

ABSTRACT

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Title of Doctoral Thesis **Study on the role of pharmacokinetic mechanisms of drug resistance in new anticancer drugs with focus on solid tumors**

Cancer chemotherapy is an important tool for the cure of cancer. Although the development of new anticancer drugs has been rapidly progressing, the phenomenon of multidrug resistance (MDR) continues to be a key issue leading to therapy failure in oncological patients. MDR is based on pharmacodynamic as well as pharmacokinetic mechanisms. Pharmacokinetic MDR includes drug efflux transporters and biotransformation enzymes that decrease the amount of (active form of) a drug in tumors. While the MDR role of transporters has been well understood, the participation of drug metabolizing enzymes is still unclear.

This thesis investigates the role of cytochromes P450 (CYPs) in cytostatic resistance. Furthermore, it focuses on the modulation of pharmacokinetic MDR using pharmacokinetic drug-drug interactions of new targeted antitumor drugs. Finally, it aims to confirm the in vitro findings in ex vivo patient-derived tumor explants.

In our latest publication, we demonstrate the significant role of CYP3A4 in resistance to docetaxel in vitro. In other papers, we report interactions of several small molecule targeted drugs with ATP-binding cassette drug efflux transporters and CYPs. By employing drug combination studies, we show that these interactions could be beneficially exploited for combatting MDR. Finally, using ex vivo primary tumor explants, we demonstrate that the response to the dual-activity MDR modulators is closely related to the expression levels of the transporters, confirming thus possible clinical value of this approach. In addition, these results emphasize the importance of adherence to the rules of personalized medicine for this therapeutic strategy.

In conclusion, we provide a mechanistic evidence on the MDR role of CYP3A4 enzyme and suggest possible combination therapies, which, following in vivo confirmation, might improve the efficiency and/or safety of anticancer treatment in number of oncological patients.