Renal Dysfunction Molecular Markers—From Cage to Clinic.

The identification and qualification of safety biomarkers facilitates the characterization of potentially toxic compounds during preclinical development, allows for troubleshooting classes of compounds, has the potential to predict and prevent post-marketing safety issues, and will generally speed preclinical safety evaluations and ultimately reduce the cost of drug development. It is critical that such biomarkers are appropriately “qualified”, that is, establishing that they are valid surrogate makers of a drug toxicity or disease process. The qualification of biomarkers and the validity of their bioanalytical assays needs to be reviewed and approved by regulatory agencies before it can be accepted as an outcome marker. The development and approval of known biomarker panels is an intriguing concept that has been pursued by partnerships between private industry and regulatory agencies, such as the Critical Path Institute consortium.

In the middle of 2008, FDA and EMEA accepted the qualification of a panel of protein nephrotoxicity markers in urine for GLP toxicology studies in rats. Although this has created considerable enthusiasm, there are limitations. It remains unclear if this biomarker panel will translate into humans and how specific it will be, especially in patient populations with underlying diseases and concomitant drug therapy. Another drawback is that these are protein biomarkers that typically have more stability problems than small molecule markers. This will complicate sample handling and logistics in larger clinical trials. Another attractive strategy that has been pursued is a genomics / transcriptomics approach, but this requires a kidney tissue sample and in most cases, such a biomarker strategy is only feasible in preclinical studies.

An alternative that has not been widely discussed is the monitoring of metabolite changes in urine. Kidney cells have differential effects on the metabolite patterns in urine depending on their metabolism which is partially driven by different osmolytic environments and their transporters and functionalities. This will potentially allow for mapping of the kidney function based on metabolic changes and will also allow for identification of the part of the kidney that is the main target of drug toxicity. Many of the metabolites in urine are already well established kidney function markers and their combination as a combinatorial biomarker, or biomarker panel, seems an attractive concept. In many cases, combinatorial metabolite markers in urine can be translated into human trials, and samples are usually easier to handle than those for protein marker analysis.

This workshop will critically discuss the available renal function biomarkers and will discuss strategies for translating molecular markers used for preclinical studies into clinical trials.