Reg. No: 2015/18/M/NZ7/00410; Principal Investigator: prof. dr hab. Marek Droździk

The liver is the major organ determining the amount of drugs reaching the body (bioavailability) after oral administration, due to its key role in the metabolism of drugs. The amount of drug that enters the liver cells and thus becomes available for drug metabolizing enzymes may be dependent on the presence of transport proteins/transporters in the cell membrane of hepatocytes that shift medications. Type of transporter as well as the quantity and activity can determine the metabolic capacity of the liver. Proper function of transporters localized in the liver is therefore extremely important to ensure their proper metabolism and elimination from the body. Furthermore, many of the transporters involved in the transport of drugs also transports endogenous compounds (e.g. bilirubin, bile salts). Their function is therefore needed to ensure homeostasis of the body. Until now the occurrence of drug transporters in the liver is not well defined, as most of the available observations only describes exactly (quantitative) mRNA expression and in a less accurate way (semi-quantitatively) transporter proteins. It does not ensure an appropriate translation to their biological role, because not always correlation between the expression of mRNA and protein abundance occurs, and as mentioned above, to what also contribute inaccurate determination of the amount of transporter proteins. Only a few reports describe in a quantitative way the protein drug transporters in the healthy liver. In contrast, almost no quantitative description of drug transporters in the pathology of this organ. Thus, it is important to determine the abundance of drug transporters at the protein level by a quantitative method (liquid chromatography coupled to tandem mass spectrometry, LC-MS/MS), both in the healthy liver as well as in pathological conditions of the liver of a different pathophysiology, i.e. virual - hepatitis type C, cholestatic - primary sclerosing cholangitis, primary biliary cirrhosis and toxic - alcoholic liver disease. These findings will allow more accurate than the currently existing (based on semi-quantitative measurement methods of protein abundance) determination of drug transporters in the liver pathologies of various etiology.
Another aspect of the study is to search for mechanisms that affect gene expression, protein abundance and post-translational modification of drug transporters' proteins in liver diseases (determination of miRNA profile, DNA methylation and S-nitrosylation). Until now, there is no detailed information on the mechanisms involved in the regulation of drug transporters in the pathology of the liver. Their defining will contribute to better understanding of pathological processes in the liver, which affect the bioavailability of drugs. Because of the involvement of the transporters to transport of many endogenous substances, the project will also provide information on the pathophysiological processes in the liver.