of developmental neurotoxicants.

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### Presentation(s):

Burgoon L.D., Kwan K.Y., Fielden M.R., Trosko J.E., Zacharewski T.R. (2002). Retinoic acid induced disruption of cAMP-induced human SVG astroglial cell differentiation: Morphology and global gene expression effects. 41st Annual Meeting of the Society of Toxicology, Nashville, TN, March 17-21, 2002.

Burgoon L.D., Kwan K.Y., Trosko J.E., and Zacharewski T.R. (2003). Cyclic-AMP and retinoic acid induced differentiation of human SVG cells: Morphologic and gene expression effects. 42nd Annual Meeting of the Society of Toxicology, Salt Lake City, UT, March 9-13, 2003.

### Peer-reviewed publication(s):

Eckel, J. E., Gennings, C., Chinchilli, V. M., Burgoon, L. D. and Zacharewski, T. R. (2004). Empirical bayes gene screening tool for time-course or dose-response microarray data. *J Biopharm Stat.* 14: 647-70.

Other publication(s): None to date.

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