8 Renal Function and Nephrotoxicity

The kidneys are an important target for drug-induced toxicity, as they are well perfused and as renal excretion is an important route of drug elimination. As kidneys have a high functional reserve, morphological damage may be advanced before it translates in significant malfunction.

In case of concern, initial screening in the early research phase can be done by in vitro methods like cell culture assays or evaluation of tissue slides (Astashkina et al. 2012). However, due to the complexity of the kidney, functional aspects are not well accessible in vitro (Pfaller and Gstraunthaler 1998). There are several cell lines available for high-throughput nephrotoxicity screening including proximal and distal tubule epithelia, kidney fibroblasts, and glomerular podocytes (Huang et al. 2014).

For more advanced candidates, in vivo evaluation for kidney toxicity can be done in the general toxicity studies with histopathology being a very sensitive technique which often detects mild morphological changes prior to any functional impairment. Whereas traditional serum markers for kidney dysfunction (BUN,[24] Crea[25] – indicators of glomerular function) are relatively insensitive, urinary markers can detect kidney injury in an early stage. In recent years, multiple novel biomarkers were evaluated which allow identification of kidney injury and can not only be used in animal studies but may also be used in clinical studies (Bonventre et al. 2010; Dieterle et al. 2010). Some markers are indicative of damage in different kidney structures, others are very specific for specific cell types. Examples of such markers are kidney injury molecule 1 (KIM-1), cytostatin C, clusterin, β2-microglobulin, GST-α, GST-μ, osteopontin, and renal papillary antigen-1 (RPA-1) (Gautier et al. 2010; Betton et al. 2012). Besides such markers, metabonomics investigation of urine as well as toxicogenomics of the kidney tissue may help in mechanistic examinations (Matheis et al. 2011).

For more detailed functional assessment, renal function tests may be performed. Such tests can be performed as dedicated safety pharmacology studies, e.g., in rats, but such function tests may also be incorporated into general toxicity studies. In order to get adequate urinary samples, use of a metabolic cage is advisable during functional testing, especially when also evaluating electrolytes.

9 Respiratory Function and Pulmonary Toxicity

Some aspects of respiratory function may be tested in isolated organs or lung cell cultures. However, respiratory function can holistically be assessed only in vivo. Frontloading of the actual safety pharmacology function test is not commonly done (Lindgren et al. 2008). The most frequently used method is rodent plethysmography

[24] Blood urea nitrogen

[25] Creatinine