Considerable interest exists in the potential for macrophages in the lung. Hi

Spleen-derived macrophages following ozone: Pulmonary inflammation following exposure to toxicants is influenced by stores of immune cells in distal organs, with varied pro- and anti-inflammatory phenotypes. Ozone inhalation predictably leads to pulmonary inflammation, but the origin of infiltrating cells is relatively uncharacterized. Francis and colleagues (pp. 182–195) considered the role that splenic macrophages may have in promoting and/or resolving the inflammatory effects of ozone. 24 h following exposure, pro-inflammatory Ly6C<sup>hi</sup> macrophages were diminished in the spleen, but these pro-inflammatory macrophages, along with anti-inflammatory and transitional macrophages were increased by 48 h postexposure. Splenectomized mice exhibited reduced airspace infiltration of inflammatory Ly6C<sup>hi</sup> macrophages yet maintained and even increased (at 72 h postexposure) anti-inflammatory Ly6C<sup>lo</sup> macrophages in the lung. Splenectomized mice also exhibited reduced signs of oxidative stress and injury in the deep lung. The study results therefore suggest that spleen-derived macrophages may be selectively injurious to the lung. As trafficking of spleen-derived macrophages is largely dependent on the angiotensin-1 receptor, and these pro-inflammatory macrophages may be a “druggable” sub-population to help mitigate lung injury from inhaled toxicants. View Abstract—Matthew J. Campen

Comparative renal toxicity of hepatitis B drugs: The advent of drugs to treat hepatitis B is an exciting clinical advance. Yet, this powerful drugs can exert adverse effects. In the study by Uteng and colleagues (pp. 283–297), the investigators examined the renal toxicity of 4 hepatitis B antiviral drugs (telbivudine, tenofovir, adefovir, entecavir) in male Spraque-Dawley rats that were given these drugs by gavage for 4 weeks at the doses of 10 or 25–40 times of human equivalence. Adefovir caused time- and dose-dependently morphological and functional alterations. The observed adefovir-induced reduction of renal function could be detected only by the super-sensitive
We read with interest the paper by Baumgart et al titled “Effect of BMS-986094, a Guanosine Nucleotide Analog, on Mitochondrial DNA Synthesis and Function” (Baumgart et al., 2016). Whereas non-clinical studies in mice and monkeys were able to identify the heart and kidney as target organs (Robertson et al., 2014), correlating with clinical adverse events, the authors conclude that the toxicity observed was not due to mitochondrial toxicity. This conclusion was based on the absence of selective depletion of mitochondrial DNA (mtDNA) and transcripts observed in vitro, and the lack of changes in mtDNA content, ATP and ex vivo mitochondrial respiration during toxicology studies in monkeys. Similarly, a distinct prodrug of the same pharmacologically active nucleotide analog, 2'-C-methyl guanosine triphosphate (2’CMeG-TP), IDX14184, was also reported to have heart and kidney toxicities in rodents and monkeys (Luo et al., 2015). In this study, swollen mitochondria were detected in the kidney but not the heart in monkeys, using transmission electron microscopy.

We have also studied the mechanism of toxicity of nucleotide analogs including BMS-986094 in vitro (Arnold et al., 2012; Feng et al., 2016). These studies demonstrated efficient incorporation of 2’-CMeG-TP by mitochondrial RNA polymerase (POLRMT), correlating with selective reduction of the protein expression of a mitochondrial gene [cytochrome c-oxidase subunit 1 (COX1)], and, ultimately, a functional reduction in mitochondrial respiration at clinically relevant concentrations of BMS-986094. Of note, a primary effect on mitochondrial function was observed both in a cultured cell-line and in freshly isolated rat cardiomyocytes. The effect on COX1 protein expression was potentiated by ribavirin, an inhibitor of endogenous guanosine triphosphate formation, consistent with competitive inhibition of a host polymerase by BMS-986094.

Whereas the results, reported in Baumgart et al. and our work, are seemingly at odds, we feel that this reflects the technical difficulties in accurately assessing mitochondrial toxicity. In particular, we question whether toxicity of a POLRMT inhibitor would necessarily be observed in the endpoints assessed by Baumgart et al. For example, mtDNA was monitored, but DNA depletion would not be expected for an inhibitor of mitochondrial transcription. Furthermore, ATP is not a specific measure of mitochondrial respiration, as it can also be formed by glycolysis. Consistent with a shift towards glycolysis, increased lactic acid was reported during in vitro incubations with BMS-986094 previously (Furman et al., 2011). In fact, the observation by Baumgart et al. of cardiomyopathy resulting in reduced left ventricular ejection fraction, in and of itself, may be suggestive of an effect on mitochondrial function. This cardiac finding has been associated with a number of mitochondrial toxicants (eg, 2’-3’-dideoxycytidine, 2’-azidothymidine, and chloramphenicol) and mutations in genes involved in mitochondrial biogenesis (Domanski et al., 1995; Haack et al., 2013; Skuta et al., 1999; Suarez and Ow, 1992).

It is important to understand the mechanistic basis for toxicity so that future clinical candidates can be appropriately assessed. In the absence of an alternative mechanism, we do not feel that the role of mitochondrial toxicity, and the inhibition of POLRMT in particular, can be definitely excluded for BMS-986094.