

Review of the PhD Thesis “Study on the role of pharmacokinetic mechanisms of drug resistance in new anticancer drugs with focus on solid tumors” by Dimitrios Vagiannis

The dissertation thesis of Mgr. Dimitrios Vagiannis is prepared as annotated set of articles/manuscripts. It is organized into 9 chapters with the main part representing five original research articles and three manuscripts. These are supplemented with a short introduction reviewing the problematics of anticancer therapy and pharmacokinetic mechanisms of multidrug resistance. Thesis further contains aims, brief description of obtained results, summary, conclusions and perspectives, list of references and list of author’s publications.

Thesis is well structured, written in concise manner and supported by appropriate number of references. The introduction is suitably supplemented with figures and schemes. The language is comprehensive with rare errors or typos.

The objectives of the dissertation aim on pharmacokinetic mechanisms of multidrug resistance, that is one of common complications of cancer pharmacotherapy. The author focused his research on various protein kinase inhibitors (dabrafenib, alisertib, tepotinib, entrectinib, ensartinib, alectinib), that could be/are used in the therapy of solid tumors. Mgr. Vagiannis tested selected kinase inhibitors for its inhibitory influence on both ABC transporters and CYP enzymes that are most relevant in the phenomenon of multidrug resistance (MDR). Results of these interactions from *in vitro* experiments are suitably supported by methods of molecular docking simulations, interaction studies with selected chemotherapeutics and *ex vivo* models in case of ABC transporters. This approach gives a complex view on the role of tested drugs in the MDR. Besides that, some of the results also clarified the role of CYP enzymes in the drug resistance to taxanes and vincristine. Entrectinib and alisertib were also identified as selective inhibitors of ABCC1 transporters, that are missing in the clinical practice. This dissertation adds another important piece of knowledge on mechanisms of MDR and could be helpful in future strategies fighting this problem in the therapy of cancer.

Methods used to obtain presented results are appropriate and in the case of patient-derived explants of non-small cell lung cancer also innovative. The quality of obtained results is proved by articles published in international journals with high impact factors. Mgr. Vagiannis is first author of two of them and co-author of another three. Another three papers that are part of the thesis are submitted or prior to submission.

As a minor remark that does not decrease the scientific quality of the thesis, I could mention, that it would be more lucid and helpful for the reader if a comprehensive chart reviewing effects of tested kinase inhibitors on ABC transporters and CYPs would be used in the part describing results of research. Another imprecision can be found in titles of journals in References, which are not unified. Full names of journals are used

together with journal abbreviations. Moreover, capitals are used in names of some journals only for the first word of title, while each word of journal name is in capitals in other references.

In conclusion, the research in the dissertation thesis of Dimitrios Vagiannis provide important new insight into the pharmacokinetic mechanisms of drug resistance to cancer chemotherapy. His work also clarifies important characteristics of new protein kinase inhibitors with respect to their possible role in MDR modulation and drug-drug interactions. I am convinced that Dimitrios Vagiannis has shown research qualities required for a successful PhD student. Therefore, **I recommend this dissertation to be accepted for the defence of the PhD degree and Dimitrios Vagiannis to be awarded the Ph.D. degree after successful defense of his thesis.**

Questions and remarks for the dissertation thesis defence:

There are various kinase inhibitors with potential therapeutic use. What were the selection criteria of kinase inhibitors used in your research?

Are there any suitable animal models to study MDR and what are their advantages/disadvantages in comparison to *in vitro* models you used?

In thesis, the influence of studied kinase inhibitors on ABC transporters and CYPs is described with its relevance to possible modulation of MDR. Nevertheless, the risk of drug-drug interactions with co-administered drugs should also be considered. Would it be possible to describe rules or measures for combinations of studied kinase inhibitors with chemotherapeutics or other co-administered drugs to maximize the inhibitory effect of kinase inhibitors on MDR while minimizing the risk of drug-drug interactions?

Another promising group of drugs for the treatment of cancer are advanced therapy medicinal products. Is there any mechanism, how these drugs could be used against MDR based on ABC transporters or CYPs?

doc. PharmDr. Ondřej Zendulka, Ph.D.

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Masaryk University | Faculty of Medicine
Department of Pharmacology
Kamenice 5 | 625 00 Brno | Czech Republic