

Novel Biomarkers of Cisplatin-induced Kidney damage.

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Introduction – In 2008, the FDA and EMEA issued a joint framework allowing for the biomarker qualification and regulatory endorsement of 7 new urinary biomarkers of drug-induced kidney injury in rats. We sought to screen for other novel biomarkers of drug induced kidney injury by utilizing the original Novartis study samples that were the source for the Predictive Safety Testing Consortium's (PSTC) submission to the FDA and EMEA.

Experimental Procedures – Control and Cisplatin study samples with previously documented proximal tubular injury were utilized as screening study to select the most promising biomarker candidates. Nine further studies with compounds inducing tubular, glomerular and collecting duct injury are used as validation set. Urine was collected at termination days 3, 7, 14 and 21, plasma at days 1, 3, 7, 21. Histopathology was performed with a standardized hierarchical lexicon. A panel of 58 protein biomarkers comprising cytokines, inflammatory markers, growth factors, and tissue factors were quantified in urine and plasma samples by multiplex immunoassays. Performance of biomarker candidates from the panel was assessed with a Receiver Operating Characteristic (ROC) analysis.

Results: - Several biomarkers significantly increased in urine and plasma which are linked to inflammatory pathways correlated to histopathological kidney damage severity. In addition, ROC analysis indicated that several of the novel analytes are sensitive and specific markers of drug-induced kidney damage with a significantly higher AUC of ROC than BUN and serum Creatinine.

Conclusions – The newly identified biomarkers have potential to complement the already known and partially qualified biomarkers for drug induced kidney injury in particular for monitoring inflammatory processes, whereas the 7 endorsed biomarkers are mechanistically linked to functional changes, cell injury and regeneration processes.