CE 12 Understanding Toxic Neuropathy in Drug Development: Both Clinical and Nonclinical Perspectives.

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The topic of risk assessment of peripheral neuropathies is timely due to the increased clinical incidence of challenges related to multiple antecedents for the clinical presentation of neuropathies. The integration of both nonclinical and clinical dialogue on peripheral neuropathies will provide greater possibilities for successful drug development and improved patient outcomes. Peripheral nervous system toxicity is a common complication of exposure to industrial chemicals and drugs such as chemotherapeutics. Neuropathy can be caused by either limited or long-term exposure to drugs or chemicals, and toxic neuropathies can be classified by their presentation (e.g. motor vs. sensory), their electrodiagnostic features or their neuroanatomical location within the peripheral nerve. Identification of toxic neuropathology prior to human exposure in the drug development process requires a multidisciplinary approach. Presentations will include information on the preclinical and clinical syndromes that have been characterized and the specific techniques for assessment. The preclinical presenters will focus on the application of preclinical data to provide risk assessment and to direct clinical assessment possibilities. The clinical presenters will emphasize the clinical situation and current treatment approaches. The course will conclude with open discussion between the presenters and the audience about opportunities for future risk assessment and the application to clinical management.

CE 13 Weighing in on Nutrition—Essential Concepts for Toxicologists.

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There has been an exponential increase in the attention focused on the potential role of nutrition in reducing the risk for numerous health complications, ranging from birth defects to age-associated vascular disease. Underscoring the above is the increasing number of presentations and publications related to this subject, and hallmarks such as the recently revamped Food Pyramid into a Plate Icon. Chronic nutritional diseases are accepted to be a current crisis in our society; three nutrition-related diseases alone, obesity, Metabolic Syndrome, and Type 2 Diabetes, afflict over one-third of the American population. To better understand the components and etiology of nutritional diseases, it's essential for toxicologists to be well versed in the science of nutrition. A comprehensive understanding of nutrition has broad applications in toxicology, especially considering that many of us have roles in investigating the safety of nutrients, food additives or food ingredients, studying nutritional disease, or designing and interpreting preclinical or clinical studies wherein the need to consider and understand nutritional homeostasis is essential. The potential for intersection of normal nutritional metabolic pathways with adverse outcome pathways is becoming even more important to delineate. This course on general nutrition, the biochemistry of nutritional pathways, the essential role of vitamins, the channeling of nutrients such as carbohydrates, proteins and fats, cellular and molecular details of nutrition, and nutritional aspects of development and reproduction, will heighten awareness of their importance in human and animal health at multiple levels. The focus will be on relevant information, starting with an introduction to nutrition, followed by a review of biochemical and metabolic reactions in nutrition, with an emphasis on their relation to toxicology. How the nutritional status of a woman can modulate the developmental toxicity of a number of diverse toxicants, including alcohol, will be presented.

S 14 Genetic and Epigenetic Determinants of Susceptibility to Environmental and Occupational Toxicants.

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The most common chronic disorders are multifactorial in nature, influenced by complex sequences of gene-gene and gene-environment interactions. While gene expression is a dynamic process that varies in response to a myriad of internal and external triggers and the surrounding microenvironment, the epigenetic mechanisms play a key role in mediating environmental influences on gene expression and epistatic interactions. In this respect, the expression of complex phenotypes should be assessed in a functional context that would look at the interplay between environmental, genetic, and epigenetic factors. Recent advances in genetic and epigenetic research offer new opportunities to integrate experimental approaches, including animal models and *in vitro*/*in vivo* translational research, with computational strategies to predict such interactions at multiple levels of complexity. The focus of this session will be on current research investigating the role of genetic factors, epigenetic factors, and gene-environment interactions in the development and outcomes of complex diseases caused by environmental and occupational toxicants.

S 15 Genetic Susceptibility to Occupational and Environmental Exposures.

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Due to their high prevalence in the general population, genetic polymorphisms in the susceptibility genes may predispose community members exposed to toxicants. Studies in genetic susceptibilities can eventually provide the following benefits: (1) to provide mechanistic insight of the etiology of disease; (2) to identify the more susceptible subpopulations with respect to exposure; (3) to provide valuable input in setting exposure limits by taking into account individual susceptibility. Research in this area has provided promising insights to occupational medicine, such as those illustrated by the NAT2 polymorphisms-aniline dyes and bladder cancer, and the HLA-DPB1Glu69 in chronic beryllium disease, a hypersensitivity-mediated inflammatory disorder. Nonetheless, even for the genetic susceptibility markers that have been shown scientifically to have a clear role in disease risk, the value of wide-scale genetic screening in occupational settings remains limited. In the general environmental setting, there are limited, but growing data on the role of common gene polymorphisms in predisposing children and adults to inflammation-related respiratory disorders induced by air pollution, and to heavy metal toxicity. The purpose of this presentation is to discuss state of knowledge with regard to gene variants interacting with environmental exposures in causing cancer and inflammatory disorders.

S 16 Toxicogenomic and Systems Biology Approaches in the Understanding of Toxicity and Leukemogenesis Induced by Benzene.

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Benzene is an established cause of acute myeloid leukemia (AML) and may cause one or more lymphoid malignancies in humans. Occupational exposure to benzene, even at levels below the current U.S. occupational standard of 1 ppm, causes hematotoxicity. Toxicogenomics (e.g. genomics, transcriptomics and epigenomics) and systems biology (study of the interactions among toxicogenomic endpoints using bioinformatics) approaches in human populations, animals, and in vitro models, exposed to a range of benzene levels, are key to understanding gene-environment interactions in benzene toxicity and can identify biomarkers of exposure, early effect and susceptibility. Through analysis of the peripheral blood mononuclear cell (PBMC) transcriptomes of 125 workers exposed to a wide range of benzene levels, we recently reported highly significant widespread perturbation of gene expression at all exposure levels, as well as alterations in AML and immune response pathways. Sequencing of the PBMC transcriptomes from a subset of the study subjects revealed additional alterations in gene expression. From preliminary epigenomic data in the human subjects, we have identified benzene-induced alterations in the DNA methylome and miRNome. Using genomic screens in yeast, with subsequent confirmation in human cells, we have identified potential biomarkers of susceptibility. We are developing bioinformatic methods to integrate these and future toxicogenomic datasets, in a systems biology approach, to further understand pathways of benzene toxicity and to reveal potential biomarkers associated with a range of exposures.

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S 17 Integrated Genetic and Genomic Approaches to Understand Susceptibility to Toxicant-Induced Lung Disease.

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Genetic background has an important role in susceptibility to complex lung diseases, and the genetic contribution to disease phenotypes varies between populations. Understanding the mechanisms of interactions between genetic background

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