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Application of *In Vitro* Models in Developmental Neurotoxicity and Pharmaceutics Research

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Introduction

There is an increasing interest in using *in vitro* models in developmental neurotoxicity and pharmaceutics researches, and their ability to bridge the gap between preclinical data and clinical practices. Because of obvious concerns, it is difficult to thoroughly explore the adverse effects of chemical compounds and/or toxicants in infants and children. Nor is it possible to obtain relevant dose-response and time-course data of pharmaceutic drugs and/or toxicants from humans. However, the availability of *in vitro* models, including primary neural cultures, cell lines, organotypic 3-dimentional (3D) neural cultures and neural stem cell (NSC) cultures, especially human neural stem cells, has provided invaluable tools to examine the etiology and severity of neurotoxicity associated with developmental exposure to the drugs and toxicants.

This editorial article is focusing on how the application of *in vitro* models, when combined with advanced research approaches and analyses, may provide a bridging platform toward decreasing uncertainty in extrapolating preclinical data to human conditions.

Neural Stem Cell Models and High Throughput Research

The nervous system is one of the earliest organ systems to differentiate in the blastula stage embryo. This differentiation can be mimicked *in vitro*. Advances in our understanding of stem cell biology and neuroscience have opened up new avenues of research for detecting early-life, stress-induced neurotoxicity and for developing potential protective strategies against toxicant-induced neuronal injuries. The availability of stem cell cultures, especially human neural stem cells of embryonic origin (because the best model for the human is the human), with their pluripotency and capacity for proliferation, has provided a valuable tool for examining the developmental effects of anesthetic agents *in vitro* [1-4]. In fact, neural stem cell models may represent some of the best systems available for evaluating the potential adverse health impacts of clinical medicine. This capability stems from several attributes of neural stem cells including : 1) source (neural stem cells can be obtained directly from humans); 2) specificity of cell types (this approach allows for examining the adverse effects of chemical compounds and/or toxicants on neural stem cells themselves, as well as neurons, astrocytes and oligodendrocytes and the processes involved with differentiation into those cell types); 3) ability to assess regeneration capacity after exposure to toxicants; 4) potential to significantly impact best clinical practices, such as pediatric anesthesia [5,6]; and 5) the ability to mimic or model particular developmental stages in animals and humans. Embryonic neural stem cells, especially those of human origin provide great opportunities for identifying potential neurotoxicity associated with exposure to toxicants and/or chemicals.

High throughput research can be defined as the automation of experiments such that large scale repetition becomes feasible. It may incorporate techniques from optics, chemistry, biology or image analysis to permit rapid, highly parallel research into how cells function, interact with each other and how pathogens exploit them in disease. This is important because many of the questions faced by life science researchers, especially for new drug development and screening, now involve large numbers. Therefore, combining the neural stem cell models with high throughput research can meet the needs of just about any application, and can allow the neurobiologists to be able to take routine neural cell biology from low scale research to the speed and scale necessary to investigate complex systems, achieve high sample size, or efficiently screen through a collection.

Primary Neural Cultures/Neural Cell Lines and Calcium Imaging

A host of mechanistic studies have been completed or are underway which have been helpful in providing rationale for the overall concern over chemical compound-, drug- and/or toxicant-induced neurotoxicity. These studies have been and will be instrumental in teasing apart the causalities, refining hypotheses, developing alternative or protective measures and suggesting clinical strategies for assessing the phenomena in children. Because of the complexity and temporal features of the manifestations of the developing brain, primary neural cultures and/or neural cell lines have great potential for helping to advance our understanding of brain-related biological processes, including neuronal plasticity, degeneration/regeneration, differentiation, toxicity and even therapeutic efficacy [7,8]. Meanwhile, the primary neural culture system provides a reliable, simple *in vitro* model, within a short time frame, when combined with advanced research approaches, e.g., calcium imaging, for evaluating potential adverse effects and investigating the cellular mechanisms which may be associated with chemical and/or toxicant-induced brain damage. In addition, the primary culture systems provide the opportunity for assessing the brain's own regenerative capacity after experiencing events related to overdoses or prolonged exposures to drugs including some general pediatric anesthetics or environmental chemicals.

It has been demonstrated that local and global elevations in neuronal cytosolic calcium are important for a variety of physiological and pathological processes [9]. Calcium imaging techniques were utilized to investigate the potential interactions between NMDA-evoked calcium influx [10] and NMDA receptor activation of mGlu receptors (metabotropic glutamate receptors) in the mediation of

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calcium signals in cultured neurons.

Therefore, combining these *in vitro* models with calcium imaging and molecular biological approaches creates great possibilities for elucidating mechanisms underlying the etiology of the neurotoxicity associated with developmental exposures to chemical compounds and toxicants, and may also help identify ameliorative strategies.

Organotypic 3-Dimentional (3D) Neural Culture

The nervous system is sensitive to the toxic effects of many chemicals including drugs, environmental agents, and certain naturally occurring substances. Neurotoxicity can result in temporary or permanent damage to the brain or peripheral nervous system and is also a major cause of neurodegenerative diseases. A good *in vitro* model for detecting neurotoxicity and/or pharmaceutic drug development or screening has to replicate the critical developmental characteristics including cell proliferation, migration, process formation, synapse formation and myelination. Although primary cultures, cell lines and stem cells *in vitro*, e.g., human embryonic stem cell (hESC)-related neurogenesis models, can mimic the *in vivo* neuronal development process and provide a simple and unlimited cell source for addressing anesthesia-related issues [1], it is difficult to make an exact comparison between developing brain (3-Dimentional components) vis-à-vis neural stem cells for toxicant-induced neurotoxicity. Also, it is difficult to determine the percent occurrence of neural stem cells in pediatric versus adult brains. However, organotypic culture system provides an invaluable platform for extrapolating preclinical data to human conditions. The organotypic cultures [11] could be prepared from developing rodents [such as postnatal day 7 (PND-7) rat or mouse pups]. The main advantage of using organotypic culture model is that this preparation maintains important anatomical relationship and synaptic connectivity, while at the same time preserving the advantages of an *in vitro* preparation. Currently, 3-D culture systems are generally available and using such systems, cell growth, migration, connectivity and more naturalistic structures and environments can be optimally supported and studied. Additionally, organotypic cultures can well be used to screen the neurotoxic effects of variable toxicants, drugs and/or chemicals, in the most sensitive developing brain at a short amount of period. Recently, comparable and functional high-throughput 3D model platforms and Micro-fluidic Cell Culture Chips have quickly captured the attention of neuroscientists. Studies are continuously revealing new information and it is hoped that therapeutic applications will be developed from both embryonic and adult sources.

In general, the use of preclinical neuronal *in vitro* research models, especially those of human origin, when combined with molecular imaging, biochemical and molecular biology approaches, holds great promise for helping to elucidate relevant mechanisms underlying the etiology of the neurotoxicity associated with developmental exposures to toxicants, drugs, and/or chemicals, and may also help identify ameliorative strategies.

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