CRITICAL PATH INSTITUTE

Breaking Down Research: Investigation of Urinary miRNAs for Early Detection of Kidney Damage in selected lab animals

Dr. Adeyemi (Yemi) Adedeji is a Distinguished Scientist-Clinical Pathologist, Head of Clinical Pathology, in the Translational Safety Department at Genentech

Drug-induced kidney injury is commonly identified during drug development and serves as a dose-limiting factor or cause of attrition for therapeutics. Serum creatinine and blood urea nitrogen (BUN) are the standard biomarkers for detecting kidney-related injury. However, these biomarkers do not significantly change until two-thirds to three-fourths of the kidney nephrons are nonfunctional. As such, the industry is continuously working to identify better biomarkers for kidney-related injury. Here, we report the results of a study conducted by Critical Path Institute's Predictive Safety Testing Consortium (PSTC), a working group of experienced biopharmaceutical industry pathologists, toxicologists, and clinicians who collaboratively validate and qualify emerging safety biomarkers for regulatory considerations for preclinical and clinical drug development applications.

This study set out to check if changes in urine microRNA (miRNA) levels could be useful as early kidney injury warning signs during toxicology tests. miRNAs are small molecules that play an important role in controlling gene expression. They function by binding to messenger RNA (mRNA) molecules and preventing the production of specific proteins from the mRNA molecules. miRNAs have been connected to kidney damage caused by drugs, but there's little information on how well they work for spotting kidney toxicity in different animals. In this study, we measured urine miRNA levels after mice, rats, and dogs were exposed to a drug, Amphotericin B (AmpB) known to cause kidney damage. Our research found 35 miRNAs with significant differences after kidney injury among the three species. Interestingly, dogs had the highest number of these changed miRNAs. Two specific miRNAs (miR-205-5p and miR-31-5p) were consistently affected across all animal species studied. In rats and mice, these two miRNAs were especially sensitive and showed results that were as good as, or even better than, the urine protein markers that had been noted before

for the same kidney-damaging drug. However, in dogs, the miRNAs that increased didn't provide the same level of sensitivity as a urine protein called clusterin, which had been highlighted in earlier studies using AmpB.

Overall, our findings suggest that testing urine for miRNAs are promising additions to the existing protein tests for tracking drug-induced kidney injury in mice, rats, and dogs in drug development studies. To the best of our knowledge, this is the first study to show how effective urinary miRNAs can be for early detection of kidney damage across these three different animal models.

Read more about this research in the co-authored publication, "Investigation of urinary miRNA profile changes in amphotericin B-induced nephrotoxicity in C57BL/6 mouse, Sprague–Dawley rats and Beagle dogs," here.

Dr. Adeyemi (Yemi) Adedeji received his Doctor of Veterinary Medicine (DVM) degree from University of Ibadan in Nigeria, after which he relocated to the United States to pursue his PhD in Molecular Microbiology at the University of Missouri-Columbia. Following the completion of his PhD, he was accepted for the veterinary clinical pathology residency training program at the University of California-Davis. After the completion of his residency training program, he became a Diplomate of American College of Veterinary Pathologists (Dipl. ACVP) after passing the board certification exam. Subsequently, he joined the College of Veterinary Medicine, Midwestern University, Glendale, Arizona, as an Assistant Professor of Clinical pathology (tenure-track), where he developed his research lab, mentored professional students interested in biomedical research and also taught clinical pathology courses. He joined Genentech in 2016 as a toxicologic clinical pathologist to provide scientific support for oncology and non-oncology therapeutic safety and development, along with translational biomarker development. He's currently the Translational Safety Therapeutic Area Lead (TS-TAL) for Cardiovascular, Renal and Metabolism disease area at Genentech. He has several peer-reviewed publications along with numerous professional awards. He is an Associate Editor for the Comparative Clinical Pathology Journal. He is also an active member of several pharmaceutical industry consortia including a member of the advisory council for the Predictive Safety Testing Consortium (PSTC) and the past chair of the PSTC-Nephrotoxicity Working Group, where he led a cross-industry effort on the development of novel safety renal biomarkers.