ABSTRACT

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Training Workplace	Department of Pharmacology and Toxicology
Doctoral Degree Program	Pharmacology and Toxicology
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Title of Doctoral Thesis	Study on interactions of new anticancer drugs and their utilization for modulation of multi-drug resistance in solid tumors

In recent years, novel targeted therapy has led to a significant breakthrough in cancer treatment. Despite this development, cancer remains the second cause of death worldwide, while part of this high mortality rate is due to multidrug resistance (MDR). Various types of cancers have been observed to exhibit this phenomenon, including non-small cell lung cancer (NSCLC). Pharmacokinetic mechanisms such as ATP-binding cassette (ABC) drug efflux transporters and cytochrome P450 (CYPs) drug metabolizing enzymes play an important role in the development of MDR in NSCLC cancer patients.

This study has aimed to investigate the interaction of novel targeted NSCLC drugs with ABC transporters and CYP enzymes and define their role in MDR. We described several new targeted drugs as potent dual activity MDR modulators acting by their own antiproliferative effect and enhancement of accumulation of conventional cytotoxic drugs through interaction with MDR mechanisms in vitro. In our latest manuscript, we further introduced three-dimensional (3D) primary NSCLC organoids and in vivo NSCLC patient-derived mice xenograft (PDX) models to verify the potential of selected drugs to act as dual activity modulators. Synergistic outcomes demonstrated in our research across in vitro, ex vivo and in vivo models underscore the potential of utilizing novel targeted therapeutics to counteract pharmacokinetic resistance mediated by ABC efflux transporters and CYP3A4 metabolic enzyme.

In conclusion, this research underscores the imperative for innovative and integrative research approaches to advance patient care in oncology. Central to our discourse is the identification of proper MDR modulators and their personalized use based on the expressional profiles of ABC transporters within a patient's tumor tissue. This approach is crucial for tailoring treatment to individual patient needs, thereby enhancing the efficacy of chemotherapy regimens.