The effect of prolonged treatment with the new antipsychotics brexpiprazole and lumateperone on human liver function using in vitro model of 3D hepatocyte spheroids

The liver is a key organ in the body that is responsible for the elimination of xenobiotics and drugs. Liver cells (hepatocytes) contain most of the enzymes necessary for drug metabolism (CYPs). Human primary hepatocytes, collected from patients, are considered the gold standard in drug metabolism and toxicity studies, as well as an effective and reliable tool for assessing induction or inhibition of cytochrome P450 enzymes by drugs. However, in conventional monolayer (2D) cultures, hepatocyte cells rapidly de-differentiate within hours of seeding and lose liver functions such as albumin production and drug metabolizing enzyme (CYP) activity. This can lead to misinterpretation in the evaluation of drug effects, therefore 2D hepatocyte cultures are not suitable for studies requiring long-term phenotypes such as chronic toxicity. Therefore, testing the toxicity and/or metabolism of new drugs or substances on 2D cell cultures cannot fully predict what may be observed in the body.

Recent studies have shown that spheroid cultures of hepatocytes (3D cell aggregates) maintained liver viability and functionality at physiological levels for at least 5 weeks in culture, as indicated by sustained high levels of liver factors such as albumin and urea secretion. Furthermore, the major CYP enzymes that are responsible for drug metabolism have not changed during long-term culture, and the 3D hepatocyte spheroids retain the metabolic profiles of freshly isolated or cryopreserved hepatocytes, making them suitable for in vitro studies of long-term metabolism. In addition, proteomic analyzes showed that in vivo molecular phenotypes of liver tissue are preserved in spheroid cultures.

The purpose of this project is to carry out comparative studies of chronic treatment with new antipsychotic drugs (brexpiprazole and lumateperone) on human hepatocytes using in vitro liver model of the culture of human 3D hepatocyte spheroids. There are four main goals of this project. The first goal will be the determination of the drug-induced liver injury (DILI) and cytotoxicity effect of long-term treatment of new atypical antipsychotics in three different cell types sources of 3D hepatocyte spheroids models. The second goal of the project is the characterization of the effect of two studied drugs on cell metabolism, liver function, bile acid and neutral lipid accumulation in 3D hepatocyte spheroid models. The third goal of the project will be the performing proteomic analysis of 3D hepatocyte spheroids after a long-term treatment with the selected new antipsychotic drugs. The fourth, and the last goal will be examining the effects of the tested atypical antipsychotics on drug metabolizing enzymes (i.e., cytochrome P450, CYP1-3) expression and activity in the human 3D hepatocyte spheroids. We will also investigate the transcription factors that regulate the activity of CYP enzymes.

The results obtained using the three 3D hepatocyte spheroids (derived from spheroid-Qualified Hepatocytes, HepaRG, and PHH) in this project will be compared, and the spheroids showing the most beneficial results in the aspects of physiology, pharmacology and toxicology, will be recommended for further applications in investigating new drugs, and for drug development. The proposed project will provide new data of the identification of pharmacological drug effects used in the long-term therapy of different illnesses, such as psychiatric disorders on human liver.