Current Standards for CNS Evaluation in Rodent Toxicity Studies

Thank You to Our Co-Sponsors
Current Standards for CNS Evaluation in Rodent Toxicity Studies

11th European Congress of Toxicologic Pathology
10th-13th September, 2013
European Society of Toxicologic Pathology
Ghent, Belgium

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Europe – Estimated that 35% of all disease burden is attributable to brain diseases and disorders, with the total estimated costs of 686 billion euros

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Neurological Diseases and Disorders</th>
<th>Annual Cost to U.S. Economy in Billions (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0 million</td>
<td>Alzheimer’s Disease</td>
<td>$91B (Ganz, 2006)</td>
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<tr>
<td>0.5 million</td>
<td>Mental Retardation</td>
<td>$51B (Ganz, 2006)</td>
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<tr>
<td>0.5 million</td>
<td>Autism Spectrum Disorders</td>
<td>$35B (Ganz, 2006)</td>
</tr>
<tr>
<td>1.5 million</td>
<td>Parkinson’s Disease</td>
<td>$23B (Huse, et.al., 2005)</td>
</tr>
<tr>
<td>2.5 million</td>
<td>Epilepsy</td>
<td>$15.5B (Yoon, et. al., 2009)</td>
</tr>
<tr>
<td>0.025 million</td>
<td>Amyotrophic Lateral Sclerosis</td>
<td>$0.3B (Society of Neuroscience, 2005)</td>
</tr>
</tbody>
</table>
Significant Global Developments Over the Past 3 Years

Improving the Standards for Nervous System Evaluations in Rodent Toxicity Studies (2010-Present)

• Increasing prevalence of neurologic diseases and disorders

• Markedly expanding knowledge base in the fields of neuroscience

• Increasing awareness of brain complexity
• Modified Sampling of the Nervous System
  – Procedures
  – Sectioning Atlas
  – Terminology

Sills and Little, Rodent CNS Protocol, NTP and NIEHS, Charles River, EPL, 2010

Rao, Little, Malarkey, Herbert, Sills, Toxicologic Pathology, 39: 463, 2011
2012

STP Position Paper: Recommended Practices for Sampling and Processing the Nervous System (Brain, Spinal Cord, Nerve, and Eye) during Nonclinical General Toxicology and Pathology

Kaufmann, Bolon, Bradley, Butt, Czasch, Garman, George, Groters, Krinke, Little, McKay, Narama, Rao, Shibutani, Sills

RENI
The Standard Reference for Nomenclature and Diagnostic Criteria in Toxicologic Pathology
NTP/NIEHS Studies: From 3 to 7 Sections of Brain

Traditional Sampling

New Sampling
Olfactory bulb: High cell turnover rate/inhaled toxicants, metals
Frontal cortex, basal ganglia: Learning and Memory, Motor activity
Parietal cortex, thalamus, hypothalamus: Integration of sensory and motor systems
Mid-brain: Substantia nigra - Parkinson’s Disease
Posterior colliculus: High neuronal metabolic rate – vulnerable site for toxicity
Cerebellum, pons: Posture, balance, muscle tone, coordination of voluntary motor activity
Posterior medulla: Hypoglossal nucleus, Vagus nerve nuclei - Amyotrophic Lateral Sclerosis
NTP/NIEHS Studies: From 3 to 7 Sections of Brain

Traditional Sampling

New Sampling
New Sampling – Section 5

MRM → Morphology → Function

- Microgliosis
- Hemorrhage

Malacia

Brainstem Auditory Evoked Responses

Morgan, Little, Johnson, Maronpot, Sills, Et. al., Toxicology and Applied Pharmacology, 200: 131, 2004

Sills, Morgan, Herr, Little, Love, Maronpot, Johnson, Et. al., Toxicologic Pathology, 32: 501, 2004
Neuroanatomical Subsite (Auditory System)
Linked to Function (Hearing)
Translation (Rat to Human)

Posterior Colliculus
Olivary Nucleus
Lateral Lemniscus
Comprehensive Sampling of the Nervous System

- Colon ganglia
- Sciatic
- Tibial
- Trigeminal and ganglion

Rao, Little, Malarkey, Herbert, Sills, Toxicologic Pathology, 39: 463, 2011
Current Standards for CNS Evaluation in Rodent Toxicity Studies
2013 European Society of Toxicologic Pathology (ESTP) Congress in Ghent

• Moderator/Introduction – Dr. Robert Sills (NIEHS/NTP)

• Use of the NTP Revised Rodent Brain Trimming Procedure for Routine Studies in CROs Dr. Alys Bradley (Charles River)

• Subsite Awareness in the NTP CNS Protocol Dr. Deepa Rao (Integrated Laboratory Systems, Inc.)

• Brain Microanatomy: Cytology, Artifacts, Neoplastic Lesions and Utilization of Special Stains Dr. Robert Garman (Consultants in Veterinary Pathology, Inc.)

• Overview of Non-Neoplastic Lesions of the Nervous System Dr. Peter Little (Consultant with Experimental Pathology Laboratories, Inc.)

• Open Floor Panel Discussion – All Speakers and Audience Chaired by Dr. Robert Sills (NIEHS/NTP)