DEPARTMENT
OF PHARMACEUTICAL SCIENCES

Description

Investigating xenobiotics-induced disturbances of hepatic sterol and bile acid metabolism

The liver is the central organ responsible for the selective uptake, metabolism and excretion of endogenous and exogenous compounds, including drugs. Drug-induced liver injury (DILI) can be caused by various chemicals and can present as an array of different pathologies, dependent on the specific function of the liver that is impaired. Numerous xenobiotics have been shown to cause liver injury but the manifestations of drug-induced hepatotoxicity are highly variable, ranging from asymptomatic alterations of liver enzymes to fulminant hepatic failure.

In the present project, we aim to investigate a selected range of xenobiotics (mainly drugs) screened by bioinformatics tools for potential inhibitory effects towards AKR1D1 and SRD5A1. AKR1D1 and SRD5A1 are two important enzymes involved in bile acid and steroid metabolism in the liver. The disruption of their function has been associated with different liver pathologies including inflammation, NASH/NAFLD, fibrosis, cancer and infections. Upon establishing activity assays for these two enzymes the most promising hits will be investigated for their potential to inhibit their enzyme activities and the consequences for bile acid and steroid homeostasis. Besides, we will investigate the potential interference of selected azole antifungal drugs with cytochrome P450 enzymes involved in hepatic bile acid synthesis. The consequences will be studies in a hepatocyte cell line.

Methods: RNA/DNA/proteins extractions and quantification, bacterial transformation and eukaryotic cell culture, cloning, DNA amplification (mini/maxiprep), transfection, cell culture and maintenance, enzyme activity assays, western blot, PCR/qPCR, protein purification.