From the Editor’s Desk

“Summertime and the living is easy.” While I appreciate some of the downtime associated with the season as depicted by the late Sam Cooke, things aren’t so easy within the scientific enterprise. Toxicology, and science in general, continues to suffer from a lack of sustained investment and commitment from academic institutions, corporations, and government entities. We are being asked to train more students, perform more experiments, complete more paperwork, and publish more papers, yet the necessary investment in the infrastructure of science has not kept pace. As toxicologists we must engage legislators (local to global), regulators, and scientific administrators to emphasize the importance of the foundation on which biomedical research is conducted. We will continue to provide high-quality summaries of our science as you will see when you look inside ToxSci for the best original research in the field of toxicology.—Gary W. Miller

Editor’s Highlight

Constitutive androstan receptor in herbicide-associated liver injury: The herbicide acifluorfen (ACI) has been shown to induce mouse liver tumors in chronic carcinogenicity studies; however, the mechanism responsible for these tumors has not been well established. This study investigated the role(s) of the nuclear receptors CAR, PXR, and PPARs as well as the contributions from oxidative stress and regenerative cell proliferation. Using wild-type and CAR knock-out mice and an initiation-promotion protocol, the authors demonstrated that CAR activation played an important role in the cytotoxicity-mediated liver tumor mode of action. In contrast, the prototypical CAR activator, phenobarbital, did not induce cytotoxicity in the wild-type or knock-out mice. There was also evidence for the activation of PPRs in both strains treated with ACI, although this nuclear receptor does not appear to play a major role in the herbicide-induced tumors. Kuwata et al. (pp. 271–285) discuss the implications of their findings to human risk assessment. View Abstract—B. Bhaskar Gollapudi

Chlorodopamine as a novel mediator of dopamine neuron injury: Environmental factors have long been implicated in Parkinson’s disease, but there is evidence that the essential neurotransmitter dopamine may itself play a role in the disease. In this issue Jeitner et al. (pp. 388–402) report that chlorinated metabolites of dopamine can cause dopamine neuron cell death and set off an inflammatory cascade. Hypochlorous acid, a reactive oxygen species produced by neutrophils and other cells, can target the catechol and amine components of dopamine to produce a potent toxin. Data showed that chlorodopamine is a substrate for the plasma membrane dopamine transporter. When chlorodopamine was administered to cells or rats, it produced dopamine neuron cell death with the predicted inflammatory response. In vivo pretreatment with a dopamine transporter inhibitor protected dopamine neurons. Investigators continue to search for an explanation as to why dopamine neurons are so vulnerable to a variety of genetic, environmental, and metabolic insults. The results described here provide a new important piece to the Parkinson’s puzzle. View Abstract—Gary W. Miller

Connectivity mapping to group chemicals using mode of action: The 2007 US National Research Council report “Toxicology Testing in the 21st Century” called for a shift in toxicology testing from a focus on apical outcomes in animals to an approach based on a mechanistic understanding in humans. In support of this, various terminologies have emerged, which evolve the existing mode of action (MOA) concept toward pathway-driven adverse outcomes (AOPs) based on the Molecular Initiating Event (MIE). This is an exciting concept that provides the opportunity to assess human risk for pharmaceuticals and chemicals based on high throughput (HTS) in vitro methods. However, one of the imperatives is to ensure that all potential perturbable pathways linked to adverse outcome are covered. De Abrew et al. (pp. 447–461) make strides toward this by assessing gene expression for 34 chemicals with predefined MOAs in 4 different human cell lines, the latter chosen to provide spread but with overlap. One key challenge that emerges is the need to characterize dose responses since for some chemicals opposite MOA linkage effects were noted for different concentrations. Overall, this manuscript advances the field of replacing animal model-based quantitative risk assessment with MOA-based methods by providing a systematic analysis of the linkage between MOA and gene expression. View Abstract—Ruth A. Roberts

Lead-induced alterations in gut microbiota composition: Toxicologists’ interest in lead (Pb) is longstanding; however, Pb has also been an intermittent subject of media scrutiny. Notable examples include the adverse effects of Pb on human health and the environment, which fueled the switch to nonleaded gasoline, concerns over children’s exposure to Pb in paint, and the immediate and long-term impact of lead in water in Flint, Michigan. Wu et al. (pp. 324–333) examine a new angle of this story by studying the effect of prenatal Pb exposure on gut microbiota. The team used a mouse model of human-relevant Pb exposure to investigate the effects of gut microbiota on perinatal exposure at adulthood. Interestingly, perinatal Pb exposure increased adult bodyweight in male but not female mice, suggesting a gender-specific effect that was highly correlated with changes in gut microbiota. Such findings not only suggest links between Pb exposure in young to obesity in adults, but also may set precedence for future epidemiological studies in human populations. View Abstract—Brian Cummings