CE 6 PREDICTIVE POWER OF NOVEL TECHNOLOGIES (CELLS TO 'OMICS): PROMISES, PITFALLS, AND POTENTIAL APPLICATIONS.

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Advances in the disciplines of cell and molecular biology have led to the development of novel biotechnologies capable of generating "global molecular profiles" for *in situ* toxicological assessment. These technologies should accelerate our understanding of the molecular basis for susceptibility to toxicants and provide new insights into mechanisms of action. Both theoretical and practical information on these emerging high-throughput technologies and their applicability, interpretation, and integration will present a more comprehensive understanding of cellular responses to chemical/toxicant stress. To begin, the course will highlight the utility of laser capture microdissection in isolating specific cell populations for toxicological assessment at the level of RNA and proteins. An overview of proteomic technologies in protein interaction studies and their relevance to changes in downstream signaling mediators involved in toxic response pathways will be presented, followed by an update of gene expression profiling approaches in toxicogenomics and systems biology research. Focus will be placed on the examination of the capabilities of high-throughput technologies for identifying single nucleotide polymorphisms (SNPs) and their value for identifying and characterizing underlying genetic susceptibilities to toxicants. Finally, high-throughput technologies available to identify genome-wide epigenetic alterations will be presented, including their role in epigenetic alterations in health, disease, and toxicant-induced biological outcomes. The goal of this course is to educate toxicologists on the array of ever-growing technologies available to gain a comprehensive understanding of the underlying mechanisms mediating complex biological responses. Using these technologies, investigators can move towards a better and more reliable prediction and extrapolation of toxic responses. This course is relevant to scientific technical and regulatory staff involved in various stages of compound development.

CE 7 REPRODUCTION AND REGULATORY IMPACT.

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Most new compounds destined for commerce, and all compounds intended for human consumption, need to be assessed for developmental and reproductive toxicity (DART). However, the underlying biology can be confusing because the jargon employed by the cognoscenti can be impenetrable and the implications of findings in these studies are often difficult to appreciate quickly. Our panel will begin this course with an open dialogue designed to lift the veil of uncertainty around many of these issues. After a quick review of some of the key biology, we will touch on the characteristic study designs which generate the necessary data. A point of focus will have the panel examine the typical effects seen in adults and juveniles, and what impact these can have on the registration and use of the compound in Europe and the U.S., respectively. Although the focal point for this course will be on environmental compounds, the final presentation will highlight drug candidates and how reproductive or developmental findings affect their journey to the marketplace. It is our goal to leave students with a better understanding of the impacts that reproductive or developmental findings have on the registration and use of environmental and pharma compounds.

CE 8 ASSESSMENT OF OCULAR TOXICITY IN TOXICOLOGY STUDIES CONDUCTED FOR REGULATORY PURPOSES.

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Ocular toxicity is known to occur following intended or unintended exposure of ocular tissues to xenobiotics. It can occur following local exposure of the eye to an agent or after exposure *via* oral or other routes of administration. In order to define the risks that pharmaceuticals, pesticides, and other toxic substances pose to the eye, an assessment of ocular toxicity is routinely included in general toxicology studies conducted for regulatory purposes. Because anatomical and physiological differences between species can impact the nature of the ocular effects observed, understanding species differences is important. Although it is possible to detect some ocular effects, such as conjunctivitis, with the naked eye, more sensitive techniques are routinely used to assess ocular toxicity. Slit lamp biomicroscopy and indirect ophthalmoscopy are routinely utilized to more closely evaluate the anterior and posterior chambers of the eye, respectively, during the course of toxicology studies. At the time of necropsy, ocular tissues are collected and processed for histopathological evaluation. More specialized endpoints, such as electroretinography, can be incorporated, as needed. Ocular anatomy and physiology and the assessment of ocular toxicity can be challenging to scientists involved in the safety assessment of pharmaceuticals, pesticides and other agents. This basic course will cover ocular anatomy and physiology in laboratory animals, established methods used to assess ocular toxicity, as well as more novel techniques for toxicity assessment. Examples of ocular toxicity that can occur following different routes of exposure will be discussed.

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CE 9 GENE-ENVIRONMENT INTERACTIONS INFLUENCE CYTOKINE BIOLOGY IN IMMUNOTOXICITY AND DISEASE: GENOMIC, GENETIC, AND EPIGENETIC PERSPECTIVES.

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Cytokines are key signaling and effector molecules that regulate many aspects of host response to exogenous stressors. To date, animal and human studies have identified individual and interacting effects of cytokines at different stages in the pathogenesis of chronic inflammatory and immune-mediated diseases. Animal studies utilizing gene knock-out and transgenic animals and expression microarrays have identified disease-related cytokine networks. Human studies using various genome screening efforts have also uncovered potential candidate genes for disease development and progression. Cytokine genes and their receptors are highly polymorphic and variations in these genes have been associated with the course of and susceptibility to a variety of diseases including infectious, inflammatory, and autoimmune. In addition, epigenetic changes including altered DNA methylation and histone acetylation can control cytokine gene expression by changing the transcription-permissive nature of chromatin structure. Environmental factors are known to modify the direction and magnitude of disease risk in an environment-specific manner. In this respect, genetic association studies have identified interactions between cytokine gene variations and environmental/occupational exposures as shown in the case of silicosis and asthma. In addition, recent studies demonstrated that environmental exposures might alter methylation states of key cytokines genes supporting an epigenetic gene-environment interaction. This course will address aspects of the current state of knowledge with respect to genomic, genetic, and epigenetic approaches in the investigation of cytokine genes associated with occupational and environmental-related diseases.

CE 10 MITOCHONDRIAL TOXICITY: ANIMAL MODELS AND SCREENING METHODS IN DRUG DEVELOPMENT.

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Mitochondria produce almost all the energy in cells, but also chronically expose the cell to cytotoxic free radicals. Mitochondrial disease and toxicity is a rapidly advancing field and the consequences of mitochondrial impairment should be appreciated by scientists in all disciplines. It is estimated that more than 75 diseases and metabolic disorders are attributable, at least in part, to mitochondrial dysfunction. Mitochondrial dysfunction can lead to many different pathologies of the liver, heart, muscle, kidney, and CNS through diverse mechanisms. Numerous widely prescribed therapeutics can undermine mitochondrial function by interfering with DNA replication or expression, and more acutely, by uncoupling or inhibiting oxidative phosphorylation, leading to organ dysfunction and damage. In addition, numerous environmental agents can contribute to diseases and toxicity through modifications of mitochondrial function, leading for example to Parkinson's Disease and Autism. This course will review fundamental concepts of mitochondrial biology and the many different mechanisms by which xenobiotics interfere with mitochondrial function. Both common and novel *in vitro* screening approaches will be described, as well as *in vivo* animal models used to study mitochondrial-mediated toxicities and pathologies, with an emphasis on both their utility and limitations. The course will also introduce Structure-Activity Relationship and systems biology approaches to reveal common factors and novel mechanisms of mitochondrial toxicity. Upon completion of this course, participants will have a deeper understanding of how xenobiotics can alter the basic biochemistry and physiology of mitochondria, how minute changes in mitochondrial processes translate into complex toxicities, organ pathologies, and diseases, as well as a basic understanding of how to study mitochondria and mitochondrial dysfunction.