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Kidney cell assays for *in vitro* safety profiling of single stranded oligonucleotides

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Chronic treatment of patients with classical low molecular weight drugs like aminoglycoside antibiotics, antivirals and immune-suppressants are known to induce kidney toxicities. Particularly molecules with high renal clearance can accumulate in proximal tubule epithelial cells (PTECs) of the kidney cortex where high tissue concentrations induce damage to tubular structures and may lead to loss of organ function. Similar toxicities have also been observed with other drug modalities such as for example some single stranded oligonucleotides (SSOs). SSOs represent a class of novel drugs to modulate gene expression in many different diseases for which there is no adequate treatment currently available. In order to secure development of renal safe drugs, we have established assays with animal and human primary as well as immortalized PTECs for profiling of nephrotoxic reference compounds side-by-side with SSOs that had previously been tested in rats for signs of organ damage. Using assays of cell function, viability, and death, we have been able to clearly discriminate safe from toxic molecules. Overall, the observed effects were similar across PTECs derived from animals and humans and correlated with the *in vivo* findings for the molecules tested in rats. Thus, we believe that our cellular assays will be useful for rapid *in vitro* profiling of SSOs for selection of safe compounds on human cells prior to clinical testing.

Biography

Marcel Gubler received his PhD in Life Sciences at the Federal Institute of Technology (Zürich, Switzerland) in 1988, followed by 2-years Post-doctoral Fellowship at the Massachusetts Institute of Technology (Cambridge, MA). Subsequently, he joined Preclinical Research at F. Hoffmann-La Roche Ltd (Basel, Switzerland), where he worked on novel targets for antibacterial therapies. In 2000, he changed to the Department of Metabolic Diseases to focus on drug treatments for obesity, diabetes and renal diseases. Since 2014, he has been investigating mechanisms of renal toxicity of different drug modalities in the Department of Drug Disposition and Safety, F. Hoffmann-La Roche Ltd.

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