Charles University
Faculty of Pharmacy in Hradec Králové
Department of Pharmacology & Toxicology
Student: Markéta Vašků
Supervisor: PharmDr. Tomáš Smutný, Ph.D.
Title of diploma thesis: Molecular mechanisms of drug-induced liver injury (DILI)

Drug-induced liver injury is a common reason for halting the development of new drugs and has led to the withdrawal of several drugs from the market in the past. This diploma thesis aims to describe the molecular mechanisms responsible for drug hepatotoxicity and present both methods of preclinical and clinical testing of drugs to detect potential hepatotoxicity and examples of hepatotoxicity.

Five mechanisms are currently known to cause DILI, namely mitochondrial damage, formation of reactive oxygen species, endoplasmic reticulum stress, lysosomal damage, inhibition of bile acid transport, and activation of the immune response. However, these mechanisms have not fully been explored yet and require further research. Unfortunately, even testing still falls short of perfection. Neither preclinical *in vitro* models nor animal models are completely satisfactory and cannot reliably detect DILI. The same applies to clinical testing. DILI is very complex and usually requires the interplay of multiple factors, which may not be reflected in clinical testing. Particulary, idiosyncratic DILI is a relatively infrequent side effect and thus often becomes apparent only in post-marketing surveillance. Some drugs withdrawn from market due to DILI inculde troglitazone, tolkapone and fialuridine.

Hepatotoxicity assessment is a key in the new drug development process to help ensure the safety and efficacy of drugs for patients. DILI represents a problem not only from a health point of view, but also from a financial perspective. Therefore, it is necessary to investigate the mechanisms further, to understand them better, and to improve the testing methods.