Effects of OATP1B inhibitors on erythropoiesis and heme biosynthesis of multipotent stem cells isolated from umbilical cord blood

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Project description:

For several clinically relevant drugs such as statins, Organic Anion Transporting Polypeptide (OATP)1B-mediated uptake into hepatocytes constitutes the rate-limiting step in drug metabolism and elimination. In accordance, co-administration of two or more drugs using OATP1B as an elimination route might result in drug-drug interactions (DDIs) with concomitant increase in drug plasma concentrations. Therefore, new molecular entities have to be tested for OATP1B interaction in early drug development.

Currently, coproporphyrins (CPs), anionic byproducts of heme biosynthesis, are investigated as biomarkers for hepatic OATP1B transporter interaction. Indeed, in several clinical studies OATP1B inhibition resulted in a significant increase in CP plasma levels supporting the role of CP as a biomarker to predict OATP1B interaction.

While the liver is the major compartment of CP elimination, the red blood cells (RBCs) is the most prominent compartment of CP synthesis. In fact, 85% of all heme (as prosthetic group of oxygen-carrier hemoglobin) is produced in the RBCs. Hence, even minor changes in heme synthesis might lead to significant changes in CP plasma levels without contribution of OATP1B inhibition.

In this project, we will investigate the effect of classical OATP1B inhibitors on erythropoiesis as well as heme/CP synthesis using multipotent stem cells isolated from umbilical cord blood received from the Frauenklinik Basel. Through our investigation, we aim to contribute to the broader understanding of CP as a biomarker.