Orally administered drugs must pass through the intestinal wall and then through liver before reaching systemic circulation, and produce therapeutic effects. During this process drugs are subjected to different processes that may determine their bioavailability (amount of drug reaching systemic circulation), and then therapeutic value, among them drug metabolism and active transport during their passage through cell membranes. Thus, activity of drug metabolizing enzymes as well as transporters in gastrointestinal tract and liver constitute very important factors determining drug actions in the body.

Definition of drug metabolizing enzymes and transporters in human liver is better defined than along human gastrointestinal tract. In the letter organ available information mainly refers to parts accessible for endoscopic evaluation, i.e. duodenum, ileum and colon. However, those segments of gastrointestinal tract are do not play the most important role in drug bioavailability, as for absorption jejunum is the most important part of gastrointestinal tract. Another weakness of the available information on drug metabolizing enzymes and drug transporters are mostly qualitative and semi-quantitative protein methods applied (mRNA data are of quantitative character). Quantitative data regarding proteins is very scarce, especially for gastrointestinal tract. So, the available data are not satisfactory, as protein abundance (assessed by quantitative methods, including the method planned to be applied in the current study) provide better information as for protein function than mRNA expression, since findings suggest that in many cases there is no correlation between mRNA expression and protein level. So, the study will cover this gap of information providing data on protein abundance of drug metabolizing enzymes and transporters both in liver and along gastrointestinal tract in humans. The latter information is very important as there is paucity of quantitative protein observation along the human gastrointestinal tract (findings from several mRNA expression studies suggest that the intestinal amount of several uptake and efflux transporters and drug metabolizing enzymes is not homogenous along the human gastrointestinal tract). Thus, drug absorption following oral administration may be influenced by the intestinal site of drug release, due to different drug metabolizing enzymes and drug transporters functions in different parts of gastrointestinal tract. Description of protein abundance of drug metabolizing enzymes and drug transporters in liver and along gastrointestinal tract will provide data to construct better models of drug pharmacokinetics as well as creates the possibility of designing tablets that release drugs in defined gastrointestinal tract segment, where the drug exposure to a metabolizing enzyme and/or drug transporter is the lowest, and thus enabling the most effective absorption.

Available data suggests that there are substantial both qualitative and quantitative differences in drug metabolizing enzymes and drug transporters mRNA expression and protein abundance in the liver and gastrointestinal tract, as well as along gastrointestinal tract. However, mechanisms involved in different distribution are not fully characterized, and epigenetic mechanisms (among them miRNA and DNA methylation) underlying differential expression of drug metabolizing enzymes and transporters in tissues/organs regulating drug bioavailability, i.e. in liver and gastrointestinal tract, have not been addressed yet. Therefore, other tasks of the proposed project include evaluation of miRNA and gene methylation involved in regulation of functions of drug metabolizing enzymes and drug transporters in the liver and gastrointestinal tract in humans (such data have not been published yet). Those data will complement information of drug metabolizing enzymes and drug transporters regulation in the human liver and gastrointestinal tract.