Developmental Neurotoxicity Modeling

Presenters: Dr. Mamta Behl, Toxicology Branch, and Dr. Robert Sills, Cellular and Molecular Pathology Branch, NIEHS, NTP

Overview

The mission of the Developmental Neurotoxicity Health Effect Innovation (DNT-HEI) is to have global public health impact by identifying environmental chemicals that have the greatest potential to affect susceptible populations (developing embryo/fetus, infants, children) and thereby prevent neurodevelopmental disorders (e.g. autism spectrum disorder and attention deficit hyperactivity disorder). The DNT-HEI will provide a forum for collaborations among NIEHS staff, including the Division of NTP, Division of Intramural Research, and Division of Extramural Research and Training, NIH, EPA, and FDA's National Center for Toxicological Research; engagement with external stakeholders, including clinicians and children health advocacy groups; and training the next generation of scientists on all aspects of neurodevelopmental disorders related to environmental exposures and on the very latest technology.

Specifically, the DNT-HEI modeling program is a high priority initiative with the aim of providing information on the potential for DNT risks for the thousands of chemicals which have not been evaluated for DNT. Importantly, DNT guideline studies are usually conducted only when there is an a priori trigger, e.g., clinical observations or histopathological changes in the brain noted from acute or subchronic studies, structural and/or use patterns of concern to known DNTs, or if there is suspected/known DNT. As a result, chemicals with unknown potential to cause DNT remain untested. Even in cases with *in vivo* DNT data, there are uncertainties in the current DNT test guidelines due to limitations with respect to sensitivity, reproducibility, and relevance to complex human diseases like autism or attention deficit/ hyperactivity disorder when extrapolating from rodent to humans. This is primarily due to issues with respect to toxicokinetics, timing of exposure in brain development, use of functional tests that may not be sensitive, and concerns that findings in rodents using guideline studies are not designed to capture many of the underlying biochemical or behavioral traits associated with these diseases. Hence, there is a need to expand beyond traditional rodent studies to incorporate models that can screen for compounds rapidly and incorporate humanized cells/tissues[1,2].

In addition, the DNT-HEI efforts are in line with recent consensus for a new framework for DNT testing since in vivo bioassays are too resource-intensive with regard to time, money, and number of animals. The proposal for a new framework is consistent with recent global consensus of regulators, the private sector, advocacy groups, health care professionals, and the public due to the increasing prevalence of learning disabilities and for which the economic costs associated with neurodevelopmental disorders are staggering[3,4].

Furthermore, the advances in technologies and sciences are making it possible to innovate our DNT practices in the areas of prediction (e.g., behavioral and imaging studies)[5,6], translation

(e.g., IVIVE extrapolation and molecular assessments), and integration of short-term assays (e.g., DNT battery of in vitro and alternate models)[2] for assessing DNT. To this end, a DNTP DNT-HEI Program Management Team was recently selected to develop a comprehensive DNT-HEI program including Drs. Mamta Behl, Christopher McPherson, Nisha Sipes, and Robert Sills and Ms. Laura Hall.

References

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