

## 2008

**Developmental Basis of Disease**—understanding birth defects and how lifelong changes in health and disease may follow the exposure to hazardous chemicals during prenatal, infantile, or early childhood stages. Recent epidemiological data suggest that chronic diseases such as diabetes and hypertension may follow a particular event early in life. The cross-cutting goal is to advance scientific understanding of the source-disease outcome from intrauterine or childhood exposure to hazardous chemicals.

**Nanotechnology**—the use of nanomaterials as the building blocks for this promising new technology. Currently being utilized in many diverse areas such as engineering, information technology, and diagnostics, nanomaterials are now routinely produced and commercialized. Because little is known about their biology or the potential health impacts of these new products, these highlighted sessions will explore the potential implication(s) of their use.

**Oxidative Signaling and Redox Biology**—the importance of reactive oxygen species (ROS) in health and disease has been long recognized by toxicologists. In addition to the uncontrolled generation of ROS associated with chemical, physical, and biological toxicities, the abnormal activation of inflammatory cells is known to play an important etiologic role in many degenerative diseases. These sessions will explore how altered conditions in the cell can lead to oxidative stress, which include: 1) increase levels of transition metals or their reactive forms, 2) depletion of non-enzymatic antioxidant defenses, 3) increased generation of ROS, 4) ionizing radiation, and 5) redox cycling.

**Stem Cell Biology and Toxicology**—understanding stem cell biology and its applications and the intense debates ignited in scientific, political, and ethical spheres. The degree to which stem cells can be used in toxicological testing to replace other experimental models is still in its infancy. Given these facts, this area of research has the potential to revolutionize toxicity testing in the academic, private and government setting. The sessions in this theme will explore some of the major challenges that must be overcome and address new issues as they arise.

**2009**

**Biomarkers Theme**

Biomarkers are generating excitement as a means of dissecting and understanding normal biological processes, measuring environmental exposures, predicting disease outcomes, and assessing beneficial or adverse responses to pharmacologic and therapeutic agents. As such, biomarkers have been invaluable to toxicologists as tools for investigating and predicting toxic responses. In addition, a large body of research from the toxicological sciences has contributed to the identification and validation of biomarkers at the molecular, biochemical, and cellular level. Sessions highlighting the many contributions of toxicology to biomarker research will be featured along with sessions highlighting new discoveries related to the identification, validation, and utilization of biomarkers to interrogate health and disease.

**Epigenetics Theme**

Heritable DNA and chromatin modifications determine gene expression patterns and underlie important biological processes including development, X chromosome inactivation, imprinting, and gene silencing and transcription. Alterations induced in key epigenetic determinants including DNA methylation and histone modifications contribute to the adverse health effect of many toxicants, including endocrine disruptors, carcinogens and teratogens. The "epigenome" is now receiving interest comparable to that formerly focused on elucidating the genome of humans and other organisms. Because of the importance of epigenetics in health and disease and the many new and emerging technologies coming into use for studying epigenetics, this theme has been selected to highlight recent advances in epigenetic research for the toxicological sciences.

**Inflammation and Disease Theme**

While the inflammatory response plays an important role in the body's response to injury and infection, it also contributes to several acute and chronic diseases including nephritis, inflammatory bowel disease, autoimmune disease, arthritis, asthma, diabetes, Alzheimer's disease, and cancer. Inflammatory mediators such as reactive oxygen species (ROS), cytokines, and eicosanoids play key roles in these processes. Similarly, the acute-phase proteins such as glucocorticoids, C-reactive protein, and serum amyloids, have beneficial effects but can contribute to diseases such as heart disease and amyloidosis. These inflammatory responses also play a significant role in the adverse response of many organs following exposure to drugs and environmental agents. The important role of inflammation and inflammatory mediators as determinants of toxic responses and disease will be highlighted in sessions featured in this theme.

**Nanotechnology Theme**

Nanomaterials are the building blocks for this promising new technology. These materials are currently being utilized in many diverse areas such as engineering, information technology, and diagnostics. Nanomaterials are now routinely produced and commercialized. Because little is known about their biology or the potential health impacts of these new products, these highlighted sessions will explore the potential implication(s) of their use.

**Neurodegenerative Disease Theme**

Neurodegenerative diseases such as Huntington's, Parkinson's, and Alzheimer's are caused by loss of cells and/or cellular function in the brain. Dementias and movement disorders are becoming increasingly more common. These diseases often have a complex etiology and have been associated with genetic alterations, specific pathogens, alterations of normal physiological

responses such as protein misfolding, and exposures to several environmental agents. The role of environmental agents, gene-environment interactions, early life exposures, and inflammatory mediators in the development of neurodegenerative disease, as well as elucidation of sequelae from acute toxic exposures to the onset of disease, will be highlighted in this theme as important areas of research for the toxicological sciences.

## 2010

### **Cell Signaling Theme**

Cell signaling encompasses the broad range of pathways involved in how cells detect and respond to external stimuli and communicate with other cells. Key cellular responses regulated by cell signaling include cell death, differentiation, and cell motility. Understanding the contribution of cell signaling pathways to toxicity is often key to determining mechanisms of toxicity or the pathogenesis of biological responses elicited by chemicals or pharmaceuticals. Sessions in this theme highlight mechanistic roles for cell signaling pathways in toxic responses and disease pathogenesis.

### **Gene-Environment Interactions Theme**

It is clear that disease susceptibility cannot be attributed only to variations in the human genome. The environment is major among the additional variables that define individual susceptibility to disease. A more precise determination of the influence of environmental exposures within a given genetic background on disease processes will be required to significantly improve the ability to predict, detect, treat, and monitor disease progression and disease response. The Gene-Environment Interaction theme has been selected to highlight recent advances in this field that are relevant to the toxicological sciences.

### **Metabolic Disease Theme**

Metabolic dysfunction, either acquired or inherited, affects biochemical reactions resulting in metabolic diseases. The incidence of acquired metabolic diseases is rising at an alarming rate. Perturbation of lipid and glucose metabolic pathways increases the risk of developing a number of chronic conditions such as obesity, diabetes, fatty liver disease, and cardiovascular disease. While genetic variability plays a role in individual susceptibility, environmental agents, drugs, and other toxicants are contributing factors. This theme will focus on the mechanistic changes in glucose and lipid metabolism induced by toxicants and the relationship to disease progression.

### **Mitochondrial Basis of Disease Theme**

Mitochondrial dysfunction has been found to be an important component in the progression of numerous human disease states. In addition, the mitochondrial genome is susceptible to oxidative stress and mutation due to the high percentage of coding DNA and its small size. Therefore, the mitochondria are a suspected target organelle of xenobiotics in different model organisms. This thematic area will highlight studies that evaluate the effect of xenobiotic exposure on mitochondrial function and the connection to the progression of disease.

### **Toxicity Testing in the 21st Century Theme**

The NRC's 2007 report "Toxicity Testing in the Twenty-first Century: A Vision and a Strategy" articulated the critical need for development and validation of predictive high-throughput assays to replace current expensive and time-consuming animal tests. This theme includes applications of genomics and *in vitro* tests to identify pathways of toxicity and methods for using advanced computer power that make it feasible to analyze large volumes of complex data and use common data platforms to link existing and new exposure and effects databases.

### **Translational Toxicology Theme**

In most settings, translational science is described by the term "Bench to Bedside." Translational Toxicology can be described as the transition of basic toxicology related-research into strategies to improve the performance of the science of toxicology. Thus, translational toxicology may be best described by the term "discovery to application." Sessions involving the translation of

fundamental mechanistic observations into bioassays, biological models and other novel approaches that can be applied to toxicology research, and studies that describe the supporting biologic or mechanistic qualification of endpoints and detailed assay validation are highlighted in this theme.

## 2011

### **Emerging Global Public Health Issues**

The global economy raises challenges to protecting human health within the United States for our regulatory agencies. Ultimately, public health issues are no longer just local issues affecting a single country or specific geographic region of the world, but have international health implications. The global public health issues theme has been selected to highlight recent advances in these areas, as well as how this knowledge is impacting regulation and policy.

### **Environment and Disease**

Growing evidence suggest that the environment is a significant factor in the susceptibility and progression of cardiovascular and neurodegenerative diseases and cancer. The environmental influence on disease theme has been selected to highlight recent advances in these areas as well as contrast how this knowledge is impacting regulation and policy.

### **Global Air Quality and Human Health**

It is becoming increasingly apparent that air pollution is not just a local issue, but has international health implications. The goal of this theme is to integrate information on individual susceptibility, disease mechanisms and levels of exposure and to demonstrate how this information can have a significant impact on the development of global air quality policies and regulations.

#### **Integration of Toxicological and Epidemiological Evidence to Understand Human Risk**

As novel technologies expand the range of biomarker assessments and the NAS vision for toxicity testing begins to be implemented, the integration of mechanistic laboratory animal testing and *in vitro* systems with human epidemiological data will require new strategies to fully utilize and integrate these data for extending the range of observations and to characterize the exposure-response of human risk. The goal of this theme is to initiate discussion on how new technologies can improve assessment of the dose-response curve and thereby improve human risk assessment from environmental exposures.

#### **Novel Approaches to Preclinical Safety Assessment: Bridging the Gap between Discovery and the Clinic through Translational Toxicology**

Toxicology can play a key role in identifying and implementing advances in toxicological mechanisms, safety assessment, and biomarkers when cross-disciplinary efforts are coordinated during the drug development process. The goal of this theme is to highlight advances in toxicology that improve translation from animal models to humans.

### **Toxicity Testing: State of Science and Strategies to Improve Public Health**

In order for Federal regulations to best reflect the current state of the science, toxicity testing paradigms need to adapt to the advances of science. The main challenge inherent in bringing this vision to fruition is to have testing strategies that provide sufficient context for evaluating potential risk. The goal of the toxicity testing theme is to initiate discussion on how toxicity testing could integrate state of the science methodologies and thereby reduce the uncertainties in the interpretation of toxicity-pathway data to humans.