The Food and Drug Administration's (FDA's)
2015 ORSI Science Symposium
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SPEAKER ABSTRACTS AND BIOGRAPHIES

Session 5: Chief Scientist Intramural Grant Annual Presentations – 3:10 -4:10 PM

Speaker	**Qiang Shi, PhD,**
Title	**Visiting Scientist**
Biography	**Dr. Qiang Shi obtained his PhD in pharmacology in Zhejiang University (China) in 2006. His PhD dissertation was on mouse liver protein modifications in drug induced liver injury (DILI). He completed his post-doctoral training in DILI in FDA NCTR from 2007 to 2010, and then became a Visiting Scientist in FDA NCTR in August 2010. Dr. Qiang Shi has a focused research area: mechanisms and biomarkers for DILI. He has nearly 15 years' experience in primary culture of hepatocytes from multiple species. For mechanistic studies, he is mainly working on drug induced mitochondrial damages and metabolism-mediated hepatocyte injury. For biomarker studies, he is using both animal models and human samples to explore novel translational DILI biomarkers, and his work is focused on circulating microRNAs in the urine and blood. He has published 25 peer reviewed manuscripts on DILI.**
Subject	**Urine microRNAs as novel biomarkers for acute liver failure patients**
Presentation Abstract	**Drug induced liver injury (DILI) is the leading cause of acute liver failure (ALF), which carries a high mortality rate. DILI is also a major reason for drug non-approvals, safety warnings or market withdrawals. The FDA endorsed DILI biomarkers lack tissue specificity and novel biomarkers are needed. Though urine microRNAs are intuitively thought and tentatively proven to be potential biomarkers for renal diseases, recent data suggest that they may help diagnose DILI. This study aimed to examine if urine microRNAs in ALF patients are perturbed. Urine samples were obtained for 53 patients and 15 healthy subjects from the Acute Liver Failure Study Group and a commercial vendor, respectively. Customized PCR arrays containing 128 microRNA probes were used to determine the perturbations. Using the criteria of absolute fold-changes > 2 and $p < 0.01$, sixty microRNAs were found to be differentially expressed in healthy and ALF subjects. Principal component analysis of differentially expressed microRNAs showed that the healthy and ALF groups were well separated. The level of 6 microRNAs appeared associated with the death status at 21 days after enrollment, as exemplified by hsa-miR-1260a, whose level was about 4-fold higher in dead patients than alive patients ($p < 0.01$). The levels of 7 microRNAs showed a good correlation to the primary cause of ALF. Specifically, the increase of these microRNAs was similar in ALF patients due to acetaminophen overdose or drug-induced hepatitis, but was significantly smaller in those due to shock/ischemia. For example, the level of hsa-miR-877-5p was increased by more than 1000-fold in drug (including acetaminophen) induced ALF, but the elevation was only about 100-fold in shock/ischemia associated ALF. Interestingly, urine and serum microRNAs seemed not related to each other, as urine microRNA-122 showed no changes despite a sharp increase in the same patients' serum. Urine microRNAs also showed no correlation to the pre-study peak levels of serum alanine transaminase (ALT) or aspartate aminotransferase (AST), though a moderate association between levels of hsa-miR-1228-3p and pre-study peak international normalized ratio (INR) was observed. These data suggest that urine microRNAs may serve as non-invasive complementary biomarkers for human ALF.**