2017–2018 Activities and Accomplishments

Committee leaders:

Dr. Bill Slikker
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HESI manager:

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HESI associate:

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This scientific program is committed to:

- Identifying and validating minimally invasive biomarkers for monitoring neurotoxicity preclinically.
- Understanding the sensitivity of biomarkers to improve prediction of neurotoxicity.
- Bridging the gap in translation from nonclinical toxicity studies to clinical outcomes.
- Identifying patterns of seizure using *in vitro* multi-electrode array (MEA) technology.

Areas of scientific focus:

- Evaluating biomarkers that are sensitive and specific for the prediction of neurotoxicity.
- Correlating initial study results to broader mechanisms or pathways of neurotoxicity.
- Partnering with outside groups to provide data used for better translation from nonclinical studies to clinical outcomes.
- Characterizing multi-site results to understand *in vitro* prediction of seizurogenic activity.

Why get involved?

- This team is working to increase understanding of the mechanisms of neurotoxicity for improved detection through minimally or non-invasive methods.
- Output provides the opportunity for earlier decision making and de-risking of compounds.
- The MEA project will standardize *in vitro* protocols for convulsive liability testing, thus helping to reduce the need for animal testing.
- Be part of an international, multi-consortium effort to develop novel approaches to be used in biomarker identification and neurotoxicity assessment.

Key accomplishments:

- Completed a pilot study to investigate circulating biomarkers that predict central and peripheral neurotoxicity resulting from exposure to trimethyltin (TMT).
- Initial pilot study results were published and an additional paper with detailed results is in progress.
- Additional rodent samples were identified for further investigation of biomarkers found to correlate in the pilot study.
- Continued collaborations with the HESI Emerging Systems Toxicology for Assessment of Risk (eSTAR) Committee, Istituto Italiano di Tecnologia, Innovative Medicines Initiative, and the National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs).
- Communicated pilot study results at the Society of Toxicology 2018 Annual Meeting and Experimental Biology 2018 Conference.
- MEA *in vitro* study data were collected on 10 known toxins from 11 sites across North America, Europe, and Japan.

The Committee's focus for May 2018–2019:

- Finalize and submit the second paper detailing additional pilot study results.
- Complete the analysis of the additional rodent samples to further correlate biomarker results and develop a manuscript with results.
- Plan and begin a second-phase study to further explore sensitivity and specificity of biomarkers identified in the pilot study.
- Analyze data from the MEA *in vitro* study and begin drafting a paper with results.

Recent publications:

Imam SZ, He Z, Cuevas E, Rosas-Hernandez H, Lantz SM, Sarkar S, Raymick J, Robinson B, Hanig JP, Herr D, MacMillan D, Smith A, Liachenko S, Ferguson S, O'Callaghan J, Miller D, Somps C, Pardo ID, Slikker W Jr, B, Pierson J, Roberts R, Gong B, Tong W, Aschner M, J Kallman M, Calligaro D, Paule MG (2018) Changes in the metabolome and microRNA levels in biological fluids might represent biomarkers of neurotoxicity: a trimethyltin study. *Exp Biol Med (Maywood)*. 243(3):228–236.

2017–2018 Participating organizations

Alpha MED Scientific
Axion Biosystems
Cellular Dynamics International, A Fuji Film Company
Colorado State University
Cyprotex
Duke University
DuPont
Eli Lilly and Company
Genentech
GlaxoSmithKline
Gunma University Graduate School of Medicine
Janssen Pharmaceuticals
Lisbon University
National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs, UK)
National Institute of Health Sciences (Japan)
National Institutes of Health
Ncardia
NeuCyte
Newcastle University
Pfizer Inc.
Pharmaceuticals and Medical Devices Agency (Japan)
Sumitomo Dainippon Pharma
Swiss Center for Applied Toxicology
Takeda Pharmaceutical Company Limited
Tohoku Institute of Technology
Tokyo Graduate School of Pharmaceutical Sciences
University of Birmingham
University of the Netherlands
University of Tübingen, Natural and Medical Sciences Institute
US Centers for Disease Control and Prevention
US Environmental Protection Agency
US Food and Drug Administration
Utrecht University
Virginia Polytechnic Institute and State University
Yeshiva University, Albert Einstein College of Medicine

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