Darlene Dixon

Title: The Toolbox for the Molecular Pathologist

With the advent of more molecular based assays, high-throughput screening, and *in vitro* approaches being used in toxicologic assessments, the pathologist in the 21st century is faced with great opportunity and challenges. This presentation will give a perspective on the role of the toxicologic pathologist in the ToxPath21 era. The use of molecular and mechanistic approaches to further define histopathology findings, and some molecular tools available to the pathologist that can be applied to tissue-based and *in vitro* analyses will be discussed.

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Brigitte Landesmann

Title: In Vitro Approaches to Modern Toxicology: Where Are We and Where Are We Going?

Animal models are still widely used in toxicity testing and biomedical research, but it is increasingly recognised that animals are not a good model for human pathologies. Besides ethical considerations the uncertain predictability of animal testing for human adverse health effects is a limiting factor in chemical risk assessment. Moreover, due to costs and time involved, it is not feasible to use these methods for testing all the chemicals that could affect human health. “Toxicity testing in the twenty-first century” aims to understand the underlying mechanisms of toxicity, rather than rely on direct observations of toxic effects. Improved mechanistic knowledge enables the development of integrated testing strategies, which rely on using *in vitro* methods, preferably based on human cells or human cell constituents that in combination with *in silico* approaches facilitate *in vivo* predictions of toxicity and chemical risk assessment.

Studies with cultured human cells, including primary cells, established cell lines, and, more recently, induced pluripotent stem cells (iPSCs) are increasingly done. However, two-dimensional cell culture systems do not adequately mimic tissue and organ-level structures and functions. Therefore, more physiologically complex and relevant cell culture formats, like three-dimensional, multicellular, “organotypic” models have been produced, which mimic functional responses of living tissue. Even more sophisticated "organ-on-a-chip" cell culture devices can mimic physico-chemical microenvironments and vascular perfusion characteristics.

Each of these models has its drawbacks and none truly reflects the manifold on-going processes in human disease. Clinical samples from healthy persons and from patients could be used as benchmark for a better understanding and improved relevance of *in vitro* testing.

Various models and their relevance and utility for predicting human pathology will be discussed.

Arun Pandiri

Title: Adverse Outcome Pathway (AOP) – A Pathologist's Perspective

An Adverse outcome pathway (AOP) contains a sequential progression of causally linked pathophysiological mechanistic events across increasingly complex biological systems that lead to an adverse outcome. AOPs leverage the cellular signaling pathway information obtained from various data sources, such as high-throughput *in vitro* data, toxicogenomics, and systems biology, to predict the eventual adverse phenotype *in vivo* (apical endpoint) for decisions on product development and regulatory purposes. This presentation will provide an overview of the AOP development and application for identifying a potential hazard. Some of the AOPs that have been well characterized are relatively linear and non-animal based tests have been successfully developed to detect the adverse effect. However, most of the biological adverse responses are made of networks and present a challenge to develop a complete AOP. This presentation will discuss some of the success stories and some challenges. Finally, a discussion on the opportunities for a toxicologic pathologist in contributing to the development of AOPs will be presented.

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Alessandro Piaia

Title: When Morphology Meets Omics – Gene Expression Profiling and Histopathology Are Truly Complementary in Toxicity Assessments

The establishment of technologies in profiling gene expression to monitor changes at cellular levels has tremendously enhanced our knowledge on the nature of test-item-related changes in toxicology. Histopathology has profited from the integration of the observations with the genomic expression profile, however the relationship between the two disciplines is far more integrative and reciprocally dependent than what can be seen at a first glance.
Three examples (one oral rat study with histology and genomics in multiple endocrine organs, one dog inhalation study with lung changes and one rat asthma model for inhalation treatment), are presented to show different levels of integration of the data between the two disciplines and how and where each discipline could complement the other.